Decompensation of Refsum Disease Caused by Ibuprofen Intake

Natacha Esber, M.D.
Thomas Schulz, M.D.
University of Kansas
School of Medicine-Wichita
Department of Internal Medicine

Introduction

Refsum disease (or heredopathia atactica polyneuritiformis) is an autosomal recessive disorder caused in most instances by mutations in the gene (*PhyH*) encoding the enzyme phytanoyl-CoA hydroxylase, located on chromosome 10pter-p11.2.[1,2] These mutations lead to the accumulation of phytanic acid in affected patients. The mainstay of treatment is a reduction in the dietary phytanic acid intake. The following case illustrates an aggressive progression of the disease in a patient who was compliant with the dietary restrictions.

Case Report

A 33-year-old white female, had a history of progressive loss of vision and hearing since the age of 20, cardiomyopathy, cardiac arrhythmias, gastroparesis, urge incontinence, decreased bone mass, bilateral hip replacement, multiple surgical interventions on the right ankle, and one surgical intervention on the right knee. At the age of 27, she was diagnosed with Refsum disease by associating the shortening of the 4th metatarsals bilaterally and the retinitis pigmentosa, along with a high phytanic acid level. She was started on the appropriate diet consisting of restrictions on green vegetables, meats from ruminating animals, and dairy products.

Since the age of 30, the patient was hospitalized four times at another facility for acute decompensation of her disease. During each hospitalization, she underwent five sessions of plasmapheresis. During her last hospitalization, her phytanic level was 105.5umol/L (reference range : $\leq$ 9.88). It decreased to zero after the completion of four sessions of plasmapheresis. She took ibuprofen 800 mg by mouth every eight hours during her hospital stay at the other facility.

The patient presented to the emergency department at our facility for acute exacerbation of her disease, including retro-orbital headaches, chest pain, nausea, vomiting, diarrhea, urinary incontinence, diffuse muscle aches, and weakness that had increased in intensity over two weeks. A detailed history revealed that she was compliant with her diet, but had a chronic ibuprofen intake for recurrent tension headaches. She was never told that ibuprofen is contraindicated in Refsum disease. The patient improved significantly after five sessions of plasmapheresis and discontinuation of ibuprofen.

Discussion

Branched-chain fatty acids are common in the human diet and related structures are common and occur in some drugs, such as ibuprofen (Figure 1).[3] The most common branched-chain fatty acid is phytanic acid, found in some meats and dairy products. Normally, it is metabolized by activation to its CoA ester, phytanoyl-CoA, then alpha-oxidation to pristanic acid.[4]

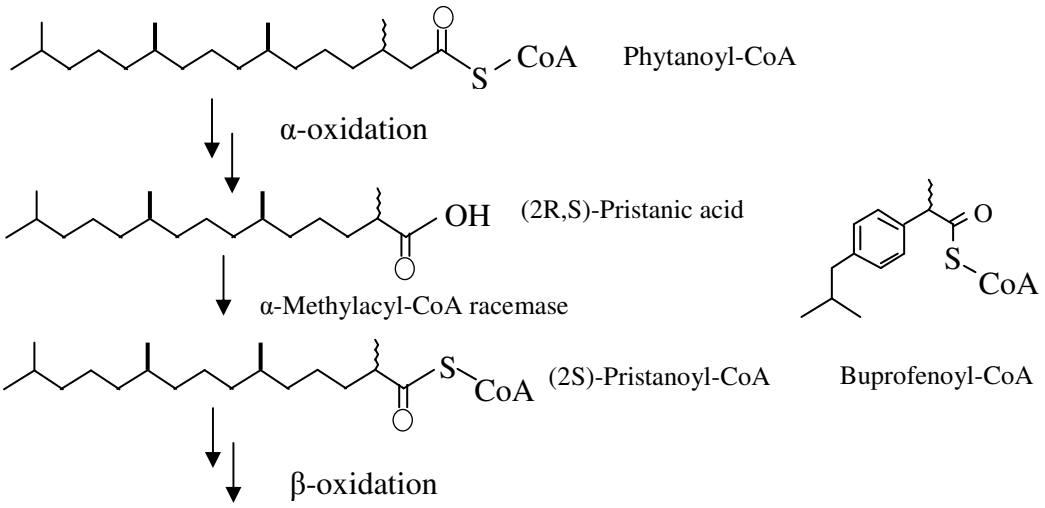

Figure 1. Peroxisomal degradation of phytanic acid to pristanic acid. [Figure from MD Lloyd and MD Threadgill.[3]]

Patients with Refsum disease are unable to degrade phytanic acid because of deficient activity of phytanoyl-CoA hydroxylase, a peroxisomal enzyme that catalyzes the first step of phytanic acid alpha-oxidation.[4] Consequently, they accumulate significant amounts of phytanic acid in plasma and tissues, which are thought to be the major cause of the pathology of the disease.[5]

Refsum disease is characterized clinically by atypical retinitis pigmentosa, peripheral polyneuropathy, cerebellar ataxia, anosmia, cardiomyopathy, conduction abnormalities, icthyosis, hyperkeratosis plantaris and palmaris, and epiphyseal dysplasia leading to characteristic shortening of the fourth toe, hammer toe, pes cavus, and osteochondritis.[4-6] The characteristic findings are slow conduction velocities on nerve conduction studies, elevated cerebrospinal fluid protein concentration (100 to 600 mg/dl) without an increase in cells, grossly abnormal electroretinogram, onion bulb formation and targetoid inclusions in Schwann cells on nerve biopsy, and plasma levels of phytanic acid of > 800 mmol.[4-7]

Treatment consists of strict reduction in dietary phytanic acid intake to 10-20mg/day (daily average: 50-100mg).[7] Plasma exchange can be considered if dietary control is inadequate.[8] This approach halts the progression of the disease, but does not reverse neurologic abnormalities completely. Ichthyosis, sensory neuropathy, and ataxia resolve in approximately that order, and electrocardiographic abnormalities may improve. However, treatment may not affect retinitis pigmentosa, hearing impairment, or anosmia.[7-9]

References

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