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Cerebrotendinous xanthomatosis presenting with progressive ataxia and dysphonia in a 33-year-old Chinese man: a case report

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Case Report

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Abstract

Background

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive lipid storage disorder caused by mutations in CYP27A1. Its early signs are nonspecific, and the diagnosis is often delayed for years, by which time neurological damage may be irreversible. We report an adult in whom progressive ataxia and dysphonia led to the diagnosis, and draw attention to the characteristic magnetic resonance imaging (MRI) findings.

Case presentation:

A 33-year-old Chinese man presented with progressive gait disturbance. Over two years he had developed slowly progressive weakness of both lower limbs, and in the month before admission he began to tire easily on walking. His speech became slurred and his verbal output decreased, progressing to dysarthria, dysphonia, and occasional choking. Examination showed cerebellar ataxia, cognitive impairment, pyramidal signs, peripheral neuropathy, and dystonia, with bilaterally positive Hoffmann and Babinski signs and patellar clonus. Both Achilles tendons were symmetrically enlarged, painless, firm, and fusiform (about 10 cm). Serum total cholesterol, triglycerides, and low-density lipoprotein cholesterol were normal, whereas high-density lipoprotein cholesterol was mildly decreased. Brain MRI showed symmetric bilateral T2 hyperintensities in the cerebellar dentate nuclei, cerebral peduncles, and posterior limbs of the internal capsules, with cerebellar atrophy (Fig. 1). Left ankle MRI showed fusiform swelling of the Achilles tendon with low signal on T1- and T2-weighted images (Fig. 2). Targeted next-generation sequencing with Sanger confirmation revealed compound heterozygous CYP27A1 variants, c.1214G > A (p.Arg405Gln) and c.1435C > T (p.Arg479Cys), confirming CTX. Because chenodeoxycholic acid is unavailable in China, the patient was treated with ursodeoxycholic acid; after four weeks his speech output increased, his responses became more fluent, his Mini-Mental State Examination score rose from 21 to 26, and his lower-limb weakness improved slightly.

Conclusions

CTX should be considered in adults with progressive ataxia and tendon xanthomas, even when the routine lipid profile is normal. Symmetric T2 hyperintensity of the dentate nuclei is a useful early clue. Because treatment can halt or slow progression, early recognition is essential.

Background

Cerebrotendinous xanthomatosis (CTX; OMIM 213700) is a rare autosomal recessive disorder of bile acid synthesis [1]. It is caused by biallelic mutations in CYP27A1, which encodes the mitochondrial enzyme sterol 27-hydroxylase. Loss of this enzyme blocks the formation of chenodeoxycholic acid

(CDCA) and cholic acid, removes the normal feedback inhibition on cholesterol 7α-hydroxylase, and leads to accumulation of cholestanol and cholesterol in the lens, brain, and tendons [2, 3]. The estimated prevalence is 3–5 per 100,000, and it is higher in Asian populations than in other continents [4].

The early symptoms—infantile chronic diarrhoea and juvenile cataracts—are easy to overlook, so the diagnosis is frequently delayed for a decade or more. By the time neurological symptoms appear (cerebellar ataxia, pyramidal signs, peripheral neuropathy, cognitive decline, and sometimes psychiatric disturbance), the damage is often partly irreversible [3, 5]. This delay is particularly consequential, because CTX is one of the few inherited metabolic disorders that can be treated: CDCA replacement reduces cholestanol synthesis and can stabilise or improve neurological function, provided it is started early [6].

We report an adult whose presentation was dominated by progressive ataxia and dysphonia. Two points stand out: the diagnosis can be made in adulthood from typical MRI findings and genetic testing, and a normal routine lipid profile should not deter the clinician, because the relevant marker is serum cholestanol, not cholesterol.

Case presentation

A 33-year-old Chinese man was admitted with progressive gait disturbance. He reported weakness of both lower limbs that had progressed over two years, and in the month before admission he had begun to tire easily when walking. He could no longer walk in a straight line and had fallen several times. His family had noticed that his speech was becoming slurred and that he spoke less; this had progressed to dysarthria, dysphonia, and occasional choking. He was described as introverted, with mild intellectual disability and cognitive impairment. He had a long-standing history of intermittent diarrhoea, nausea, and vomiting, and had noticed progressive visual decline without cataract formation beginning three years earlier. He also reported distal limb pain. There was no family history of similar illness, and his parents were not consanguineous.

