

12.9 Disorders of peroxisomal metabolism in adults

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ESSENTIALS The peroxisome is a specialized organelle which employs molecular oxygen in the oxidation of complex organic molecules including lipids. Enzymatic pathways for the metabolism of fatty acids, including very long-chain fatty acids (VLCFA), enable this organelle to carry out β -oxidation in partnership with mitochondria. A peroxisomal pathway for isoprenoid lipids derived from chlorophyll, such as phytanic acid, utilizes α -oxidation, but a default mechanism involving ω -oxidation may also metabolize phytanic acid and its derivatives. The biochemical manifestations, molecular pathology, and diverse clinical features of many peroxisomal disorders have now been clarified, offering the promise of prompt diagnosis, better management, and useful means to provide appropriate genetic counselling for affected families. At the same time, specific treatments including rigorous dietary interventions and plasmapheresis to remove undegraded toxic metabolites offer credible hope of improvement and prevention of disease in affected individuals. Inborn errors of peroxisomal metabolism usually present in infancy and childhood, but some disorders typically become manifest later in life and in adults, in whom the progress is often slow. Particular adult peroxisomal disorders X-linked adrenoleukodystrophy (X-ALD)—due to mutation in the gene for an ATP-binding cassette (ABC) protein of unknown function and characterized by accumulation of unbranched saturated VLCFAs, particularly hexacosanoate (C26), in the cholesterol esters of brain white matter, adrenal cortex, and certain sphingolipids of the brain. The disease has multiple phenotypes: it may present in adolescence with slowly progressive stiffness, clumsiness, weakness, weight loss, and skin pigmentation typical of Addison's disease; it may present in adults with primarily psychiatric manifestations. Most cases develop increasing handicap; management is palliative and supportive in most instances. Adult Refsum's disease—due in most cases to

mutations in the gene for phytanoyl-CoA hydroxylase (PHYH) such that patients are unable to detoxify phytanic acid by α -oxidation and have greatly elevated levels of this in their plasma. Usually presents in late childhood with progressive deterioration of night vision, the occurrence of progressive retinitis pigmentosa, and anosmia; late features include deafness, ataxia, polyneuropathy, ichthyosis, and cardiac arrhythmias. Treatment is by restriction of dietary phytanic acid, with or without its elimination by plasmapheresis or apheresis.

Neuropsychiatric adult peroxisomal disorders

Historical perspective The likely first description of X-linked adrenoleukodystrophy (X-ALD; OMIM 300100) was in 1910 when a 6-year-old child developed abnormal eye movements, apathy, and mental deterioration. His gait then deteriorated and skin darkening was noted prior to his death a few months later. Examination of the brain by Schilder showed central demyelination, perivascular lymphocytes, foam cells, and gliosis which he termed encephalitis periaxialis diffusa. Other cases he later described are likely due to other leukodystrophies.

Adrenoleukodystrophy was defined in 1970, with its characteristic adrenal changes of excess very long-chain fatty acids (VLCFAs) and cholesterol esters present in cell inclusion bodies. These VLCFAs were later recognized as pathognomonic and identifiable in plasma samples and the primary defect was identified as an inability to metabolize them. The gene was mapped to Xq18 and identified as a member of the ATP-binding cassette (ABC) transporter family. X-ALD was localized to the peroxisome. Subsequently, mouse models have been developed which show some clinical features of human disease such as adrenomyeloneuropathy but typically lack the cerebral changes seen in man.

Aetiology Adrenoleukodystrophy is characterized by the accumulation of unbranched saturated VLCFAs with a chain length of 24 to 30 carbons, particularly hexacosanoate (C26), in the cholesterol esters of brain white matter, in the adrenal cortex, and in certain sphingolipids of the brain. The disorder shows X-linked inheritance with expression in female heterozygotes. The disruptive effects of the accumulation of VLCFAs, especially hexacosanoic acid (C26:0), on cell membrane structure and function may explain the neurological manifestations seen in adrenoleukodystrophy patients. VLCFAs cause alterations in membrane fluidity and affect cortisol secretion from cultured cells.

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section 12 Metabolic disorders 2158 of adrenal cortical origin. In addition, albumin has only one C26 binding site compared with more than six for shorter fatty acids, so limiting its efficacy as a reverse transport protein for excess VLCFAs.

Clinical features X-ALD is heterogeneous: seven phenotypes occur in males and five are recognized in females. Childhood cerebral adrenoleukodystrophy presents between the ages of 5 and 10 years with emotional lability, hyperactivity/withdrawal, and mental deterioration, mimicking attention deficit disorder which evolves to parietal lobe dysfunction with apraxia, astereognosis, and later dementia. MRI shows a characteristic pattern of symmetric involvement of the posterior parieto-occipital white matter in 85% of patients, frontal involvement in 10%, and an asymmetric pattern in the rest. The clinical phenotype of X-ALD shows a variable progression which may be interrupted by periods of arrest on MRI sometimes lasting 5 to 10 years. The adolescent form is adrenomyeloneuropathy which presents with slowly progressive stiffness, clumsiness, weakness, weight loss, and skin pigmentation typical of Addison's disease. Autonomic function including micturition and erectile function are affected later. Somatosensory, auditory, and brainstem evoked potential are abnormal with some cases of abnormal visual and peripheral nerve conduction abnormalities. Brain MRI scans are abnormal in 50% of men and 80% of women, usually affecting corticospinal tracts with later parenchymal changes. Depression and emotional lability are common. Adult cerebral

adrenoleukodystrophy is a variant of adrenomyeloneuropathy occurring after age 20 without spinal cord symptoms. The primary signs are psychiatric with a presentation of psychotic mania and may include schizophrenia or dementia. Some cases show a pure initial Addisonian picture with no neurological involvement; all are autoantibody negative. The onset of Addison's disease is usually in childhood but the neurological changes follow in 20 to 30 years. Subtle hyper-reflexia or impaired vibration sense and subtle MRI or neurophysiological signs may be detected earlier in these cases. It had been considered that neurological changes were mild or absent in carriers of X-ALD, but up to 20% are symptomatic. Women who are X-ALD heterozygotes usually present with adrenomyeloneuropathy at age 30 to 40. Subtle signs are often detected prior to presentation but eventually the full picture occurs, with late-onset dementia. A recent prospective study of 46 female carriers found an age-dependent phenotype of myelopathy occurring in 63% and faecal incontinence in 28% independent of X-inactivation status. These were associated with abnormalities in plasma VLCFAs and decreased fibroblast β -oxidation of VLCFAs. In female adrenoleukodystrophy heterozygotes, adrenal cortical insufficiency rarely develops, although isolated mineralocorticoid insufficiency may occur but may be difficult to diagnose. Furthermore, adrenoleukodystrophy heterozygotes are predisposed to hypoaldosteronism related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs). A subclinical decrease in glucocorticoid reserve, as measured by synthetic ovine corticotropin-releasing hormone testing, may be present in most of these women. Aldosterone levels should be included in ACTH stimulation testing done to detect adrenal insufficiency in affected women. NSAIDs should be considered a risk factor for the development of hypoaldosteronism in women who are heterozygous for adrenoleukodystrophy. Rare presentations include olivopontocerebellar atrophy which has been described as X-ALD ataxia in Japanese. Other uncommon presentations include unilateral masses which can mimic brain tumours and cases of spontaneous remission of neurological symptoms. A clinical syndrome that mimics features of ALD is acyl-coenzyme A (CoA) oxidase deficiency but most cases present with severe neonatal disease.

Neuropathology There are two distinct forms of neuropathology associated with X-ALD. Pure adrenomyeloneuropathy is a distal axonic neuropathy while the cerebral forms are associated with inflammation. In cerebral X-ALD, brain pathology is often grossly normal though with signs of cerebral atherosclerosis. Grey matter is unaffected but white matter disease occurs in a rostrocaudal direction with demyelination prominent in the parieto-occipital cortex and the cerebellum. The detailed pathology shows oligodendroglial cell loss, astrocytosis, and a perivascular inflammatory infiltrate. In the noncerebral form, demyelination is seen in the corticospinal tracts with no obvious inflammation and only mild gliosis and occasional macrophages. In the adrenal cortex, cells are filled with lamellar deposits of cholesterol esters with primary cortical atrophy and no evidence of inflammation or antibodies, with milder changes in the adrenomyeloneuropathy form. In men with X-ALD, the testes show Leydig cell alterations, again with lamellar deposits. It has been estimated that at least 10% of males with Addison's disease (adrenocortical failure) have X-linked adrenomyeloneuropathy or unrecognized X-ALD.

Metabolism of VLCFAs VLCFAs are derived from the diet and endogenous synthesis, with between 20 and 80% derived from synthesis depending on the study. The synthetic pathway occurs in brain microsomes with repeated additions of malonyl-CoA units to palmitic (C16:0) or stearic (C18:0) acid precursors. There are probably separate pathways for C20:0 and C22:0 (behenic) fatty acids with the C22:0 pathway also elongating C22:1 (erucic) acid. Synthesis of VLCFAs starts with use of a specific activator protein SLC27A4—the fatty acid transport protein 4 (FATP4). The synthesis of saturated VLCFA, monounsaturated VLCFA (MUFA), and polyunsaturated fatty acids (PUFAs) occurs in the endoplasmic reticulum by four distinct enzymes; elongation of very long-chain fatty acids

ligase (ELOVL), 3-ketoacyl-CoA reductase (HSD17B12), 3-hydroxyacyl dehydratase (HACD3), and trans-2,3-enoyl-CoA reductase (TECR). The initial condensation reaction catalysed by ELOVL is usually rate limiting. Mammals have seven different ELOVL enzymes (ELOVL1–7) but only a single enzyme has been identified so far for each synthetic pathway. ELOVL1, ELOVL3, ELOVL4, and ELOVL6 are involved in the synthesis of saturated and monounsaturated fatty acids and ELOVL2, ELOVL4, ELOVL5, and ELOVL7 are essential for PUFA metabolism. The synthesis of C24:0 and C26:0 VLCFAs is carried out by the concerted action of ELOVL6 (C18:0–C22:0) and ELOVL1 (C24:0–C26:0) of which the latter is the key rate-limiting step. Degradation of VLCFAs occurs by β -oxidation within peroxisomes after activation by specific acyl-CoA ligases which are chain-length specific. Again, FATP4 plays a key role in activating the fatty acid.

