Cerebrotendinous Xanthomatosis: A Rare Cause of Bilateral Achilles Tendon Swelling and Ataxia. A Case Report

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J. Bone Joint Surg. Am. 88:1340-1344, 2006. doi:10.2106/JBJS.E.00872

CEREBROTENDINOUS XANTHOMATOSIS: A RARE CAUSE OF BILATERAL ACHILLES TENDON SWELLING AND ATAXIA

A CASE REPORT

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Cerebrotendinous xanthomatosis is a rare autosomal recessive lipid-storage disease caused by a mutation in the sterol 27-hydroxylase (CYP27) gene[1,2]. It is important that orthopaedic surgeons be aware of this condition because the initial presentation may be symmetric, painful enlargement and deformity of the Achilles tendons. Early diagnosis is the key to treatment because medical therapy is effective in halting progression of, although not reversing, the devastating neurological lesions of this condition.

Case Report

The subject of this case report was aware that data concerning the case would be submitted for publication.

A thirty-one-year-old man presented to the clinic of the senior author (J.W.B.) with a six-year history of bilateral, slowly progressive, painful swelling of the Achilles tendon. He stated that it interfered with his ability to walk, which was already affected by a neurological condition. The pain was exacerbated by walking, was relieved somewhat by rest, and at the time of presentation restricted the patient's walking distance to a maximum of two city blocks.

A neurologist had previously diagnosed multiple sclerosis on the basis of the clinical findings of tremor, sensory neuropathy in the extremities, an ataxic gait, and plaque-like changes in the cerebral cortex on magnetic resonance imaging. The patient had a family history of type-2 diabetes mel-

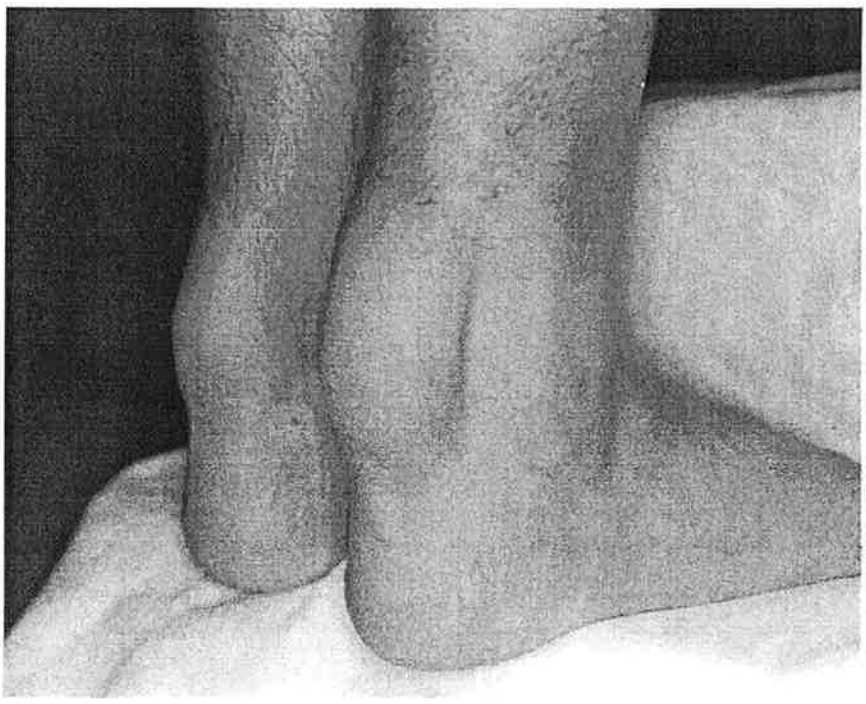

Fig. 1

Clinical photograph demonstrating bilateral symmetrical fusiform swelling of the Achilles tendon.