On examination, he had cerebellar ataxia, cognitive impairment, pyramidal signs, peripheral neuropathy, and dystonia. The Hoffmann and Babinski signs were positive bilaterally, and patellar clonus was present. Both Achilles tendons were symmetrically enlarged, painless, firm, and fusiform, each about 10 cm in length.

Laboratory tests showed a normal serum total cholesterol of 2.87 mmol/L, triglycerides of 1.81 mmol/L, and low-density lipoprotein cholesterol of 1.76 mmol/L, whereas high-density lipoprotein cholesterol was mildly decreased (0.57 mmol/L; reference 1.16–1.42 mmol/L). A complete blood count showed mild normocytic anaemia (haemoglobin 123 g/L), and serum potassium, sodium, and total calcium were mildly reduced, findings attributable to his chronic diarrhoea. Serum cholestanol was not measured because this assay is not routinely available in Chinese clinical laboratories; the diagnosis therefore rested on genetic testing together with the characteristic clinical and imaging findings.

Brain MRI demonstrated symmetric bilateral T2 hyperintensities in the cerebellar dentate nuclei, cerebral peduncles, and posterior limbs of the internal capsules, with cerebellar atrophy (Fig. 1). MRI of the left ankle showed a fusiform swelling with smooth margins and low signal on both T1- and T2-weighted images, consistent with xanthomatous infiltration of the Achilles tendon (Fig. 2).

Targeted next-generation sequencing of a hereditary metabolic disease gene panel (covering 819 nuclear genes and the 37 mitochondrial genes), followed by Sanger sequencing confirmation, identified compound heterozygous variants in CYP27A1 (NM_000784.4): c.1214G > A (p.Arg405Gln), classified as pathogenic, and c.1435C > T (p.Arg479Cys), classified as likely pathogenic. This genotype, together with the clinical and imaging features, confirmed the diagnosis of CTX.

Because chenodeoxycholic acid (CDCA) is not marketed in China, the patient was treated with ursodeoxycholic acid (UDCA) at 8–10 mg/kg/day, taken in divided doses with breakfast and dinner. After four weeks of treatment and nursing care, his speech output increased and his responses became more fluent; his Mini-Mental State Examination (MMSE) score improved from 21 before treatment to 26 after treatment, and his lower-limb weakness improved slightly (Table 2). The medication was well tolerated.

Table 2
Clinical assessment before and after four weeks of ursodeoxycholic acid treatment

Assessment	Before treatment	After four weeks
Mini-Mental State Examination score	21	26
Speech output	Reduced	Increased
Fluency of verbal responses	Dysfluent	More fluent
Lower-limb weakness	Present	Slightly improved

Discussion and Conclusions

This patient shows how CTX can first present in adulthood with progressive ataxia and dysphonia, and how the diagnosis can be reached from two characteristic imaging findings—symmetric dentate-nucleus hyperintensity and Achilles-tendon xanthomas—supported by genetic testing.

The underlying defect is a disturbance of bile acid synthesis [1, 2]. Deficiency of sterol 27-hydroxylase impairs the conversion of cholesterol into CDCA and cholic acid. The resulting loss of negative feedback on cholesterol 7α-hydroxylase diverts the pathway towards cholestanol, which deposits in the lens, central nervous system, and tendons [2, 3]. This explains the unusual combination of a normal cholesterol level with tissue cholesterol deposition: in most patients it is cholestanol, not cholesterol, that is elevated in serum. Our patient's lipid profile—normal total and low-density lipoprotein cholesterol with a mildly reduced high-density lipoprotein—is therefore entirely consistent with the diagnosis and should not have excluded it.

The MRI features are helpful. Symmetric T2 and fluid-attenuated inversion recovery (FLAIR) hyperintensity of the cerebellar dentate nuclei is regarded as a hallmark of CTX [5, 7, 11]. In later stages, subcortical, periventricular, brainstem, and cerebellar white-matter lesions appear, together with supratentorial and infratentorial atrophy [5]. Tendon xanthomas provide a second clue: on MRI the Achilles tendon shows fusiform enlargement with low signal on both T1- and T2-weighted images, reflecting deposition of cholestanol and cholesterol with foamy macrophages [8]. Both features were present in our patient, which narrowed the differential diagnosis considerably.

