

Cerebrotendinous xanthomatosis: clinical and imaging clues of a rare treatable cause of ataxia

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DESCRIPTION

Cerebrotendinous xanthomatosis (CTX) is a rare, autosomal-recessive lipid storage disease.¹ We present the case of a man in his 40s (patient 1) with a prior history of persistent childhood diarrhoea and cognitive-developmental delay. The patient presented to our neurology outpatient clinic with a 10-year history of progressive gait impairment and recent episodes of falls. The patient has one healthy brother and three sisters, two of whom (labelled as patients 2 and 3) also manifested cognitive impairment—see [figure 1](#). All impaired siblings reported cataract extraction before the age of 20. Patient 2 had previously complained of ankle swelling in an orthopaedic evaluation 15 years earlier and performed ankle-joint MRI, deemed inconclusive. On examination, all patients exhibited low stature, appendicular ataxia, pyramidal signs and broad-based ataxic gait. Patient 2's lower limb examination also showed marked pes cavus, clawing of the toes and Achilles' tendon xanthomas ([figure 2A](#)). Brain MRI sagittal T1-weighted image revealed cerebellar atrophy ([figure 2B](#)) and axial T2-weighted image displayed hyperintensities within the dentate nuclei ([figure 2C](#)) in patient 1. The combination of cerebellar ataxia, early-onset cataracts and tendon xanthomas prompted testing for serum cholestanol, which was significantly raised (patient 1: 119 µmol/L; patient 2: 120 µmol/L; patient 3: 84 µmol/L, N: 3.5–23.8 µmol/L). Screening for variations on the CYP27A1 gene revealed two heterozygous variants (c.1420C>T, p.(Arg474Trp)) and (c.1016C>T, p.(Thr339Met)). These variants were previously reported as pathogenic, which confirmed CTX suspicions. All patients started

therapy with chenodeoxycholic acid (CDCA). At the 6-month follow-up, patient 1 reported noticeable improvement in balance.

Here, we report a rare case of three siblings diagnosed with CTX. CTX is caused by mutations in the CYP27A1 gene, resulting in a mitochondrial enzyme sterol 27-hydroxylase defect. Loss of function in this enzyme decreases the synthesis of CDCA and leads to the accumulation of both cholestanol and cholesterol within lipophilic tissues, such as the central nervous system and tendons.¹ Frequent symptoms are early-onset cataracts and tendon xanthomas, present in 85% of patients. Furthermore, childhood diarrhoea is reported as one of the earliest clinical manifestations of the disease, as was the case with our patient.² A broad range of clinical features may contribute to delay diagnosis, but the triad of tendon xanthomas, early-onset cataracts and neurological dysfunction, particularly cerebellar ataxia, strongly suggests this diagnosis. Most patients are diagnosed only in late adulthood when their disease has already progressed to an advanced state.³ When suspected, the diagnosis is easily confirmed by either elevated values of serum cholestanol or genetic testing. Treatment with CDCA may halt disease progression and ameliorate neurological manifestations, particularly when initiated early. Indeed, a recent case study review of 56 individuals with CTX demonstrated that the age of diagnosis and initiation of CDCA therapy strongly correlate with prognosis.⁴

In summary, this case highlights the importance of recognising the typical clinical and imaging signs of CTX, a rare cause of ataxia that benefits from early treatment.

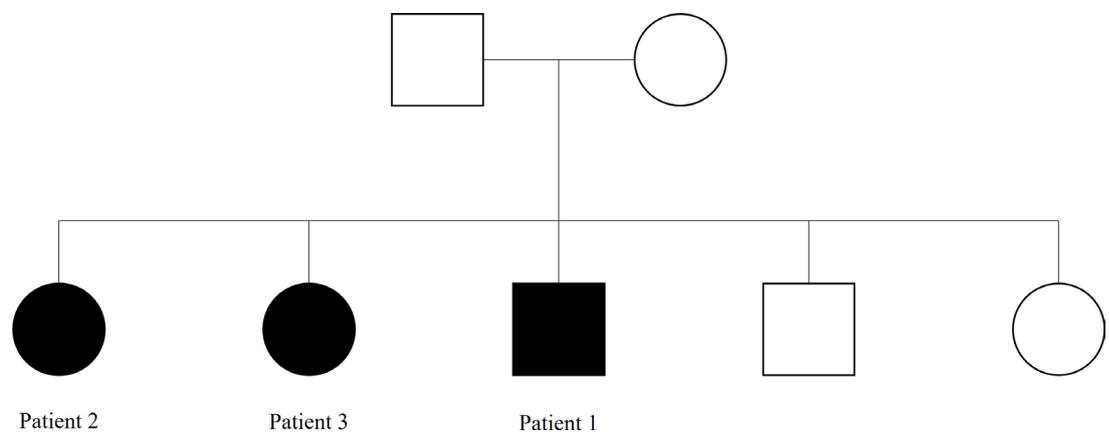


Figure 1 Pedigree chart of the family.



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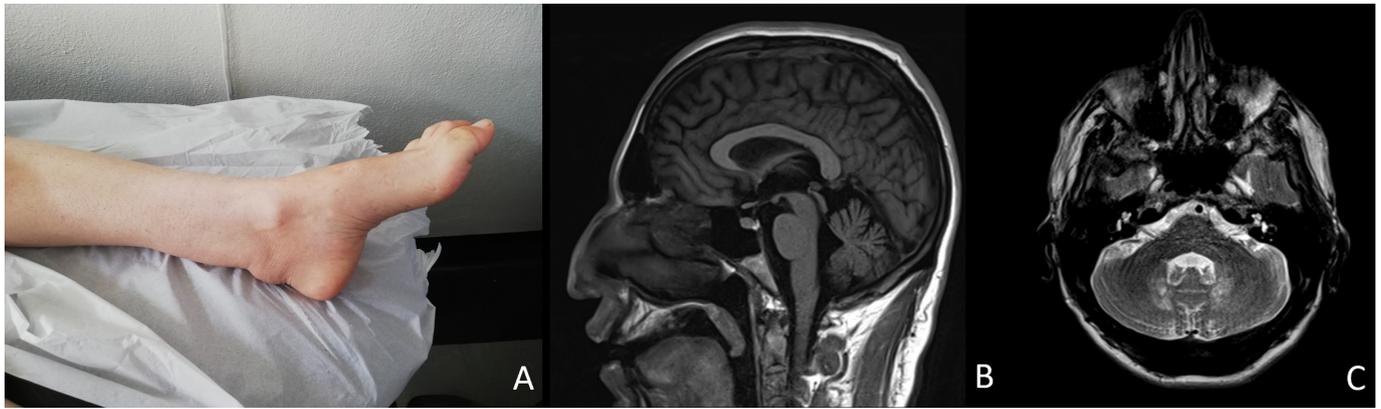


Figure 2 Achilles' tendon xanthomas and pes cavus in patient 2 (A). Brain MRI sagittal T1-weighted image showing cerebellar atrophy (B) and axial (C) T2-weighted image showing hyperintensities within the dentate nuclei in patient 1.

Learning points

- ▶ Cerebrotendinous xanthomatosis (CTX) is a rare treatable cause of ataxia that benefits from early treatment.
- ▶ The triad of tendon xanthomas, early-onset cataracts and cerebellar ataxia strongly suggests CTX.
- ▶ Hyperintensities within the dentate nuclei are a common finding in the brain MRI of CTX patients.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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