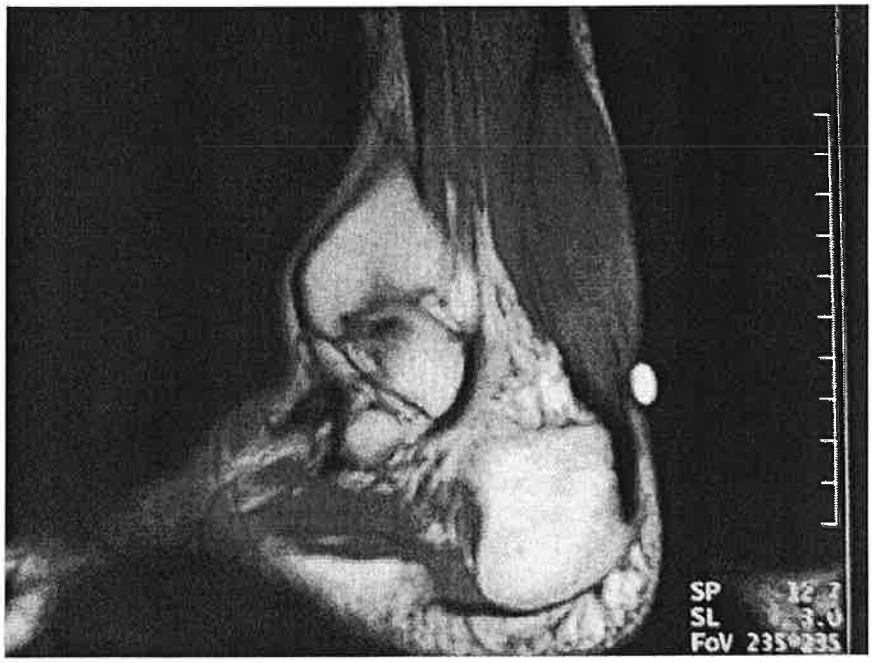

Fig. 2-A

Sagittal T1-weighted magnetic resonance imaging scan demonstrating fusiform swelling of the right Achilles tendon just proximal to its insertion. All other tendons around the foot and ankle appear normal.

litus but no other inherited disorders.

An examination revealed symmetrical, bilateral fusiform enlargement of the Achilles tendon. The deformity was distributed over the distal 7.5-cm segment of each tendon (Fig. 1). The feet were plantigrade and had no deformity, although ankle dorsiflexion was symmetrically limited to 5°. The tendon swelling was slightly tender, but the overlying skin was not inflamed and there was no local crepitus to suggest synovitis. There was no evidence of xanthomas of the eyelids or at other sites, and an ophthalmological examination revealed normal findings.

T1 and T2-weighted magnetic resonance images demonstrated diffuse enlargement of each Achilles tendon with multiple areas of increased signal interspersed between areas of intermediate signal (Figs. 2-A through 3-B). This appearance has been interpreted as representing sites of lipid deposit between areas of reactive inflammatory tissue[3].

An incisional biopsy of the right Achilles tendon showed fatty yellow infiltration of the tendon. Tissue samples were fixed in both alcohol and formalin, and light microscopy showed the tissue to be heavily infiltrated with foamy macrophages and foreign-body-type giant cells bordering on clear spaces representing sites of lipid deposition (Fig. 4). No crystals were seen in any of the specimens.

A custom-made polypropylene ankle-foot orthosis, lined with Plastazote (Apex Foot Products, South Hackensack, New Jersey), was prescribed to relieve pain and improve gait.

On the basis of the clinical evidence and the results of the biopsy, it was suspected that lipid deposition in both ten-

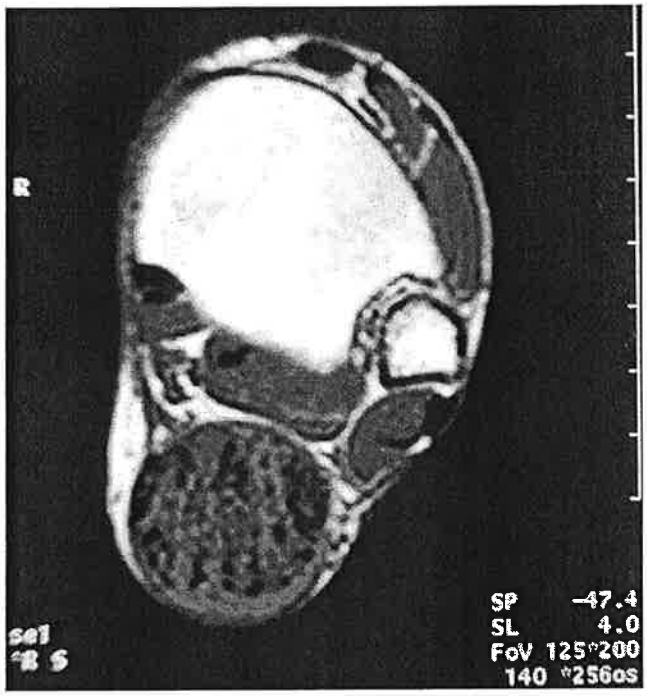

Fig. 2-B

Axial T1-weighted image of the right Achilles tendon 2.5 cm proximal to the tibial plafond. A heterogeneous signal can be observed in the tendon. Remaining fibers of normal tendon (black) are interspersed between areas of intermediate signal (gray), representing inflammatory tissue, and high signal (white), representing areas of lipid deposit.