12.9 Disorders of peroxisomal metabolism in adults 2159 Molecular genetics: the X-ALD protein and its homologues The X-ALD gene was mapped to a region of the X-chromosome close to the glucose-6-phosphate dehydrogenase gene. The gene was established to code for an ABC protein of still unknown function but likely to involve the translocation of a variety of substrates across extra- and intracellular membranes, including lipids, sterols, and drugs. The ABCD1 protein (adrenoleukodystrophy protein) maps to Xq28 and is mutated in X-ALD. ABCD1 is a member of the ABC transporter superfamily. It expresses a half transporter which is located in the peroxisome. The gene has an open reading frame of 2235 bases which encodes a 745-amino acid protein with 38.5% amino acid identity and 78.9% similarity to another peroxisomal protein (ABCD3). Mutations in ABCD1 result in X-ALD in animal models, with elevated VLCFAs. ABCD1 is one of four related peroxisomal transporters that are found in the human genome, the others being ABCD2 (adrenoleukodystrophy related protein) (OMIM 601081), ABCD3 (peroxisomal membrane protein 70) (OMIM 170995), and ABCD4 (P70R/PMP69) (OMIM 603214). The adrenoleukodystrophy protein and the adrenoleukodystrophy-related protein are expressed on oligodendroglia, while the adrenoleukodystrophy-related protein and peroxisomal membrane protein 70 are found in neurons of the central nervous system. These genes are highly conserved in evolution, and two homologous genes are present in the yeast genome, PXA1 and PXA2, which also transport long-chain fatty acids. The 80-kDa protein encoded by this gene is absent in patients with X-ALD, in whom X-ALD mRNA was undetectable. Most of the ABCD1 mutations (>450) in X-ALD are point mutations, but large deletions have been described. There is no correlation between genotype and phenotype. In 15 to 20% of obligate female heterozygotes, false-negative results occur for plasma VLCFAs. Mutation analysis is the only reliable method for the identification of heterozygotes. Overexpression of the adrenoleukodystrophy protein and its homologue, the adrenoleukodystrophy-related protein (ABCD2), can restore the impaired peroxisomal β -oxidation in the fibroblasts of adrenoleukodystrophy patients. However, it seems that functional replacement of the adrenoleukodystrophy protein by adrenoleukodystrophy-related protein is not due to stabilization of the mutated adrenoleukodystrophy protein. Similarly, the adrenoleukodystrophy-related protein and peroxisomal membrane protein 70 could restore the peroxisomal β -oxidation defect in the liver of adrenoleukodystrophy protein-deficient mice by stimulating Aldr and Pmp70 gene expression through a dietary treatment with the peroxisome proliferator fenofibrate. These results suggested that a correction of the biochemical defect in adrenoleukodystrophy might be possible by drug-induced overexpression or ectopic expression of the adrenoleukodystrophy-related gene. The adrenoleukodystrophy protein transporter may facilitate the interaction between peroxisomes and mitochondria, the two sites within the cells where β -oxidation of VLCFAs occurs. The phenotype of X-ALD was thought to be based on

microglial activation for cerebral effects, while inflammation is less involved in adrenomyeloneuropathy but transcriptome studies show that a combination of effects of the deficiency on oxidative phosphorylation and adipocytokine and insulin signalling are responsible for the phenotypes. Many papers have described mutations in the ABCD1 gene in X-ALD patients, indeed more than 600 different mutations have now been described (<http://www.x-ald.nl>) of which 51% are missense, 28% frame-shift, and 12% nonsense mutations; 6% are small insertions/deletions and 13% are exon deletions. About 75% of all nonrecurrent ABCD1 mutations result in the absence of ABCD1 protein (<http://www.x-ald.nl>). Nonsense and frame-shift mutations as well as large deletions lead to a truncated protein. Many missense mutations result in unstable protein whose detection is likely to be dependent on the specificity and sensitivity of the method used. The lack of anti-ABCD1 immunofluorescence (IF) using microscopy in cultured fibroblasts is commonly used to assess ABCD1 protein expression. However, fibroblasts express relatively low levels of ABCD1 and so this method may miss ABCD1 expression detectable by the more sensitive western blot methods. Re-investigation of 'IF negative' cell lines using improved techniques has confirmed this supposition, hence some previously suspected cases may require re-analysis. Disease-associated missense mutations are not equally distributed over the ABCD1 protein. Analysis of 300 missense mutations showed clustering in two major regions (Fig. 12.9.1).

Epidemiology Screening and diagnostic records suggest that the prevalence is a minimum of 1 in 22 500 to 1 in 62 000. In contrast, the use of the Hardy-Weinberg approach and genetic frequency data suggests a combined male to female frequency of 1 in 18 000 similar to phenylketonuria (1 in 12 000).

Differential diagnosis The differential diagnosis of neuropsychiatric abnormalities is shown in Table 12.9.1. X-ALD can mimic attention deficit disorder, multiple sclerosis, organic dementias, and psychoses among neurological diseases, and Addison's disease and hypogonadism among endocrine disorders (Table 12.9.2). The critical clinical differential element is the finding of abnormal ACTH concentrations and skin pigmentation with neurological signs, however subtle.

Clinical investigation

Clinical biochemistry The primary abnormality in X-ALD is an accumulation of VLCFAs (>C22) which occur in myelin. C26:0 can account for up to 5% of brain cerebroside and sulphatides. In X-ALD, both saturated and unsaturated forms of C26:0 (cerotic) and C24:0 (lignoceric) acids accumulate with reductions in C24:1(n-9) (nervonic) acid. Normally, shorter fatty acids accumulate in brain cholesterol esters, but in X-ALD, by contrast, these are mostly C26:0 and are enriched in myelin and in areas of demyelination. Similarly, C26:0 accumulates in white matter phosphatidylcholine phospholipids, C24:0 and C24:1 in gangliosides. Erythrocytes, plasma, and cultured fibroblasts all contain a 2- to 10-fold excess of VLCFAs. The diagnostic test relies on measurement of C26:0 levels and the ratios of C26 to C22:0 (docosahexaenoic acid) and C26:0 to C24:0 (tetracosanoic acid). Some neonatal paediatric screening programmes have begun to implement screening for C26:0 phosphatidylcholine as a marker of X-ALD in their dried blood spot analysis programmes. Results can be confirmed by fibroblast studies or by the use of sequencing techniques. Highly elevated VLCFA levels are also found in peroxisomal biogenesis disorders but these show a different clinical presentation to X-ALD or transiently with ketogenic diets for seizures. False-negative results may occur in patients consuming excess C22:1;

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Table 12.9.1 Psychiatric signs and inborn errors of metabolism in adolescents and adults

Disorder	Confusion	Mental retardation	Behavioural disturbance	Catatonia	Visual hallucination	Psychosis	Depression	Urea cycle defect	Homocysteine disorders	Porphyrria	Wilson's disease	CTX
	+	+	+	+	+	+	+	+/–	+	+	+/–	+

MLD + + GM2 gangliosidosis + + + + + Mannosidoses + + + + + X-ALD + + + Acyl-CoA oxidase (pseudoneonatal adrenoleukodystrophy) + + + Nonketotic hyperglycinaemia + + Monoamine oxidase A deficiency + + Creatine transporter deficiency + + Succinic semi-aldehyde dehydrogenase deficiency + + Niemann-Pick C + + + + + CTX, cerebrotendinous xanthomatosis; MLD, metachromatic leukodystrophy; X-ALD, X-linked adrenoleukodystrophy. Reproduced from Sedel F et al. (2007a). Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inher Metab Dis*, 30, 631–41, with permission. 10 8 6 4 2 0 50 100 N mPTS Transmembrane domain Number of disease-causing mutations per block of 10 amino acids Evolutionary conservation (% AA identity per block of 10 amino acids) Walker A Walker B C 0 20 40 60 80 100 150 200 250 300 350 400 450 500 550 600 650 700 750 Fig. 12.9.1 The degree of interspecies conservation and location of human mutations in the ABCD1 gene. The first region of conservation/disease-causing mutations is located in the transmembrane domain region (amino acids 83–344) and the second is located in the ATP-binding domain (amino acids 500 and 668). The N-terminal 73 amino acids and the C-terminal 50 amino acids are mostly spared, hence caution is warranted when interpreting sequencing data suggesting missense mutations outside these key regions. Reproduced with permission from Wiersinger C, Eichler FS, Berger J. The genetic landscape of X-linked adrenoleukodystrophy: inheritance, mutations, modifier genes, and diagnosis. *Appl Clin Genet*. 2015; 8: 109– 121. Copyright © 2015 Wiesinger et al.

