Cerebrotendinous xanthomatosis: A report of 3 cases

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INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal recessive, metabolic disease affecting bile acid synthesis. *CYP27A1* gene mutations result in a faulty sterol 27-hydroxylase, leading to derangements in lipid metabolism, with the accumulation of cholestanol and cholesterol in the form of xanthomas throughout the central nervous system, eyes, and tendons.[1] The incidence is as high as 5 per 100,000 individuals of European ancestry, with approximately 300 reported cases worldwide.[1,2] While individuals often develop signs and symptoms early in life, most are diagnosed during the fourth decade, when their disease has progressed to an advanced state.[2] We report 3 cases of CTX with similar clinical symptoms in order to emphasize the importance of early detection.

Abbreviation used:

CTX: cerebrotendinous xanthomatosis

CASE REPORTS

Case 1

A woman in her 30s, with no reported family history of CTX, first experienced symptoms with an early onset of frequent diarrhea in infancy. She developed cataracts by the age of 6 years. At the age of 14 years, she was formally diagnosed with CTX, which was confirmed by genetic testing. Chenodiol (chenodeoxycholic acid) therapy was initiated at diagnosis, and she has remained on chenodiol since that time. Tendon xanthomas required surgical debulking by the age of 17 years. She has had xanthomas of the Achilles, elbow, and plantar foot and extensor tendons of the fingers and toes. She reported minimal increases in the left Achilles xanthoma over 8 years, with no new xanthomas. The most recent magnetic resonance imaging of the brain showed a mild increased T2 signal within the dentate nucleus, which can be seen in CTX. Despite these findings, she has not clinically expressed any neurologic motor deficits. She has reported a significant cognitive delay. She has no known cardiovascular disease.

Case 2

A woman in her 40s, who had 2 family members with CTX, struggled with irregular bowel movements from an early age. She developed cataracts at the age of 11 years and was diagnosed with CTX at age 27. The diagnosis was confirmed by genetic testing, with the prompt initiation of chenodiol therapy. She has been on chenodiol consistently since the diagnosis at age 27. During adolescence, she developed tendon xanthomas on the fingers and toes, which required debulking, as well as plantar and Achilles xanthomas. She reported no new xanthomas and no changes in the existing xanthomas over 10 years. She was followed-up by neurologic examinations, and the most recent imaging showed cerebellar lesions; however, the patient did not have neurologic deficits. She had no known cardiovascular involvement. She has one daughter, who does not have the genetic mutation for CTX.

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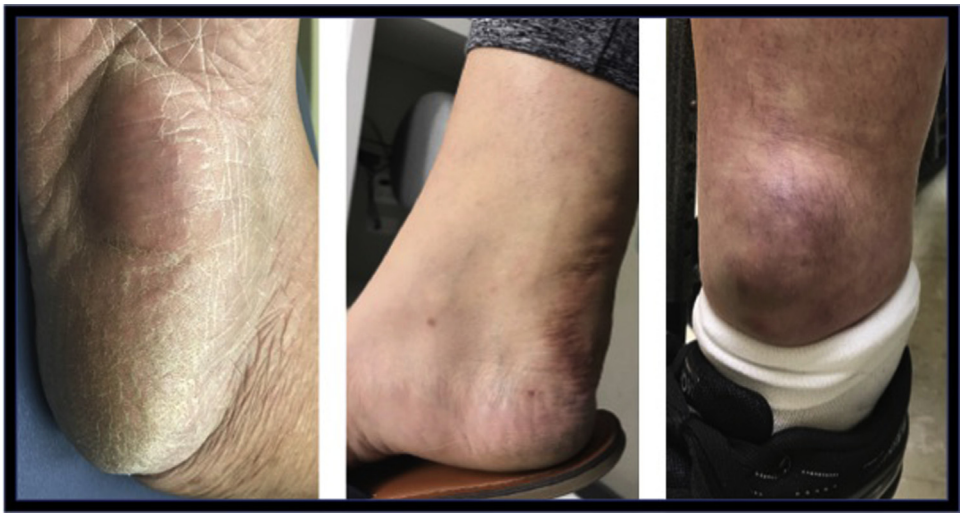

Fig 1. Bulky tendon xanthomas in patients 1, 2, and 3, respectively.

Case 3

A woman in her 50s, who has 2 family members formally diagnosed with CTX, had loose stools from childhood. She was diagnosed with cataracts at the age of 20 years and with CTX at 38 years, which was confirmed by genetic testing. She started chenodiol at the time of the diagnosis but had a 10-year interruption in the therapy. She restarted chenodiol at the age of 48 years and has since remained on the medication without further interruption. She acquired xanthomas of the Achilles, knee, and elbow. Her existing xanthomas have remained stable, with no new xanthomas. Significant neurologic involvement developed in the patient, which progressively led to her becoming nonambulatory and wheelchair-bound. The patient is cared for by her mother. The patient has severe cognitive decline and visual impairment. She has no known cardiovascular disease.