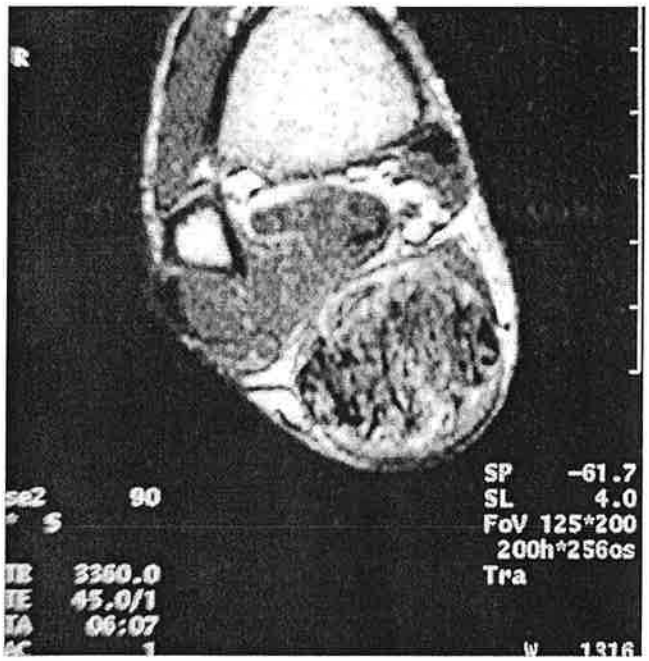

Fig. 3-A

Axial T2-weighted image without fat suppression, demonstrating marked thickening of the Achilles tendon with an abnormal rounded (biconvex) morphology. Increased signal representing fat and edema is interspersed between normal tendon fibers.

don and neurological tissues was responsible for the symptom complex. The patient was referred to a physician with expertise in lipid metabolism disorders. The serum cholestanol level was 3.2 mg/dL, which is sixteen times the normal mean value of 0.2 ± 0.2 mg/dL. Increased concentrations of bile alcohols were present in plasma and urine, which, together with the high level of cholestanol, confirmed the diagnosis of cerebrotendinous xanthomatosis.

The patient was started on bile acid replacement therapy with ursodeoxycholic acid and treatment with chenodeoxycholic acid. He was accepted into a research program for patients with cerebrotendinous xanthomatosis in February 1998, which provided him with 250 mg of chenodeoxycholic acid orally three times per day. The serum cholestanol level decreased to one-fourth of the pretreatment level (from 3.2 mg/dL to 0.77 mg/dL) within four months, but it had briefly increased in the year 2000 as a result of temporary unavailability of chenodeoxycholic acid. An orphan-drug program of Rare Disease Therapeutics (Nashville, Tennessee) enabled the patient to increase the dosage of chenodeoxycholic acid to 250 mg four times per day, and the last measured level of cholestanol, in August 2004, was 0.53 mg/dL.

At the time of writing, the patient had been receiving chenodeoxycholic acid replacement therapy for more than five years. The tendon xanthomas had softened but had not changed in size. The neurological symptoms had improved modestly, and the neurological deficits had not progressed.