12.9 Disorders of peroxisomal metabolism in adults 2161 ω -9 (erucic acid; Lorenzo’s oil) which is found in mustard and rapeseed oils. A few affected males (0.1%) have borderline normal C26:0 levels and 15% of obligate female carriers have normal results. Effective mutation detection in these families is therefore fundamental to the unambiguous determination of genetic status. Of particular concern are female members of kinships with segregating X-ALD mutations, because normal levels of VLCFA do not guarantee a lack of carrier status. Prenatal diagnosis is possible from cultured amniocytes or chorionic villus cells. Abnormal liver function tests are a common finding in adrenoleukodystrophies and occur secondary to disturbances in di- and trihydroxycholestanic acid (DHCA and THCA) metabolism. Radiology A MRI scan often reveals biochemical changes before the development of clinical symptoms. Eighty per cent of childhood cerebral adrenoleukodystrophy patients have symmetric periventricular white matter changes in the posterior parietal and occipital lobes with a dorsocaudal progression with time (Fig. 12.9.2a). Patients with adrenomyeloneuropathy typically have abnormalities in the pyramidal tracts (Fig 12.9.2b). Contrast studies show up areas of active demyelination, inflammation with breakdown of the blood-brain barrier, and gliosis. The Loes score (34-point X-ALD severity score) based on the five patterns of disease visible on MRI is used to determine severity and prognosis and is used as a decision aid prior to bone marrow transplantation. The presence of demyelination and gadolinium enhancement are used to differentiate stable from likely progressive inflammatory changes on MRI scanning (Fig. 12.9.2c). Proton magnetic resonance spectroscopy shows only mild reduction in N-acetyl aspartate, normal choline and myo-inositol, and normal lactate in patients Table 12.9.2

Differential diagnosis of X-ALD Presentation Differential diagnosis Childhood neurological with normal endocrinology Hyperactivity, attention deficit disorder Epilepsy/seizures Brain tumour Metachromatic/globoid leukodystrophy Postencephalitic syndromes, e.g. subacute sclerosing panencephalitis Myelinoclastic diffuse sclerosis Childhood neurological with hypoadrenalism Addison’s disease with post-hypoglycaemic damage X-linked glycerol kinase deficiency Central pontine myelinolysis Glucocorticoid deficiency with achalasia Hypoadrenalism Secondary causes of hypoadrenalism Adrenomyeloneuropathy Multiple sclerosis Familial or other spastic parapareses

Spinocerebellar/olivopontocerebellar degeneration Cervical spondylosis Spinal cord tumour, e.g. ependymoma Adult cerebral Schizophrenia Depression Epilepsy/organic psychosis Alzheimer's disease or other dementias Brain tumour Heterozygote with symptoms Multiple sclerosis Chronic spinal disease Spinal cord tumour Cervical spondylosis (A) (a) (B) (C) (D) Fig. 12.9.2 (a) MRI of the brain in a case of childhood cerebral adrenoleukodystrophy (ALD) showing characteristic extensive white matter changes in the parieto-occipital region and internal capsules on FLAIR sequences (A). This area is initially affected in about 80% of cases of cerebral ALD. The rim enhances after administration of gadolinium on T1 sequences (B). In about 20% of cases the site of initial involvement in cerebral ALD is the frontal white matter as shown on this FLAIR image of a different patient with cerebral ALD (C), with prominent rim enhancement after administration of gadolinium on a T1-weighted image (D). (b) MRI of the brain in a patient with adrenomyeloneuropathy showing increased signal in the pyramidal tracts on T2-weighted coronal (A) and axial (B) images indicative of Wallerian degeneration. (c) MRI of the brain (T2 (A) and FLAIR (C) images; T1 with gadolinium (B, D)) of a patient with adrenomyeloneuropathy who rapidly deteriorated clinically with new symptoms of cognitive decline. On MRI, extensive white matter changes were seen in the parieto-occipital white matter and corpus callosum (A), but no enhancement of the lesion after administration of gadolinium (B). A follow-up MRI about 3 months later shows progression of the white matter lesion (C) and there is now faint enhancement of the rim of the lesion after gadolinium administration (D). Reproduced with permission from Engelen M, Kemp S, de Visser M, van Geel BM, Wanders RJ, Aubourg P, Poll-The BT. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis.* 2012 Aug 13;7:51. doi: 10.1186/1750-1172-7-51.

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section 12 Metabolic disorders 2162 with arrested as compared with progressing disease where N-acetyl aspartate levels are significantly reduced while choline compounds, myo-inositol, and lactate are raised. 18Fluorodeoxyglucose positron emission tomography shows increased glucose uptake in the frontal lobes with decreased activity in the temporal lobes and cerebellum in patients with X-ALD. The increase in frontal activity correlated with scores from psychological evaluations. Proton spectroscopy using N-acetyl aspartate shows up neuronal loss, while choline compound studies assaying phosphocholine and glycerophosphocholine indicate membrane turnover and demyelination, and myo-inositol compounds seem to be indices of gliosis. The presence of lactate indicates the anaerobic metabolism of the inflammatory cell infiltrate. In the adrenomyeloneuropathy brain, MRIs may be normal in 50% of men and 80% of women but diffuse spinal cord atrophy is present. Endocrinology Overt hypoadrenalism occurs in 40% of patients with childhood cerebral adrenoleukodystrophy and 80% have a deficient cortisol response on Synacthen testing. In childhood disease, 80% show abnormal adrenal stimulation test results, while in adrenomyeloneuropathy, between 30 and 50% show normal responses. Clinical Addison's disease is found in 1% of female heterozygotes. In adrenoleukodystrophy heterozygotes, adrenal cortical insufficiency rarely develops, although hypoaldosteronism may occur, especially if NSAIDs are being used. ACTH levels are increased in male patients. Levels of follicle-stimulating hormone or luteinizing hormone are increased in 50 to 70% of patients with adrenomyeloneuropathy, while testosterone levels are reduced in 20% with low normal levels of dehydroepiandrosterone sulphate. Neurophysiology Hearing is normal but brainstem auditory evoked potentials are abnormal in 95% of adrenomyeloneuropathy patients and 42% of heterozygote patients. Abnormalities in visual evoked potentials are also found as latencies and are increased in 20% of men with

adrenomyeloneuropathy but in more than 70% with childhood cerebral disease. Electroretinograms are normal. Subtle demyelination and axonal loss patterns of nerve conduction are found in 90% of men and 67% of women with adrenomyeloneuropathy, usually affecting the legs more than the arms. Neuropsychological tests can show up deficits in parieto-occipital function affecting visuospatial parameters and auditory processing, while frontal lobe lesions affect executive functions, emotions, problem solving, and anticipatory processing. Treatment The progressive nature of X-ALD means that comprehensive family and professional management support services are required. Leukodystrophies are associated with progressive learning difficulties, psychiatric disturbance, and increasing disability. Painful muscle spasms are common and should be managed with diazepam, baclofen, or gabapentin. Bulbar muscle function may be lost with disease progression, thus requiring special attention to feeding to reduce the risk of aspiration pneumonia. The routine management of patients with X-ALD includes regular clinical reviews allied with MRI scanning at approximately 3–6-month intervals depending on the rate of progression. Endocrine assessment is performed at baseline and repeated if the clinical syndrome includes features of hypoadrenalism. Dietary therapy was based on the restriction of the intake of C26:0 to less than 15% of normal intake, but early trials showed no effect of this on levels of VLCFA levels. Addition of oleic acid normalized VLCFA levels in fibroblasts and oral glyceryl trioleate reduced VLCFA levels by 50% with an improvement in nerve conduction measures. A 4:1 combination of glyceryl trioleate and trierucate (Lorenzo's oil) normalized VLCFA levels within 1 month and prompted mass use of this intervention. No evidence of a clinically relevant benefit from dietary treatment with Lorenzo's oil has been seen in many studies of patients with neurological involvement and X-ALD, and asymptomatic thrombocytopenia was noted in 30% of patients. The fatty acid composition of the plasma and liver, but not that of the brain, improves with this therapy, suggesting that (A) (B) (b) (A) (c) (B) (C) (D) Fig. 12.9.2 Continued

12.9 Disorders of peroxisomal metabolism in adults 2163 little erucic acid crossed the blood-brain barrier. Thus, dietary supplementation with Lorenzo's oil is of limited value in correcting the accumulation of saturated VLCFAs in the brain of patients with established neurological adrenoleukodystrophy. In a study of 89 asymptomatic boys with X-ALD who had normal MRI scans, Lorenzo's oil and moderate fat restriction were prescribed for 6.9 ± 2.7 years. Plasma fatty acids and clinical status were followed as measures of outcome. Twenty-four per cent developed MRI abnormalities and 11% developed neurological and MRI abnormalities. The trial concluded that the reduction of C26:0 by Lorenzo's oil was associated with a reduced risk of developing MRI abnormalities. Lorenzo's oil therapy is indicated in asymptomatic boys with X-ALD who have normal brain MRI scans. Experience with other adrenoleukodystrophy patients indicated that total fat intake in excess of 30 to 35% of total calories may counteract or nullify the C26:0-reducing effect of Lorenzo's oil. Patients who develop progressive MRI abnormalities should be considered for haematopoietic stem cell transplantation, but the 5-year mortality is 38% and survival is increased by 8 months on average. Results in 283 boys with X-ALD who received haematopoietic cell bone marrow transplantation showed that the estimated 5-year survival was 66%. The leading cause of death was disease progression. Donor-derived engraftment occurred in 86% of patients. Demyelination involved parietal-occipital lobes in 90%, leading to visual and auditory processing deficits in many boys. Bone marrow transplantation must be considered very early, even in a child without symptoms but with signs of demyelination on MRI, if a suitable donor is available. There are few data on the usefulness of bone marrow transplantation in adrenomyeloneuropathy. Adrenal function must be monitored since 80% of asymptomatic patients with adrenoleukodystrophy

