Refsum’s Disease

A Unique Case

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Hereditary sensory neuropathy is a relatively rare disorder and often goes undiagnosed. It is classified as either congenital or familial. The congenital form is sporadic and nonprogressive and may affect intelligence. The familial form is usually dominantly inherited and progressive, with onset in late childhood; it primarily affects the distal extremities and does not affect intelligence. Hereditary sensory neuropathy with spinal-cord involvement is found in Charcot-Marie-Tooth disease, lumbosacral syringomyelia, and Refsum’s disease. Sensory pathways are involved, with loss of perception of deep pain, touch, and temperature.1 Refsum’s disease can be differentiated from the other two disorders in that it is recessive and always affects the motor neuronal network.

Etiology

Refsum’s disease is a familiar-recessive peroxisomal disorder. Phytanic acid accumulates in the body owing to the absence or abnormality of the subcellular peroxisome organelle. The peroxisomes function as an oxidizer in the breakdown of lipids.2 Phytanic acid is not naturally synthesized by the body; therefore, the disease can be controlled entirely through dietary restriction of phytanic acid and its precursor, phytol. Phytanic acid is found principally in plants and in the fat of herbivorous animals. Foods high in phytanic acid include dairy products, all vegetables except potatoes, fatty meats, fish, chocolate, and nuts.2,3 The normal metabolism of phytanic acid is by beta-oxidation of the fatty-acid chain, and the failure of this process causes accumulation in fat and in the central and peripheral nervous systems.4 With this accumulation, sensory and motor nerve conduction velocities are markedly slowed in the lower and upper extremities. Histologically, peripheral nerves may have hypertrophic interstitial changes and onion-bulb formations.3 Phytanic acid may also accumulate in the kidneys and the liver.2 With reduction of dietary intake, slowly progressive reduction of phytanic acid in the blood and cerebrospinal fluid may correlate with slow improvement in muscle strength.3

Symptoms and Signs

Onset is usually in early childhood between the ages of 4 and 7, but in some cases it is delayed until the fifth decade.4 Progressive night blindness usually appears in the first or second decade, followed by con-
centric constriction of visual fields, progressive deafness due to cochlear involvement, polyneuropathy of both motor and sensory nerves, cerebellar ataxia, and loss of the sense of smell. Symptoms are progressive, with abrupt exacerbation following illnesses, febrile episodes, surgery, or pregnancy.2-4

The major manifestation of the disease is peripheral neuropathy, but clinical diagnosis depends on other features. Cerebellar ataxia of gait and limbs is prominent, and ichthyosis, atypical retinitis pigmentosa, nystagmus, cataracts, miosis, and pupillary asymmetry may all be present. Cerebrospinal fluid protein is elevated, and motor and sensory nerve conduction velocities are slowed. There are detectable quantities of phytanic acid in the blood, urine, cerebrospinal fluid, and liver.2, 5, 6 The skeletal system may also be greatly affected, with signs of pes cavus, bone deformities, shortened metatarsals, epiphyseal dysplasia, and kyphoscoliosis.1-3 Death may occur from cardiomyopathy or respiratory paralysis.1, 3, 4

Case Report

A 74-year-old white man presented to the Life Support Unit at Phoenix Veterans Affairs Medical Center with pain and weakness of his neck and shoulders. The patient had fallen and bumped his head 24 hours prior to admission. He had a long-standing history of Refsum’s disease with documented physical findings of cerebellar ataxia, legal blindness, retinitis pigmentosa, eighth cranial nerve deafness, peripheral neuropathy, coronary artery disease, angina pectoralis, grade III/VI systolic murmur, enlarged prostate, and multiple exostoses throughout the skeletal system. The patient had no known allergies and denied any use of alcohol or tobacco. He reported that he was on a very strict diet of whole-wheat or seven-grain bread, white-meat turkey, low-fat fish, safflower-based margarine, and some fruit.

A family history revealed that the patient had five siblings. One brother and one sister were also affected by Refsum’s disease. The sister had died, but the brother was still alive. It was determined that the brother suffers from ataxia, shortened fourth digits bilaterally, and blindness. All other siblings were unaffected. Neither parent had Refsum’s disease, but it was learned that the parents were first cousins.

Upon admission, x-ray evaluation revealed a fracture of the sixth cervical vertebra. The patient’s condition rapidly deteriorated following development of a neurogenic bladder. The patient developed respiratory failure and massive pleural effusions, and died 12 days after admission.

Examination of old records revealed that the patient had been seen in the podiatry department five years previously, with the following findings: The ankles were equinus, with decreased subtalar joint range of motion bilaterally. The patient had an ataxic gait and was legally blind. Multiple bony nodules and calcified tendons were seen in the knees, hips, back, wrists, and fingers (Fig. 1). There were three posterior calcaneal exostoses, two of the right heel and one of the left heel (Fig. 2). Bilateral brachymetatarsia of the fourth ray was also noted (Fig. 3). Custom-molded shoes were made for the patient for accommoda-
tion and comfort. Nerve conduction studies revealed normal peroneal and tibial velocities, but absent hamstring reflex and Babinski's sign bilaterally.

X-rays taken of the lower extremities prior to the patient's death were very revealing of the skeletal effects of the disease. Extreme symmetrical spurring of the calcaneus plantarly and posteriorly was noted, with multiple fusions throughout the tarsal joints (Fig. 4). Bilateral pes cavus and bilateral brachymetatarsia of the fourth and fifth metatarsals were also evident (Fig. 5). Severe hyperostosis and fusion of the patella to the tibia were seen bilaterally (Fig. 6).
Summary

Refsum’s disease is a peroxisomal disorder leading to the accumulation of phytanic acid throughout the body. The disease affects sensory and motor neurons and the skeletal system. Peripheral neuropathy, ataxia, blindness, deafness, and skeletal hyperostosis are significant signs and symptoms in the diagnosis of the disease. The podiatric physician can be integral to the diagnosis and treatment of the disorder because of the resulting deformities of the feet and the presence of motor and sensory neuropathy. Because the disorder is rare, the podiatrist may never encounter a case; however, heightened awareness of the disease may lead to an increase in the number of documented cases.

References


Additional References