Refsum Disease Presenting with a Late-Onset Leukodystrophy

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Abstract Adult Refsum disease is an autosomal recessive peroxisomal disorder characterized by phytanic acid storage. Clinical symptoms usually begin in late childhood before the age of 20. Typical clinical presentation includes nyctalopia caused by retinitis pigmentosa, and anosmia. After 10–15 years, deafness, cerebellar ataxia, polyneuropathy, ichthyosis, and cardiac arrhythmia can occur.

We report the case of a very late-onset adult Refsum disease presenting with marked cognitive decline and severe leukoencephalopathy, without peripheral nervous system involvement. Brain MRI showed a leukoencephalopathy involving the periventricular white matter, subcortical area, and the brainstem with relative sparing of juxtacortical U fibers. This was associated with severe cortical and subcortical atrophy with ventricle dilatation. MR spectroscopy showed a marked increase in the

choline/NAA ratio. Elevated plasma phytanic acid level was found, whereas plasma levels of pristanic and very long chain fatty acids were normal. The patient is homozygous for a previously undescribed *PHYH* frameshift mutation. Whether the very unusual phenotype is related to this peculiar mutation remains unclear.

This 72-year-old woman with a past history of left-eye congenital amaurosis, insulin-requiring diabetes, and elevated blood pressure came to medical attention because of progressive dementia and walking difficulties. She had no noticeable neurological problem until the age of 69, when she experienced balance difficulties and memory problems. A year later, after a fall, a C2 vertebra fracture was discovered. Within the next months, apraxia (inability to wash or dress) was noticed along with a severe memory loss (she forgot the number and names of her children), nycthemeral rhythm inversion, and urinary incontinence. Neuropsychological tests showed severe frontal syndrome, dementia with spatiotemporal disorientation, and memory loss. Clinical examination disclosed gait apraxia reminiscent of frontal lobe dysfunction with no clear cerebellar ataxia.

A brain magnetic resonance (MR) imaging showed a leukoencephalopathy involving the periventricular white matter, subcortical area, and the brainstem with relative sparing of juxtacortical U fibers (Fig. 1a, b). This was associated with severe cortical and subcortical atrophy with ventricle dilatation. MR spectroscopy showed a marked increase in the choline/NAA ratio (Fig. 1c).

Electromyography showed no polyneuropathy but only bilateral carpal tunnel syndrome. Electroretinogram was normal in the right eye (not evaluable on the left). Cardiac

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Fig. 1 Brain magnetic resonance imaging. (a) Axial FLAIR: extensive leukoencephalopathy, (b) axial T1: subcortical atrophy with ventricle enlargement, (c) spectroscopy: increased choline/NAA ratio

echography only showed left ventricle hypertrophy consistent with her past history of elevated blood pressure.

Cerebrospinal fluid (CSF) showed two white cells/mm³, with slightly increased protein content (0.46 g/L).

A metabolic workup disclosed very high plasma phytanic acid level (458 μmol/L; control <10) later confirmed at 704 μmol/L. In contrast, plasma pristanic acid level was normal (0.27 μmol/L) as were very long chain fatty acids.

Genetic analysis of the *PHYH* gene revealed a novel homozygous mutation in exon 1, c.42-60dup, a frameshift mutation resulting in a premature stop codon at position 56 of the mutated sequence (which corresponds to codon 50 of the normal sequence). The patient also had 3 *PHYH* polymorphisms: the first was homozygous in exon 3 (c.153C>T, p.Asn51Asn), the second was heterozygous in intron 4 (c.415-11delT), and the third was homozygous in exon 6 (c.636A>G, p.Thr212Thr).

The severe cognitive decline was not compatible with a phytanic acid-restricted diet. LDL apheresis was not

performed because of the patient's age with little expectable benefit.

Discussion

We report the very unusual case of a 72-year-old woman presenting with 2 years' history of progressive dementia, walking problems, and diffuse leukoencephalopathy. Diagnosis of Refsum disease was established by elevated plasma levels of phytanic acid and *PHYH* mutations.