develop evidence of adrenal insufficiency and adrenal hormone replacement therapy should be provided when indicated by laboratory findings. Given the inflammation associated with X-ALD, a number of immunosuppressive regimens have been investigated. Studies of cyclophosphamide, immunoglobulin, and interferon- β have been unsuccessful. Prognosis The prognosis in X-ALD depends on the presentation. As yet, there are no methods of determining which type of disease will result from a given mutation as genotype-phenotype correlation is poor. Once leukodystrophy begins, the prognosis is poor as progression is inevitable. Data from inherited error bone marrow transplant regimens shows prolongations in life with transplantation in X-ALD but do not record improvements in quality of life. Future developments Other potential therapeutic approaches to X-ALD include the use of lipid-lowering drugs. Lowering cholesterol activates human ABCD2 in cultured cells. In mice, a sterol regulatory element exists in the Abcd2 promoter and overlaps sites for liver X receptor/retinoid X receptor heterodimers. Adipose Abcd2 is induced by SREBP1c, whereas hepatic Abcd2 expression is down-regulated by concurrent activation of liver X receptor- α and SREBP1c. Hepatic Abcd2 expression in liver X receptor- α/β mice is inducible to levels vastly exceeding wild type. Statins (3-HMG-CoA reductase inhibitors) are capable of normalizing VLCFA levels in primary skin fibroblasts derived from X-ALD patients. They block the induction of proinflammatory cytokines through effects on rho kinase. Twelve patients with X-ALD were treated with lovastatin for up to 12 months. Levels of C26:0 declined from pretreatment values and stabilized at various levels during a period of observation of up to 12 months, which does not correlate with the type of adrenoleukodystrophy gene mutation. In six patients, erythrocyte C26:0 levels fell by 50%. All patients with adrenomyeloneuropathy remained neurologically stable. However, follow-up trials have been unsuccessful. The PPAR- α agonist-mediated induction of ABCD2 expression seems to be indirect and possibly mediated by the sterol-responsive element-binding protein 2 in mice. In addition PPAR- α is involved in the regulation of ELOVL1, a key step in VLCFA synthesis. In vitro CoA esters of both bezafibrate and gemfibrozil inhibit ELOVL1 and could form starting points for novel drug development. However, a study of the pan-PPAR agonist bezafibrate in 10 male patients failed to show any effects of plasma or erythrocyte VLCFA concentrations despite reducing plasma triglyceride levels as predicted. Studies in animal models have suggested that the PPAR- γ (with some PPAR- α activity) agonist pioglitazone may reduce axonal degeneration but there have been no studies in humans. Sodium 4-phenylbutyrate reduces VLCFA levels through its effects on peroxisomal function and increases adrenoleukodystrophy-related protein levels. However, human studies have failed to show consistent beneficial effects. ω -Oxidation is an alternative oxidation route for VLCFAs. These fatty acids are substrates for the ω -oxidation system in human liver microsomes and are converted into ω -hydroxy fatty acids and further oxidized to dicarboxylic acids via cytochrome P450 (CYP)-mediated reactions. The high sensitivity towards the specific CYP inhibitor 17-octadecynoic acid suggested that ω -hydroxylation of VLCFAs is catalysed by the CYP4A/F subfamilies, particularly CYP4F2 and CYP4F3B, and that therapies capable of increasing ω -oxidation may have the potential to reduce the progression of the disease. Previously gene therapy has been attempted for X-ALD using lentivirus transformation of white cells and 9 to 14% of cells showed reconstitution of ABCD1 expression over 24 months. A more modern gene therapy approach using an adeno-associated virus construct AAV-9/ABCD1 shows appropriate neurological tropism following intracerebroventricular or intravenous injection and reduces plasma and brain VLCFA levels in Abcd1-deficient mice. Given the extensive oxidative stress associated with demyelination in X-ALD there has been interest in antioxidant therapies in the treatment of X-ALD. A combination of the antioxidants α -tocopherol, N-acetyl-cysteine, and α -lipoic acid reduced demyelination in Abcd1-deficient mice. There are no

studies of this approach in humans. There has been an explosion of interest in novel therapeutic strategies for inherited errors of metabolism. Classical enzyme replacement therapy for X-ALD is impossible given the need to replace a peroxisomal transporter molecule, but other strategies utilizing technologies such as stabilized mRNA technology combined with liposome or other shielded delivery technologies allied with various methods of delivering tissue specificity may be more successful. These show promise in cell culture models but no studies have yet been performed in human X-ALD. None of these technologies

section 12 Metabolic disorders 2164 have reached animal models let alone human trials in peroxisomal diseases. Neuro-ophthalmic adult peroxisomal disorders Introduction Though survival is improving for peroxisomal biogenesis disorders and more subtle defects are now diagnosed, most still present in the neonatal period or in infancy. This is also true for most single enzyme peroxisomal deficiencies. Only one group of disorders presents later, with the onset of symptoms often in early teenage years but, due to delays in diagnosis, many are not identified until they reach adulthood. In contrast to the neuropsychiatric or endocrine presentation associated with adrenoleukodystrophy, these peroxisomal disorders present as central and peripheral neuropathies—a neuro-ophthalmic picture. They are often termed Refsum's disease though, given the multiple underlying genetic defects, it would be better to refer to them as Refsum's syndrome. The syndrome comprises three genetic disorders: phytanoyl-CoA hydroxylase deficiency (classical adult Refsum's disease), atypical rhizomelic chondrodysplasia punctata type 1, and the newly described α -methylacyl-CoA racemase deficiency. Historical perspective Adult Refsum's disease (OMIM 266510), also called hereditary ataxia polyneuritis, is a hereditary sensory motor neuropathy type IV. It was first described in 1947, but only recognized as a syndrome by Refsum in 1962. He described a constellation of signs comprised of retinitis pigmentosa, anosmia, deafness, ataxia, and polyneuropathy allied with raised levels of protein in the cerebrospinal fluid. The biochemical defect was identified in 1963 when phytanic acid was noted in the plasma of affected patients and defective α -oxidation was later suggested as the cause of adult Refsum's disease. This disease was thought to be unifactorial with admittedly some rare aberrant complementation studies until 1995 when, after the localization of the gene for phytanoyl-CoA hydroxylase, up to 50% of cases in one series were shown not to be linked to chromosome 10 but to chromosome 6. Eventually, the novel defect was identified as a variant of rhizomelic chondrodysplasia punctata type 1 and caused by mutations in peroxin 7. In parallel with this discovery, three patients were described in 1997 with a phenotype of sensory neuropathy and a subtle bile acid disorder but whose families included siblings with a Refsum's-like syndrome which was identified as due to a deficiency in α -methylacyl-CoA racemase. A clinical phenocopy associated with polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (PHARC) (OMIM 612674) has recently been described. In contrast to other Refsum-like syndromes, phytanic acid levels are normal in this condition. Clinical features In contrast to Zellweger's syndrome (OMIM 214100), neonatal adrenoleukodystrophy (OMIM 202370), infantile Refsum's disease (OMIM 266500), and rhizomelic chondrodysplasia (OMIM 601757), adult Refsum's disease usually presents in late childhood with progressive deterioration of night vision, the occurrence of progressive retinitis pigmentosa, and anosmia (Table 12.9.3). Anosmia, contrary to early reports, is a constant feature of adult Refsum's disease. After 10 to 15 years, deafness, ataxia, polyneuropathy, ichthyosis, and cardiac arrhythmias can occur. Short metacarpals or metatarsals are found in about one-third of patients. Rare findings include psychiatric disturbance and proteinuria. Premature death may result from cardiac arrhythmias. α -Methylacyl-CoA racemase (OMIM 604489)

presents with adult-onset sensorimotor neuropathy (Table 12.9.3). It may be accompanied by retinitis pigmentosa, visual field restriction and loss of acuity, axonal sensorimotor neuropathy, and myopathy-like adult Refsum's disease. Other features described have included primary hypogonadism, hypothyroidism, spastic paraparesis, epileptic seizures, and mild developmental delay. More severe childhood-onset cases have shown a phenotype of defects in bile acid synthesis allied with fat-soluble vitamin deficiencies, coagulopathy, and cholestatic liver disease and a resemblance to a Niemann-Pick type C phenotype. Table 12.9.3 Comparison of clinical features of underlying metabolic defects associated with adult Refsum's disease

Adult Refsum's disease (n c. 300)	Rhizomelic chondrodysplasia (n c.5)	α -Methylacyl-CoA racemase (n c.6)	PHARC (n c.30)
Retinitis pigmentosa	Age >12	Age >12	Age >20
Cataract	Age >30	Age >30	Age >30 ?
Anosmia	All	All ?	Absent
Sensorineural deafness	Age >40	Age >40 ?	Age >5
Sensory neuropathy	Age >20	PA dependent	Age >20
PA dependent	Age >20	PA dependent	Age >30
Axonal/ demyelinating	Age >30	Variable	Progressive
Ataxia	Age >20	PA dependent	Age >20
PA dependent	Variable	Progressive	Cholestasis
No	No	Yes	No

Biochemistry: Phytanic acid (μmol/L)

“ 300 <0.2 100 <0.2 <200 10 Normal (<10) Normal (0.5–3) PA, phytanic acid; PHARC, polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract.