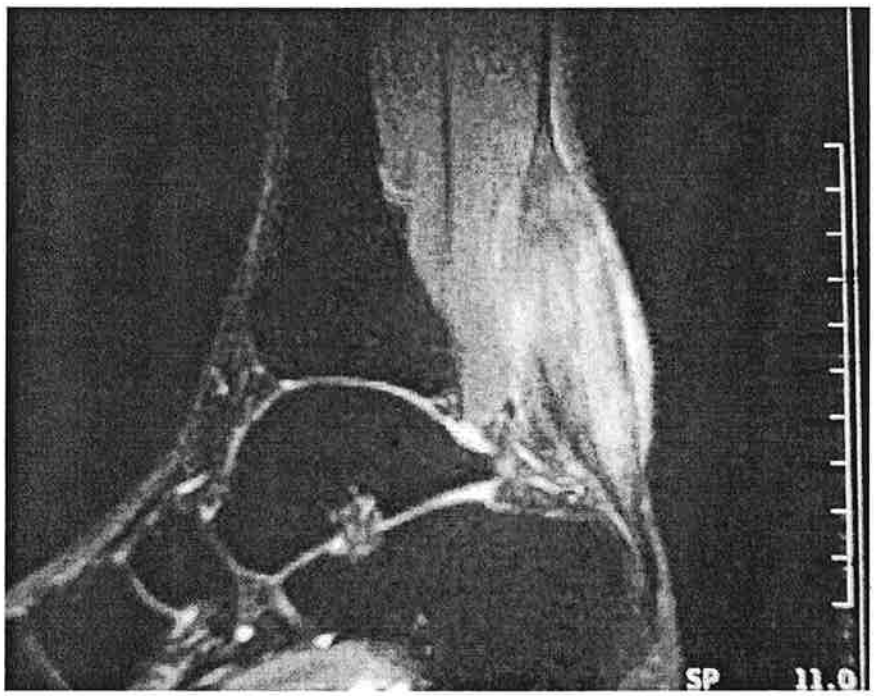

Fig. 3-B

Sagittal inversion recovery image demonstrating thickening of the Achilles tendon with linear increased interstitial signal in a longitudinal fashion indicating inflammatory edema without focal traumatic disruption.

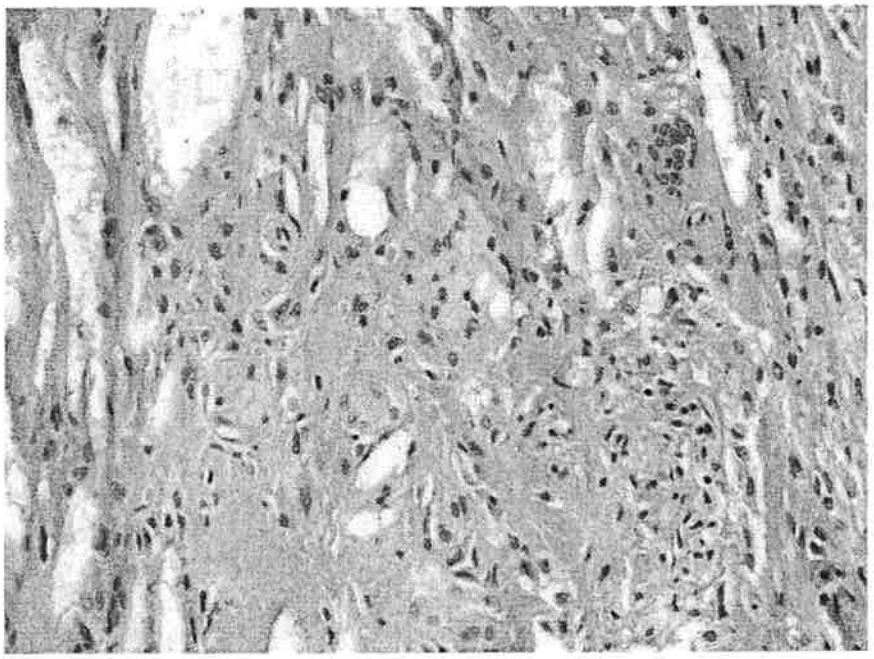

Fig. 4

Light photomicrograph of tissue obtained with incisional biopsy of the right Achilles tendon. The normal dense connective tissue of the tendon has been replaced by an infiltrate of foamy histiocytes, multinucleated giant cells, and elongated cholesterol clefts (hematoxylin and eosin, original magnification ×200).

The patient could walk 0.75 mi (1.2 km), with less fatigue than before treatment. He walked with a flexion deformity of both knees and a mild footdrop, which was worse on the left than on the right. He did not have trouble with limb advancement, but weakness of push-off prevented him from having a true heel-to-toe gait. The enlargement of each Achilles tendon measured a maximum of approximately 10 cm in circumference and remained basically unchanged.