DISCUSSION

Patients with CTX often present with diarrhea, cataracts, tendon xanthomas, and progressive neurologic sequelae.[2] Cataracts are an early sign, commonly appearing in childhood and affecting up to 70% of individuals.[2] Due to the neurotoxicity of cholestanol, progressive cognitive decline begins during adolescence, affecting 74% of patients.[2] Xanthomas develop in up to 77% of patients, forming on tendons, such as the Achilles, extensor elbow, extensor hand, patellar, and neck tendons (Fig 1).[2,3] Tendon xanthomas and the presence of affected siblings are the strongest indicators of CTX.[4] Other indicators include cataracts, diarrhea, neonatal cholestatic jaundice, intellectual impairment, and ataxia.[4] Chenodeoxycholic acid is decreased in the blood, but serum cholestanol and bile alcohol levels are elevated.[2] Neuroimaging reveals leukodystrophic features with white matter changes, atrophy, and cerebellar xanthomas.[5] Biopsies of subcutaneous nodules show xanthomas with foamy histiocytes (Fig 2). The genetic testing for the *CYP27A1* gene mutation is confirmatory. Chenodiol (chenodeoxycholic acid) reduces *CYP7A* transcription, thus decreasing cholestanol synthesis (Fig 3). Studies have shown that chenodiol improves the symptoms and reduces the progression of the disease.[6] Reversal of neurologic damage and resolution of the xanthomas has been reported, especially when treatment is started early in the disease course.[2,6] Our patients experienced diarrhea from infancy or childhood, and cataracts developed at very early ages. The diagnoses of cataracts at an early age prompted the diagnoses of CTX, all of which were confirmed by genetic testing. Clinical xanthomas developed in each patient prior to the initiation of chenodiol, which had minimal impact on the xanthomas over decades of exposure. However, no new xanthomas were noted to have developed while on the long-term therapy. All 3 patients receive annual follow-up neurologic examinations and show evidence of neurologic involvement on imaging. However, only patient 3 has significant neurologic motor decline. These patients follow-up annually with dermatology for monitoring of changes in their xanthomas and continue to receive 250 mg of chenodiol 3−4 times daily. In addition, the patients follow-up annually with ophthalmology for their eye examinations. All three follow-up with orthopedics as needed. Early diagnosis and treatment, either by symptoms

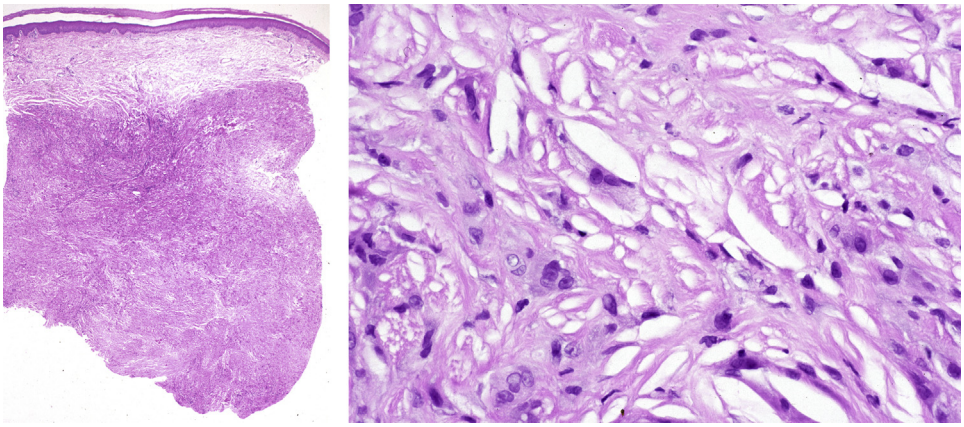

Fig 2. The dense sheets of foamy histiocytes in a tendinous xanthoma in patient 2.

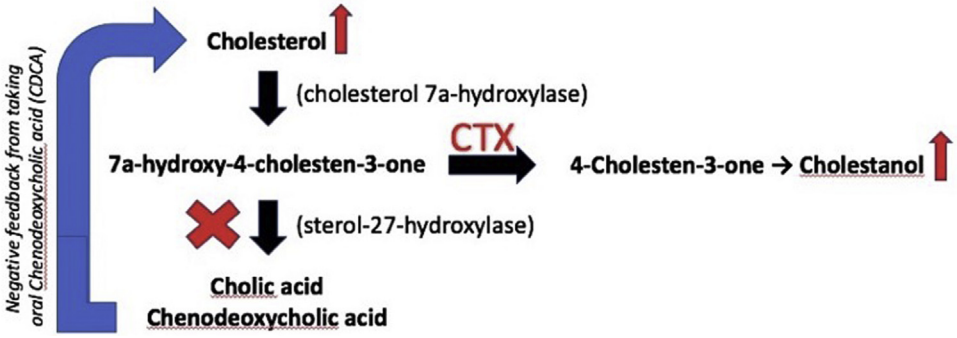

Fig 3. A representation of the dysfunctional biochemical pathway in CTX. The *red arrows* indicate abnormally elevated levels of cholesterol and cholestanol when sterol-27-hydroxylase is dysfunctional. The *blue arrow* represents the negative feedback loop, which indicates how chenodeoxycholic acid lowers cholesterol and cholestanol production. *CTX*, Cerebrotendinous xanthomatosis.

or newborn screening, could potentially limit both xanthoma formation and neurologic sequelae of this rare metabolic disease.

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