12.9 Disorders of peroxisomal metabolism in adults 2165 PHARC shares many clinical features of Refsum's disease but lacks the anosmia and possibly the osteological changes (Table 12.9.3). Some mitochondrial disorders in the Leigh's syndrome spectrum, including neurogenic muscle weakness, ataxia, and retinitis pigmentosa (NARP), caused in many cases by mutations in mitochondrial MT-ATP6, may also share some clinical features with adult Refsum's disease. Aetiology Phytanic acid (3R,S,7R,11R,15-tetramethylhexadecanoic acid) is an isoprenoid lipid derived from the phytol side chain of chlorophylls by bacterial degradation in ruminants, invertebrates, or pelagic fish (see Fig. 12.9.3). Phytol can be oxidized to an unsaturated fatty acid, phytenic acid, and this is saturated to phytanic acid by a pathway involving fatty aldehyde dehydrogenase 10 (FALDH-10) in microsomes. The significance of this pathway in humans is unclear though high phytanic acid levels have been described in some patients deficient in FALDH-10 with Sjögren-Larsson syndrome. Most phytanic acid is ingested from the adipose tissue and muscle of herbivores or pelagic fish. The average human daily dietary intake of phytanic acid in Western societies is between 50 and 100 mg, of which about 50% is absorbed and metabolized. Phytanic acid is transported in plasma bound to very low-density lipoprotein and later low-density lipoprotein, with its elimination allied to reverse cholesterol transport (high-density lipoprotein). Phytanic acid is preferentially taken up by the liver and may account for up to 50% of the free fatty acid pool in hepatocytes. This pool is labile and can be acutely mobilized by stress, infection, or starvation, resulting in rapid phytanic acid release. Plasma phytanic acid concentrations are less than 10% of the levels found in adipose tissue and neurons, which accumulate phytanic acid because of its hydrophobicity. The elimination half-life of total body phytanic acid is usually between 1 and 2 years. Most fatty acids are metabolized by the β -oxidation pathways in peroxisomes and mitochondria. Phytanic acid cannot be metabolized by this route due to the presence of a β -methyl group. Instead, phytanic acid is metabolized either by α -oxidation to pristanic acid, or by ω -oxidation from the other end of the molecule. Using radiolabelled [14C]-phytanic acid as a substrate, an enzyme activity responsible for the α -oxidation of phytanic acid in

cell lysates was described in 1967. This activity was eventually localized within peroxisomes and, after 30 years, the pathway responsible for α -oxidation has been clarified. α -Oxidation of phytanic acid. Most phytanic acid metabolism occurs in the liver and kidney by α -oxidation, though skin fibroblasts are used for clinical diagnostic purposes. Phytanic acid from plasma enters the peroxisome in association with the sterol carrier protein-2 (SCP-2) and is metabolized by a four-step initial α -oxidation pathway (Fig. 12.9.4). Unusually, it appears this pathway can metabolize two stereoisomers of its substrate equally well. One carbon atom is then removed from the latter in a lyase reaction to give pristanal and formyl-CoA. Pristanal is then oxidized to pristanic acid which is thio-esterified using CoA to give a racemic mixture. The action of α -methylacyl-CoA racemase converts the (2R)-epimer to the (2S)-epimer. Further degradation of (2S)-pristanic acid by the stereospecific β -oxidation pathway then occurs, with the release of propionyl and acetyl-CoA units. Further β -oxidation reactions (including epimerization) are required to generate the dimethylundecanoic and dimethylnonanoic and methyl-heptanoic acid derivatives, which are finally exported for mitochondrial β -oxidation. Disordered ω -oxidation of phytanic acid. Patients with adult Refsum's disease are unable to detoxify phytanic acid by α -oxidation, and so the ω -oxidation pathway is the only metabolic pathway available for its degradation (Fig. 12.9.5). This pathway produces 3-methyladipic acid as the final metabolite, which is excreted in the urine. Thus, 3-methyladipic acid concentrations can be used as an index of the molar activity of the ω -oxidation pathway.

Age (years) 0 10 20 30 40 50 60
 Number of patients 0 2 4 6 8 10 12 14 16

Fig. 12.9.3 Cumulative incidence of clinical features on presentation of 15 patients with Refsum's disease. RP, retinitis pigmentosa. Reproduced from Wierzbicki AS, et al. (2002). Refsum's disease: a peroxisomal disorder affecting phytanic acid α -oxidation. *J Neurochem*, 80, 727–35, with permission.

section 12 Metabolic disorders 2166 ω -oxidation pathway. After ingestion of a test load of phytanic acid, 3-methyladipic acid is detected in the urine of healthy controls and adult Refsum's disease heterozygotes showing that ω -oxidation plays a significant role in postprandial metabolism of phytanic acid in humans. The activity of the ω -oxidation pathway is approximately doubled in patients with adult Refsum's disease, but this microsomal pathway has considerable reserve capacity. The balance of intake of phytanic acid and its ω -oxidation is likely to determine long-term concentrations of the lipid. Patients with adult Refsum's disease often clinically relapse during episodes of illness or drastic weight loss. Fasting induces ketosis and lipolysis and acute mobilization of phytanic acid in hepatocyte and adipocyte fatty acid pools. This process can induce a release of 5000 mg (c.15 mmol) per day of phytanic acid (50 times normal). In experimental ketosis, following acute starvation, phytanic acid doubled in 29 h in patients with adult Refsum's disease and an 80% rise was seen in urinary 3-methyladipic acid levels, indicating that ω -oxidation was buffering part of this rise. Phytanic acid concentrations can exceed the capacity of the residual α - and ω -oxidation pathways. Excess phytanic acid is excreted by low-affinity pathways. Phytanic acid can be glucuronidated and it can also be lost nonspecifically in the urine as nephropathy is a feature of adult Refsum's disease. The enzymology of the ω -oxidation pathway in adult Refsum's disease has been clarified and occurs through the microsomal CYP4A system as well as the peroxisome. The capacity of the ω -oxidation pathway has been measured by the excretion of 2,6-dimethyloctanedioic acid (the C10 ω -2-methyl thioester derivative of phytanic acid) at 30 mg phytanic acid (89 μ mol) per day. However, other studies measuring 3-methyladipic acid excretion showed a far lower capacity of 6.9 mg (20.4 μ mol) per day. These differences in activity may reflect the metabolic fates of the respective markers. Both 2,6-dimethyloctanedioic

acid and 3-hexanedioic acid are products of the initial steps of ω -oxidation and may be dependent on carnitine ester formation for activation and further metabolism. The initial steps of ω -oxidation appear to have a greater capacity than that of the whole pathway when measured by the final product 3-methyladipic acid. Molecular toxicology of Refsum's syndrome The exact mechanism of the toxicity of phytanic acid to neuronal, cardiac, and bone tissue is gradually being clarified.

Structural Fig. 12.9.4 Metabolic pathway for α -oxidation of phytanic acid and β -oxidation of pristanic acid producing 4,8 dimethynonanoyl-CoA, propionyl CoA, and acetyl-CoA as end-products. This pathway is integrated with PXMP-2 porin responsible for transport of small molecules, PMP34 for ATP, and a transporter for phytanoyl-CoA. Reproduced with permission from Wanders RJA, Komen J, Ferdinandusse S. Phytanic acid metabolism in health and disease.

Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. Copyright © 2011 Elsevier B.V. Fig. 12.9.5 ω -Oxidation mediated by a microsomal CYP4A enzyme yields phytane 1,16 dioic acid which can be metabolized to a wide spectrum of metabolites by β -oxidation. Reproduced with permission from Wanders RJA, Komen J, Ferdinandusse S. Phytanic acid metabolism in health and disease. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids. Copyright © 2011 Elsevier B.V.

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homology between phytanic acid and vitamin A, vitamin E, geranyl pyrophosphate, and farnesyl pyrophosphate has been noted and it has been suggested that phytanic acid may have a role in the regulation of isoprenoid metabolism and protein prenylation. Recent studies have identified that phytanic acid and also pristanic acid are direct toxins to mitochondria and it has been found that phytanic acid has a rotenone-like action in uncoupling complex I in the oxidative phosphorylation chain in the mitochondrial inner membrane, with subsequent likely production of reactive oxygen species, causes secondary calcium-driven changes through GPR40, and induces apoptosis in neuronal cells through a histone deacetylase-mediated mechanism. This metabolic toxicity may explain why neuronal or allied retinal pigment tissues rich in mitochondria are the prime tissues affected in adult Refsum's disease. The molecular toxicology of pristanic acid is unknown, although it is likely that the mild ophthalmic features seen in some cases may relate to phytanic acid toxicity as for phytanoyl-CoA hydroxylase deficiency. Although both di- and trihydroxycholestanoic acids levels are elevated in α -methylacyl-CoA racemase, there is no phenotype of itching associated with this disorder. The cause of the sensory neuropathy in α -methylacyl-CoA racemase still remains to be determined. Molecular genetics The defect in adult Refsum's disease was soon identified as being due to the lack of an α -oxidase. It took 30 years for the enzyme responsible, phytanoyl-CoA hydroxylase, to be identified. Two groups identified the gene for phytanoyl-CoA hydroxylase simultaneously in 1997. The phytanoyl-CoA hydroxylase gene includes nine exons and codes for a 338-amino acid protein including the 30-amino acid signal domain, which is cleaved on entry into the peroxisome. Like all the peroxisomal targeting sequence type 2 proteins, phytanoyl-CoA hydroxylase is transported into the peroxisomes by the protein transporter peroxin 7. Deficiency in this transporter is responsible for rhizomelic chondrodysplasia punctata (RCDP) type 1. Phytanoyl-CoA hydroxylase is an iron (II) and 2-oxoglutarate-dependent oxygenase, with little overall sequence similarity to other human oxygenases. Numerous point and splice mutations in phytanoyl-CoA hydroxylase have now been described in adult Refsum's disease patients, many of which affect 2-oxoglutarate conversion. Significantly, all cause complete inactivation of the protein; no partial function mutations have yet been identified. Genetic mapping studies have shown that in most cases, but not all, classical adult Refsum's disease maps to chromosome 10. The locus for the

second form of adult Refsum's disease, comprising about 10% of cases, was localized to chromosome 6q22-q24 and biochemical studies of fibroblasts from patients with adult Refsum's disease established that these patients have subtle deficiencies of peroxisomal targeting sequence type 2-dependent enzyme functions (plasmalogen synthesis) consistent with mild variants of RCDP, though they lack any clinical signs specific to childhood-onset form of RCDP where significant deficiencies in plasmalogen synthesis result in intellectual impairment and other neurological signs. Ironically, one of the original patients described with adult Refsum's disease turned out to have the RCDP variant. A limited number of mutations have been described that cause Refsum's-RCDP and it is unclear why these mutations should preferentially lead to specific mislocalization of phytanoyl-CoA hydroxylase in contrast to the other peroxin 7 imported proteins.