Discussion

Cerebrotendinous xanthomatosis is a rare disorder of lipid metabolism that was first described by van Bogaert et al. in 1937[4]. It is inherited as an autosomal recessive trait and is caused by a mutation of the gene for sterol 27-hydroxylase. Sterol 27-hydroxylase is a hepatic mitochondrial enzyme that oxidizes the side chain of cholesterol, a metabolic step in the formation of bile acids. Deficiency of this enzyme results in a block in bile acid synthesis and an overproduction of bile acid intermediates, which leads to an increased production of cholestanol. Because cerebrotendinous xanthomatosis occurs as a result of defective bile acid synthesis, with overproduction of sterol intermediates, which then are converted into cholestanol, the condition is treated with bile acid replacement therapy. Ursodiol (ursodeoxycholic acid) is the only commercially available bile acid in the United States. Because it is not an endogenous human bile acid (it was discovered in bears), ursodeoxycholic acid does not provide feedback regulation for human bile acid synthetic pathways. Thus, administration of Ursodiol does not reduce the overproduction of bile acid intermediates or serum cholestanol in patients with cerebrotendinous xanthomatosis. Chenix (chenodeoxycholic acid) does reduce cholestanol levels and had been available in the United States for dissolution of gallstones. However, its production was stopped in 1997 as a result of diminishing clinical usage related to the efficacy and convenience of open and laparoscopic cholecystectomies.

The gene for sterol 27-hydroxylase is on chromosome two, and several different mutations resulting in the same phenotype have been described. The reported prevalence of the condition is highest in the Japanese and North African Jewish communities, although most of the reported cases are sporadic[5]. Our patient was from neither of those ethnic groups.

Cerebrotendinous xanthomatosis is classically characterized by (1) bilateral Achilles tendon xanthoma; (2) bilateral cataract formation; and (3) progressive neurological dysfunction with mainly pyramidal tract signs, cerebellar ataxia, and cognitive impairment. Other orthopaedic manifestations of cerebrotendinous xanthomatosis include osteoporosis with an increased risk of fracture[6-8] and peripheral neuropathy[9] with secondary neuropathic deformity and/or ulceration of the feet[10,11].

The age at presentation is variable but usually is in the second or third decade of life. A common presentation is bilateral cataract formation in association with neurological deterioration. Achilles xanthomas usually develop later, in the fourth decade of life[12]. Presentation with an Achilles tendon xanthoma alone is uncommon but has been previously

reported[13]. The case reported in the present paper was unusual because of its delayed nature and mode of presentation as well as the absence of cataract formation.

The diagnosis of cerebrotendinous xanthomatosis can be difficult because routine biochemical analyses of blood, urine, and cerebrospinal fluid often reveal normal findings. Serum cholesterol levels are usually within normal limits or low. Our patient had a high serum cholesterol level, which is atypical and was probably due to another inherited disorder causing a mixed hyperlipidemia. Diagnosis depends on the finding of an elevated serum cholestanol level and the use of capillary gas chromatography to study bile alcohols present in the urine[14,15]. More recently, molecular biological techniques have been developed to assist in the diagnosis of cerebrotendinous xanthomatosis in asymptomatic homozygote family members of symptomatic patients. Heterozygotes can also be identified in these families, which is important for genetic counseling and prenatal diagnosis[5].

The differential diagnosis for a patient with xanthoma of the Achilles tendon includes heterozygous familial hypercholesterolemia (the most common cause) and, rarely, homozygous familial hypercholesterolemia, cerebrotendinous xanthomatosis, and sitosterolemia (a lipid storage disorder in which plant sterols are excessively absorbed and deposited).

Xanthomatous Achilles tendon deposits have been reported to regress with chenodeoxycholic acid therapy[16-19], although they did not do so in our patient. Treatment of cerebrotendinous xanthomatosis with chenodeoxycholic acid, a bile acid, will arrest but generally will not reverse the frequently devastating neurological deterioration seen in these patients[17,20]. Medical therapy, therefore, should be instituted at the time of diagnosis, and family members should be screened for subclinical disease. ■

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The authors did not receive grants or outside funding in support of their research for or preparation of this manuscript. They did not receive payments or other benefits or a commitment or agreement to provide such benefits from a commercial entity. No commercial entity paid or directed, or agreed to pay or direct, any benefits to any research fund, foundation, educational institution, or other charitable or nonprofit organization with which the authors are affiliated or associated.

doi:10.2106/JBJS.E.00872

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