Adult Refsum disease is an autosomal recessive peroxisomal disorder characterized by phytanic acid storage, due to deficient activity of phytanoyl-CoA hydroxylase that catalyzes the first step of phytanic acid alpha-oxidation (Wanders and Komen 2007). Phytanic acid accumulates in fat-containing tissues (i.e., nerve, brain, retina, and adipose tissue).

Clinical symptoms usually begin in late childhood before the age of 20, but late-onset forms (around 50 years) have

also been described. The disease often starts with nyctalopia caused by retinitis pigmentosa, and anosmia. After 10–15 years, deafness, cerebellar ataxia, polyneuropathy, ichthyosis, and cardiac arrhythmia can occur. About one third of the patients present with shortened metacarpal and 4th metatarsal bones (Wierzbicki et al. 2000, 2002; Rüether et al. 2010).

Two causative genes have been identified. The first one is *PHYH* encoding phytanoyl-CoA hydroxylase. The second one is *PEX7* encoding peroxin 7, a receptor required to import several proteins into the peroxisomal matrix. Although in most cases *PEX7* mutations lead to rhizomelic chondrodysplasia punctata, some mutations have been associated with a Refsum disease phenotype (Van den Brink et al. 2003).

Treatment of Refsum disease may consist in a special diet avoiding phytanic acid-rich food (dairy products, fish, meat, and fat of ruminant animals). Plasma exchange or LDL apheresis can be used in addition to the diet when phytanic acid plasma level is dangerously high (above 300 $\mu\text{mol/L}$) (Weinstein 1999).

Interestingly, the classical clinical features of Refsum disease were absent in our patient: she had no retinitis pigmentosa, no polyneuropathy, no cerebellar ataxia, no anosmia, no ichthyosis, no hyperproteinorachia, no cataract, no hearing loss, and no skeletal abnormalities. In addition, the association of marked cognitive decline and severe leukoencephalopathy is uncommon and not yet reported. This very unusual phenotype might be related to the particular (yet undescribed) mutation carried by our patient. The homoallelic c.42-60 duplication event in exon 1 found on the genomic DNA creates a premature stop codon. There was no notion of consanguinity in the family. The homozygous polymorphisms in exons 3 and 6, which do not change the amino acid sequence (Jansen et al. 2004), have probably no consequence on the phenotype. The c.42-60 duplication could result in nonsense-mediated mRNA decay. However, this was not the case as the duplication was also detected on cDNA prepared from the patient's lymphocytes. Such a mutation is expected to result in the synthesis of a markedly truncated (only 55 amino acids out of the normal 338 residues), very small, and therefore nonfunctional polypeptide. Thus, this mutation appears as a severe molecular defect. This translates into an increased plasma phytanic acid level, which demonstrates the causal link between the molecular defect and the metabolic abnormality. Nevertheless, at the moment, we have no clear explanation for the absence of the classical symptoms. One possibility to account for the unusual and late presentation of the disease would be that for a long period of her life the patient had a phytanic acid-poor diet, which

would have delayed the onset (and possibly changed the symptoms) of the disease.

This observation expands the spectrum of Refsum disease that may also present as a very late onset leukodystrophy with no peripheral nervous system involvement.

One Sentence Take-Home Message

A 69-year-old female patient, homozygous for a novel *PHYH* mutation, presented with an unusual Refsum disease phenotype including progressive dementia, gait apraxia, and memory loss, associated with diffuse leukoencephalopathy.

Compliance with Ethics Guidelines

Conflict of Interest

Dr. Flavie Bompaire, Dr. Véronique Marcaud, Mrs. Emmanuelle Le Trionnaire, Dr. Frédéric Sedel, and Prof. Thierry Levade declare that they have no conflict of interest.

Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from the patient for being included in the study.

Animal Rights

This article does not contain any studies with animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Drs. Bompaire, Marcaud, and Sedel took care of the patient and diagnosed adult Refsum disease. Mrs. Le Trionnaire and Prof. Levade performed the genetic analysis and its interpretation. Dr. Bompaire wrote the text under the supervision of Dr. Sedel and Prof. Levade, with the help of Dr. Marcaud.

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