Epidemiology Neuropathic adult peroxisomal disorders are rare, with a prevalence of 1 in 106 in Europe and, for unexplained reasons, 10-fold less in the United States of America. As with all recessive conditions, they are more common in cultures or localities with strong founder effects where consanguineous marriages are frequent. The classical Refsum's phenotype is usually found in genetic ophthalmic services where it may represent 1% of retinitis pigmentosa cases. No surveys have been performed on the incidence of α -methylacyl-CoA racemase among patients with neuropathy.

Differential diagnosis The differential diagnoses of the neuropathic disorders and relevant signs and investigations are shown in Tables 12.9.4 and 12.9.5. With classical adult Refsum's disease, the differential diagnosis includes the various genetic retinitis pigmentosa syndromes if neurological signs are subtle and other rare neurological disorders (Table 12.9.6).

Clinical investigation The key investigations in the case of suspected neuropathic adult Refsum's disease are the measurement of phytanic acid (for adult Refsum's disease) and pristanic acid (for suspected α -methylacyl-CoA racemase). These are diagnostic. For clinical staging purposes, electroretinograms are often performed but often show flat responses characteristic of well-established retinitis pigmentosa. Visual fields should be assessed regularly as functional diplopia is a long-term complication of adult Refsum's disease. Slit-lamp examination for cataracts is also indicated, as these can be treated. Ideally, retinal photography should be performed so that the extent of retinitis pigmentosa and its progression can be monitored on a long-term basis. Anosmia can be detected by screening using the standard four-bottle smell test, but is best quantified by more extensive profiles (e.g. the University of Pennsylvania smell identification test). Auditory function should be assessed by auditory evoked potentials and hearing tests and monitored every 5 years. Peripheral neuropathy should be investigated by peripheral nerve conduction studies for somatosensory potentials and electromyography. A nonspecific demyelination pattern is typical of adult Refsum's disease. Osteo- or chondrodysplasia is best identified by a radiological survey of hands and feet for short metatarsals and knee radiology for signs of current or previous chondrodysplasia. Subtler signs that may accompany these definitive tests include an electrolyte profile showing mild hypokalaemia and a Fanconi-like aminoaciduria which can occur in adult Refsum's disease. Liver function tests should be performed. If bilirubin is raised or α -methylacyl-CoA racemase is suspected, a detailed bile acid profile should be performed by mass spectrometric methods. As the differential diagnoses include vitamin deficiencies, vitamin A and E levels should be measured to exclude retinol-deficiency retinopathy and tocopherol-deficient ataxia. Vitamin B12 and folate determinates are used to exclude cobalamin/folate deficient neuropathy. To differentiate phytanoyl-CoA hydroxylase from peroxin 7 adult Refsum's disease, it is necessary to measure plasma VLCFAs and plasmalogens. However, often the deficiencies are subtle and these

section 12 Metabolic disorders 2168 investigations may appear normal. For a definitive diagnosis, a skin biopsy should be taken, fibroblasts grown, and detailed enzyme and immunofluorescence profiles examined in a specialist peroxisomal laboratory. Criteria for diagnosis The pathognomonic finding in adult Refsum's disease is greatly elevated phytanic acid concentrations in the plasma ($>200 \mu\text{mol/litre}$; normal $<30 \mu\text{mol/litre}$), in contrast to other peroxisomal disorders where levels are usually lower and other metabolic abnormalities are also present. Unlike in rhizomelic chondrodysplasia punctata or the peroxisomal biogenesis disorders, no intellectual defects are seen, bone abnormalities are mild (if present at all), and there is no defect in plasmalogen synthesis. In infantile Refsum's disease, which is a mild clinical variant of the peroxisomal biogenesis disorder encompassing Zellweger's disease as its most severe form, numerous

Table 12.9.4 Differential diagnosis of treatable adult neuropathies caused by inborn errors of metabolism

Disease	Onset	Neurology	Signs	Chemistry	Treatment	Screening
Fabry's disease	10–20	Small fibre, sensory	Stroke; cardiomyopathy; renal	Low α -galactocerebrosidase	ERT	WBC
α -galactocerebrosidase	Serine deficiency	10–20	Axonal	Growth delay; ichthyosis	Low CSF/plasma serine	Serine
Serine	Plasma amino acids	Cerebrotendinous xanthomatosis	10–40	Axonal, demyelination, sensorimotor	Mental retardation; ataxia, spastic paraparesis. Tendon xanthomata	Cholesterol
Chenodeoxycholate	Cholesterol	Adult Refsum's disease/syndrome	10–50	Demyelination, sensorimotor	Retinitis pigmentosa, ataxia, anosmia	Phytanic acid
Low phytanic acid diet	Phytanic acid	Porphyrias	10–50	All	Neuropsychiatric	Dermatological
PBG and δ ALA	Various	PBG and δ ALA	Wilson's disease	15–50	Axonal, demyelination, sensorimotor	Movement disorder
Copper/caeruloplasmin	Chelation	Copper/ caeruloplasmin	CSF, cerebrospinal fluid; δ ALA, δ -aminolaevulinic acid; PA, phytanic acid; PBG, porphobilinogen.	Reproduced from Sedel F et al (2007) Peripheral neuropathy and inborn errors of metabolism in adults. J Inherit Metab Dis, 30, 642–53, with permission.	Table 12.9.5 Differential diagnosis of other adult neuropathies caused by inborn errors of metabolism	Disease
Age of onset	Neuropathy	Signs	Chemistry	Treatment	Screening	Mitochondrial myopathy
15–50	All	Retinitis pigmentosa, epilepsy, ataxia	CSF/plasma lactate	None	Lactate, muscle biopsy	Metachromatic leukodystrophy
15–50	Demyelination, sensorimotor	Psychiatry, ataxia	Aryl-sulphatase A	None/bone marrow transplant	Aryl-sulphatase A	Krabbe's disease
15–50	Demyelination, sensorimotor	Spastic paraparesis	WBC	galactocerebrosidase	None/Bone marrow transplant	WBC
galactocerebrosidase	GM2 gangliosidosis	15–50	All	Psychiatry; ataxia, Hexosaminidase	None	WBC
hexosaminidase	AMACR	10–50	Demyelination, sensorimotor	Retinitis pigmentosa, ataxia, anosmia, IQ	Pristanic acid, D/ THCA	Low
PA diet	Pristanic acid	Abetalipoproteinaemia	5–20	Axonal, sensory, sensorimotor	Ataxia, movement disorder, retinitis pigmentosa, acanthocytes	Low cholesterol, low apolipoprotein B, vitamins A and E
Vitamins A and E	Apolipoprotein B	Vitamin E deficiency	10–20	Axonal, demyelination, sensorimotor	Ataxia, movement disorder, retinitis pigmentosa, acanthocytes	Vitamin E
Vitamin E	Homocysteine metabolism (CblC)	15–50	Axonal, motor neuron disease, sensorimotor	Psychiatric, stroke, leukoencephalopathy; Macrocytosis	Homocysteine; methylmalonic acid	Folate, vitamins B12 and B6, betaine
Homocysteine	X-ALD	15–50	Axonal, demyelination, sensorimotor	Neuropsychiatric leukoencephalopathy; adrenal failure	Very long-chain fatty acids	?Lorenzo's oil
Very long-chain fatty acids	NARP	5–20	Demyelination, sensorimotor	Retinitis pigmentosa	ataxia	Mitochondrial—MT- ATP6
None; supportive	Mitochondrial DNA	PHARC	10–30	Demyelination, sensorimotor	Retinitis pigmentosa	ataxia, cataract
Endocannabinoid(?)	None	None	AMACR, α -methylacyl-CoA racemase; CSF, cerebrospinal fluid; D/THCA, di-/trihydroxycholestanoic acid; PA, phytanic acid; WBC, white blood cell.	Adapted from Sedel F, et al. (2007). Peripheral neuropathy		

and inborn errors of metabolism in adults. J Inherit Metab Dis, 30, 642–53, with permission.

12.9 Disorders of peroxisomal metabolism in adults 2169 subtle peroxisomal defects are present and the condition presents from birth. In α -methylacyl-CoA racemase neuropathy, the pathognomonic findings are raised levels of pristanic acid ($>100 \mu\text{mol/litre}$) allied with increases in di- and trihydroxycholestanoic acids. A secondary elevation of phytanic acid may be seen, but levels are usually between 50 and $100 \mu\text{mol/litre}$. Treatment Long-term prospects for the treatment of adult Refsum's disease (or at least for some forms) are good as it is one of the few inherited disorders of metabolism with an exogenous precipitating cause. The disease is treated symptomatically by restriction of phytanic acid intake in the diet or its elimination by plasmapheresis or apheresis. These regimens reduce plasma phytanic acid levels by between 50 and 70%, to values typically around 100 to $300 \mu\text{mol/litre}$, and can eliminate phytanic acid completely from fat stores in some patients. There is long-term efficacy and safety data for a phytanic acid restrictive diet and to a lesser extent for plasmapheresis/apheresis, which are used in a few centres. Treatment is generally most effective in resolving symptoms of ichthyosis, less so sensory neuropathy and least so ataxia, and it has uncertain effects on the progression of retinitis pigmentosa, anosmia or deafness, although it seems to stabilize these signs. Prognosis The prognosis in adult Refsum's disease depends on the degree to which phytanic acid concentrations are decreased. In untreated disease, presentation is with progressive weakness and neuropathy usually following an acute infective illness which leads to anorexia and acute hepatic phytanic acid release exacerbating the condition. Concentrations of phytanic acid in the plasma usually exceed $1000 \mu\text{mol/litre}$. Left untreated, cardiomyopathy and sudden death can occur. If phytanic acid levels are reduced by plasmapheresis and by adequate parenteral nutrition, and then a low phytanic acid diet is followed, prognosis is good. Any myopathy usually resolves within 2 to 3 weeks, though acute visual and auditory deterioration may be irrecoverable. In long-term cases, patients are blind, deaf, and anosmic, have extensive peripheral myopathy, and are often wheelchair bound. In acute adult Refsum's disease, once phytanic acid levels fall to less than $500 \mu\text{mol/litre}$, ichthyosis resolves followed by improvement in

Table 12.9.6 Differential diagnosis of retinitis with neurological signs (apart from adult Refsum's disease)

Presentation	OMIM
Neurological and other signs	
Abetalipoproteinaemia	200100
Ataxia, movement disorder, retinitis pigmentosa, acanthocytes	
Vitamin E deficiency	600415
Ornithine aminotransferase deficiency	258870
Gyrate atrophy	
Myopathy	
Usher's syndrome Ia	276900
Congenital deafness, ataxia	
Usher's syndromes II	276901
Moderate progressive deafness	
Bardet-Biedl-Moon syndrome	209900
Polydactyly	
Truncal obesity	
Hypogonadism	
Short stature	
Mental retardation	
Kearns-Sayre syndrome	530000
Ophthalmoplegia	
Cardiomyopathy	
Ceroid lipofuscinosis (Batten's disease)	204300
Seizures	
Dyskinesia	
Dementia	
X-linked macular degeneration	304020
Ataxia	
Myoclonic encephalopathy	
NARP	551500
Neurogenic proximal muscle weakness	
Ataxia	
Dementia	
Seizures	
PHARC	612674
Polyneuropathy	
Hearing loss	
Ataxia	
Cataract	

OMIM, Online Mendelian Inheritance in Man.

section 12 Metabolic disorders 2170 myopathy and neuropathy. If phytanic acid levels can be restored to normal values, then it is likely that ophthalmological changes will be minimal or slow, but sudden step-like deteriorations can occur. The principal long-term disability is increasing loss of visual field with subsequent diplopia and progressive cataract formation. Auditory function generally remains good unless phytanic acid levels are substantially raised, in which case audiological deterioration occurs with the need for cochlear implants. Although acute myopathy re-

solves, patients may have muscle spasms or contractures which may be either related to the adult Refsum's disease or secondary to the osteodystrophy. Splints and the surgical correction of osteopathy may be required. Other issues Adult Refsum's disease is a potentially treatable cause of retinitis pigmentosa or neuropathy. The average delay to diagnosis is 12 years and a simple biochemical screening test exists for these disorders. Given that earlier implementation of dietary restriction of phytanic acid would likely arrest the disease process before retinitis is established, screening for phytanic and pristanic acidaemias should be considered as an important investigation in retinitis pigmentosa or peripheral neuropathy. Future developments The causes of neuropathic adult peroxisomal disorders are incompletely delineated. Cases of pristanic acidaemia with an adult Refsum's disease phenotype exist for which no cause has yet been found. Similarly, all cases of adult Refsum's disease currently described are null-function variants, so the phenotype associated with low partial function has not been identified. It may be entirely normal, but it is possible that some cases of retinal dystrophy or peripheral neuropathy may actually be caused by mild phytanoyl-CoA hydroxylase mutations. No cases of deficiency of phytanic acid lyase have been described, although the condition should show signs of an adult Refsum's disease phenotype with some overlap into the α -oxidation pathway-associated features of α -methylacyl-CoA racemase and possibly non-neurological effects of 2-hydroxy-fatty acid deficiency. A number of lyase enzymes with peroxisomal targeting signal motifs remain to be placed on the α -oxidation pathway and these may be associated with neuropathy or retinitis pigmentosa syndromes. Reduction of dietary phytanic acid is already successful in ameliorating most nonophthalmic symptoms in long-term studies with diet and to a lesser extent apheresis. Orlistat has been shown to reduce phytanic acid in some patients. Newer, more efficacious, therapies are still required to fully reverse the progression of this disease. The signalling pathways which regulate α -oxidation in humans are unclear. In rodents, the retinoid X receptor β and peroxisomal proliferator-activating receptor α pathways control α -oxidation and thus fibrate (PPAR- α agonist) therapy increases activity, but this does not seem to be true in humans. As ω -oxidation is capable of large increases in activity and is principally mediated through CYP enzymes, it forms a good candidate for therapeutic interventions to induce enzyme activity and reduce phytanic acid levels in Refsum's disease. However, at the present time, no drug therapy trials of compounds capable of modulating either the α - or the ω -oxidation pathways have been conducted in humans. PHARC (polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract) syndrome A phenocopy sharing many features of adult Refsum's disease has recently been described (Table 12.9.3). This disorder forms part of a newly designated group of phospholipid, sphingolipid, and fatty acid synthesis disorders. The synthesis of phospholipids involves multiple steps from dihydroxyacetone phosphate (DHAP) and glycerol (Fig. 12.9.6). Clinical features PHARC is a progressive syndrome and has the key clinical features of polyneuropathy, hearing loss, ataxia, retinitis pigmentosa, and cataract (MIM 612674). It is marked by early-onset cataract and hearing loss, retinitis pigmentosa, and involvement of both the central and peripheral nervous systems, including demyelinating sensorimotor polyneuropathy and cerebellar ataxia. Approximately 30 cases have been described. Most seem to have an adult Refsum's disease-type phenotype but lack the key feature of anosmia which is universally present in adult Refsum's disease. PHARC seems to be a progressive disorder, unlike adult Refsum's disease, and seems not to show temporal or environmental variability in symptoms. Clinically, the onset of retinitis pigmentosa seems to be later in PHARC than in adult Refsum's disease (approximately age 35–40 vs 15–20 years), cataracts occur earlier (age 20–30 vs 30–50 years), and early-onset deafness is common (age <15 years vs 50 years in adult Refsum's disease). Patients have a demyelinating neuropathy and develop chronic ataxia at varying ages.

Cerebellar atrophy is more common on MRI (25%) than in adult Refsum's disease, but milder phenotypes have retinitis pigmentosa associated with only mild sensorineural hearing loss and cataract and no other signs or symptoms. **Diagnosis** The biochemical profile differs from adult Refsum's disease or other α -oxidation disorders in showing no abnormality in phytanic or pristanic acid concentrations or in any other peroxisomal metabolites. PHARC was originally mapped to chromosome 20 and is caused by mutations in α/β hydrolase-12 (ABHD12), an enzyme involved in hydrolysing the endocannabinoid 2-arachidonyl-glycerol and possibly other structurally related substrates including very long chain fatty acids. ABDH12 can be inhibited by triterpenoids (e.g. betulonic acid). Phytol and phytanic acid are diterpenes. The metabolism of 2-arachidonyl-glycerol in the brain is complex as 85% is metabolized by mono-acylglycerol lipase (MAGL) or ABDH6, while ABDH12 has a far greater role in microglial 2-arachidonyl-glycerol metabolism suggesting that microglial dysfunction is the pathogenic mechanism behind PHARC. Both ABDH12 and ABDH16 are involved in cellular lyso-phosphatidylserine metabolism and modulate cytokine production. How these biochemical findings relate to causing the full clinical phenotype is unclear. **Treatment** No specific treatment has been defined for PHARC. Symptomatic treatment is recommended for individual deficits. The effectiveness of a dietary restriction of phytanic acid in this condition is

12.9 Disorders of peroxisomal metabolism in adults 2171 Dihydroxyacetone 3-phosphate Glycerol-3-phosphate Glycerol Monoacylglycerol ADP ATP CTP PPi 14 18 15 16 17 O P O O O CO CH₂ CH₂ CH₂ CO CH O CH₂ CH₂ CO Cardiolipin CO O O O C O H HO P CH O 19 4 3 5 7 8 6 1 1 2 4 Lysophosphatidic Acid Phosphatidic Acid ADP ATP CDP Diacylglycerol Diacylglycerol Diacylglycerol Triacylglycerol Phosphatidyl Serine Phosphatidyl Inositol Phosphatidyl Choline Phosphocholine ADP ATP CMP CDP- choline Phosphatidyl Ethanolamine Myoinositol CMP Phosphoglycerophosphate Phosphatidyl- Glycerol Phosphoglycerol Lyso- phospholipids COOH Prostaglandins Leukotriens Arachidonic Acid 2-Arachidonoyl Glycerol Glycerol H₂O H₂O H₂O Fatty acid Fatty acid 10 9 9 13 12 11 + Acyl CoA CoA-SH Acyl CoA CoA-SH Fig. 12.9.6 Major reactions involved in phospholipids biosynthesis: CDP, cytidyldiphosphate; CMP, cytidylmonophosphate; CoA, coenzyme A; CTP, cytidyltriphosphate. Phospholipids are synthesized de novo from glycerol or from glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (DHAP). Glycerol- 3-phosphate is esterified twice with acyl-CoA by acyl-CoA transferase (1) to form lysophosphatidic (LPA) acid and then phosphatidic acid (PA). In adipose, muscular tissues, and skin, LPA is converted into PA by α/β -hydrolase-5 (ABHD5) (2). In mitochondria, PA and LPA are obtained from monoacylglycerol (MAG) and diacylglycerol (DAG), respectively, a reaction catalysed by acylglycerol kinase (4). PA can be converted either into DAG by phosphatidic acid phosphatase (3), or into CDP-DAG by phosphatidic acid cytidyltransferase (14). DAG is an essential intermediate for the synthesis of triglycerides and of various phosphoglycerides: phosphatidyl serine (PS) by PS-synthase (5), which is transformed to phosphatidyl ethanolamine (PE) by PS-carboxylase (6), phosphatidyl inositol (PI) by PI-synthase (7) and phosphatidyl choline (PC) by PC-synthase (8). On the other side, CDP diacylglycerol is converted, by the sequential action of phosphatidic acid glycerol phosphate synthase (15) and phosphatase (16), into phosphatidylglycerophosphate—a precursor of cardiolipin, an important phospholipid of the mitochondrial membrane. This is catalysed by cardiolipin synthase (17) and enriched by linoleic acid by the remodelling enzyme, monolysocardiolipin acyl transferase (also called tafazzin). The alternative pathway for DAG and fatty acids synthesis is their release from membrane phospholipids by specific phospholipases (PLA₂) (9) and lysophospholipases (Neuropathy target esterase) (10). Phospholipase C (11) leads to the membrane release of DAG and its further conversion by diacylglycerol lipase (12) into 2-arachidonoyl glycerol, which can be

hydrolysed into arachidonic acid by α/β -hydrolase-12 (ABDH12) (13). Arachidonic acid is the starting molecule of many complex fatty acids like prostaglandins and leukotrienes. Reproduced with permission from Lamari, F., Mochel, F., Sedel, F. et al. *J Inherit Metab Dis* (2013) 36: 411. <https://doi.org/10.1007/s10545-012-9509-7>. Copyright © 2012 SSIEM and Springer.

section 12 Metabolic disorders 2172 unknown, but unlikely to be completely efficacious given the different aetiology. FURTHER READING Ahmed RM, et al. (2014). A practical approach to diagnosing adult onset leukodystrophies. *J Neurol Neurosurg Psychiatry*, 85, 770–81. Aubourg P, et al. (1993). A two-year trial of oleic and erucic acids ('Lorenzo's oil') as treatment for adrenomyeloneuropathy. *N Engl J Med*, 329, 745–52. Baldwin EJ, et al. (2010). The effectiveness of long-term dietary therapy in the treatment of adult Refsum disease. *J Neurol Neurosurg Psychiatry*, 81, 954–7. Berger J, Forss-Petter S, Eichler FS (2014). Pathophysiology of X-linked adrenoleukodystrophy. *Biochimie*, 98, 135–42. Brown PJ, et al. (1993). Diet and Refsum's disease. The determination of phytanic acid and phytol in certain foods and application of this knowledge to the choice of suitable convenience foods for patients with Refsum's disease. *J Hum Nutr Diet*, 6, 295–305. Budka H, Sluga E, Heiss WD (1976). Spastic paraplegia associated with Addison's disease: adult variant of adrenoleukodystrophy. *J Neurol*, 213, 237–50. Cartier N, et al. (2009). Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science*, 326, 818–23. de Beer M, et al. (2014). Frequent occurrence of cerebral demyelination in adrenomyeloneuropathy. *Neurology*, 83, 2227–31. Engelen M, et al. (2014). X-linked adrenoleukodystrophy in women: a cross-sectional cohort study. *Brain*, 137, 693–706. Engelen M, Kemp S, Poll-The BT (2014). X-linked adrenoleukodystrophy: pathogenesis and treatment. *Curr Neurol Neurosci Rep*, 14, 486. Engelen M, et al. (2015). Bezafibrate for X-linked adrenoleukodystrophy. *Biochim Biophys Acta*, 1851, 231–7. Ferdinandusse S, et al. (2000). Mutations in the gene encoding peroxisomal α -methylacyl-CoA racemase cause adult-onset sensory motor neuropathy. *Nat Genet*, 24, 188–91. Ferdinandusse S, et al. (2010). Adult peroxisomal acyl-coenzyme A oxidase deficiency with cerebellar and brainstem atrophy. *J Neurol Neurosurg Psychiatry*, 81, 310–2. Fiskerstrand T, et al. (2010). Mutations in ABHD12 cause the neurodegenerative disease PHARC: an inborn error of endocannabinoid metabolism. *Am J Hum Genet*, 87, 410–17. Goldman JM, et al. (1985). Screening of patients with retinitis pigmentosa for hereditary ataxia polyneuritis formis (Refsum's disease). *Br Med J (Clin Res Ed)*, 290, 1109–10. Gong Y, et al. (2015). Adeno-associated virus serotype 9-mediated gene therapy for X-linked adrenoleukodystrophy. *Mol Ther*, 23, 824–34. Griffin JW, et al. (1977). Adrenomyeloneuropathy: a probable variant of adrenoleukodystrophy. *Neurology*, 27, 1107–3. Haberfeld W, Spieler F (1910). Zur diffusen Hirn-Rueckmarksclerose im Kindesalter. *Dtsch Z Nervenhe*, 40, 436–63. Huffnagel IC, et al. (2019). The Natural History of Adrenal Insufficiency in X-Linked Adrenoleukodystrophy: An International Collaboration. *J Clin Endocrinol Metab*, 104, 118–26. Jangouk P, et al. (2012). Adrenoleukodystrophy in female heterozygotes: underrecognized and undertreated. *Mol Genet Metab*, 105, 180–5. Jansen GA, Waterham HR, Wanders RJ (2004). Molecular basis of Refsum disease: sequence variations in phytanoyl-CoA hydroxylase (PHYH) and the PTS2 receptor (PEX7). *Hum Mutat*, 23, 209–18. Jansen GA, et al. (1997). Refsum disease is caused by mutations in the phytanoyl-CoA hydroxylase gene. *Nat Genet*, 17, 190–3. Kamat SS, et al. (2015). Immunomodulatory lysophosphatidylserines are regulated by ABHD16A and ABHD12 interplay. *Nat Chem Biol*, 11, 164–71. Kemp S, et al. (2012). X-linked adrenoleukodystrophy: clinical, metabolic, genetic and pathophysiological aspects. *Biochim Biophys Acta*, 1822, 1465–74. Lamari F, et al. (2013). Disorders of phospholipids, sphingolipids and fatty acids biosynthesis: toward a new

category of inherited metabolic diseases. *J Inher Metab Dis*, 36, 411–25. Loes DJ, et al. (2003). Analysis of MRI patterns aids prediction of progression in X-linked adrenoleukodystrophy. *Neurology*, 61, 369–74. Mahmood A, et al. (2007). Survival analysis of haematopoietic cell transplantation for childhood cerebral X-linked adrenoleukodystrophy: a comparison study. *Lancet Neurol*, 6, 687–92. Mihalik SJ, et al. (1997). Identification of PAHX, a Refsum's disease gene. *Nat Genet*, 17, 185–9. Morita M, Imanaka T (2012). Peroxisomal ABC transporters: structure, function and role in disease. *Biochim Biophys Acta*, 1822, 1387–96. Moser AB, et al. (1999). Plasma very long chain fatty acids in 3000 peroxisome disease patients and 29,000 controls. *Ann Neurol*, 45, 100–10. Moser HW, et al. (1991). Clinical aspects of adrenoleukodystrophy and adrenomyeloneuropathy. *Dev Neurosci*, 13, 254–61. Moser HW, et al. (2005). Follow-up of 89 asymptomatic patients with adrenoleukodystrophy treated with Lorenzo's oil. *Arch Neurol*, 62, 1073–80. Nishiguchi KM, et al. (2014). Exome sequencing extends the phenotypic spectrum for ABHD12 mutations: from syndromic to non-syndromic retinal degeneration. *Ophthalmology*, 121, 1620–7. Odone A, Odone M (1989). Lorenzo's oil. A new treatment for adrenoleukodystrophy. *J Pediatr Neurosci*, 5, 55–60. Parikh S, et al. (2015). A clinical approach to the diagnosis of patients with leukodystrophies and genetic leukoencephalopathies. *Mol Genet Metab*, 114, 501–15. Purdue PE, et al. (1999). Rhizomelic chondrodysplasia punctata, a peroxisomal biogenesis disorder caused by defects in Pex7p, a peroxisomal protein import receptor: a mini-review. *Neurochem Res*, 24, 581–6. Refsum's S (1946). Heredopathia atactica polyneuritiformis. *Acta Psychiatr Scand*, 38 Suppl, 9–15. Schilder P (1924). Die Encephalitis periaxialis diffusa. *Arch Psychiatr Nervenkr*, 71, 327–35. Sedel F, et al. (2007). Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inher Metab Dis*, 30, 631–41. Sedel F, et al. (2007). Peripheral neuropathy and inborn errors of metabolism in adults. *J Inher Metab Dis*, 30, 642–53. Steinberg D, et al. (1967). Refsum's disease: nature of the enzyme defect. *Science*, 156, 1740–2. van den Brink DM, et al. (2003). Identification of PEX7 as the second gene involved in Refsum's disease. *Am J Hum Genet*, 72, 471–7. Wanders RJ (2011). Phytanic acid metabolism in health and disease. *Biochim Biophys Acta*, 1811, 498–507. Wanders RJ, Ferdinandusse S (2012). Peroxisomes, peroxisomal diseases, and the hepatotoxicity induced by peroxisomal metabolites. *Curr Drug Metab*, 13, 1401–11. Wanders RJ (2018). Peroxisomal disorders: Improved laboratory diagnosis, new defects and the complicated route to treatment. *Mol Cell Probes*, 40, 60–9.

12.9 Disorders of peroxisomal metabolism in adults 2173 Wierzbicki AS, et al. (2002). Refsum's disease: a peroxisomal disorder affecting phytanic acid alpha-oxidation. *J Neurochem*, 80, 727–35. Wierzbicki AS, et al. (2003). Metabolism of phytanic acid and 3-methyl-adipic acid excretion in patients with adult Refsum's disease. *J Lipid Res*, 44, 1481–88. Websites Adult Refsum's Disease website (information for patients, carers and clinicians): <http://refsumdisease.org>. United Leukodystrophy Foundation website: <http://www.ulf.org>. X-linked Adrenoleukodystrophy database: <http://www.X-ald.nl>.

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