The main conditions to consider in an adult with ataxia, spasticity, and tendon enlargement are Marinesco–Sjögren syndrome, multiple sclerosis, and sitosterolaemia (Table 1). Marinesco–Sjögren syndrome usually presents in childhood with cataracts, myopathy, and cerebellar atrophy, is caused by SIL1 mutations, and does not cause tendon xanthomas. Multiple sclerosis can produce ataxia and pyramidal signs, but symmetric dentate-nucleus signal abnormality and tendon xanthomas are atypical. Sitosterolaemia (mutations in ABCG5 or ABCG8) causes tendon xanthomas and premature atherosclerosis, but not the characteristic neurological syndrome. In our patient, tendon xanthomas combined with dentate-nucleus hyperintensity pointed strongly to CTX, and genetic testing confirmed it (Table 1).

Table 1
Differential diagnosis of adult-onset ataxia with tendon xanthomas

Feature	Cerebrotendinous xanthomatosis (CTX)	Marinesco–Sjögren syndrome	Multiple sclerosis	Sitosterolaemia
Inheritance	Autosomal recessive	Autosomal recessive	Acquired (autoimmune)	Autosomal recessive
Gene	CYP27A1	SIL1	—	ABCG5 / ABCG8
Typical onset	Juvenile cataracts/diarrhoea; neurological signs in adulthood	Childhood	Young adulthood	Childhood (atherosclerosis)
Key clinical features	Tendon xanthomas, ataxia, pyramidal signs, peripheral neuropathy, cognitive decline	Cataracts, myopathy, cerebellar atrophy, intellectual disability	Relapsing neurological deficits, optic neuritis	Tendon xanthomas, premature atherosclerosis, haemolysis
Tendon xanthomas	Present	Absent	Absent	Present
Dentate-nucleus T2 hyperintensity	Characteristic	Cerebellar atrophy, no dentate signal change	Atypical	Absent
Serum cholestanol	Elevated	Normal	Normal	Normal (elevated plant sterols)
Lipid profile	Normal (or low) cholesterol	Normal	Normal	Normal (elevated plant sterols)
Diagnostic test	Serum cholestanol + CYP27A1 sequencing	SIL1 sequencing	MRI + CSF oligoclonal bands	Serum plant sterols + ABCG5/ABCG8 sequencing

Treatment is available and works best when started early. CDCA restores negative feedback on bile acid synthesis, lowers serum cholestanol, and can halt or partially reverse neurological progression [6, 9, 10, 13]; the usual dose is 750 mg daily in adults and 15 mg/kg/day in children [6]. Because CDCA is not marketed in China, our patient was treated with UDCA at 8–10 mg/kg/day, a commonly used substitute in Chinese practice when CDCA is unavailable. The effect of UDCA on cholestanol is less well established than that of CDCA, but after four weeks the patient nevertheless showed modest early improvement—increased speech output, more fluent responses, a rise in MMSE score from 21 to 26, and slightly better lower-limb strength (Table 2)—consistent with a partial treatment response. Patients diagnosed late, after fixed deficits have developed, respond less well [10, 11], which underlines the importance of early recognition. A Japanese nationwide survey reported a mean diagnostic delay of 16.5

years, even though treatment lowered cholestanol in all patients and improved symptoms in 40.5% [12], and a recent case series from China likewise emphasises that early recognition is essential to avoid irreversible neurological decline [11].

This report describes a single patient with a short (four-week) follow-up, and serum cholestanol could not be measured because the assay is not routinely available in China. Even so, it is a useful reminder that CTX can present in adulthood and that a normal lipid profile does not rule it out.

In conclusion, CTX should be part of the differential diagnosis of adult-onset progressive ataxia, particularly when tendon xanthomas or dentate-nucleus hyperintensity are present. Early genetic confirmation and prompt treatment may prevent irreversible neurological deterioration.

Abbreviations

CDCA
chenodeoxycholic acid
CTX
cerebrotendinous xanthomatosis
FLAIR
fluid-attenuated inversion recovery
MMSE
Mini-Mental State Examination
MRI
magnetic resonance imaging
UDCA
ursodeoxycholic acid

Declarations

Ethics approval and consent to participate

This retrospective single-case report is based on routine clinical, laboratory, and imaging data, together with follow-up information obtained during standard care. No prospective intervention or additional examination beyond routine clinical practice was performed. Per the policy of the Ethics Committee of the First Hospital of Hohhot, retrospective case reports of this nature are exempt from ethical review.

Consent for publication

Written informed consent for publication of the patient's clinical details and images was obtained from the patient himself.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JF collected the clinical and imaging data and drafted the manuscript. LL acquired the MRI images. HX compiled the laboratory findings. HW revised the manuscript critically. All authors read and approved the final manuscript.

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We thank the patient and his family for consenting to the publication of this case. During the preparation of this work the authors used a large language model to assist with language editing and to improve the readability of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Authors' information

Not applicable.

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Figures

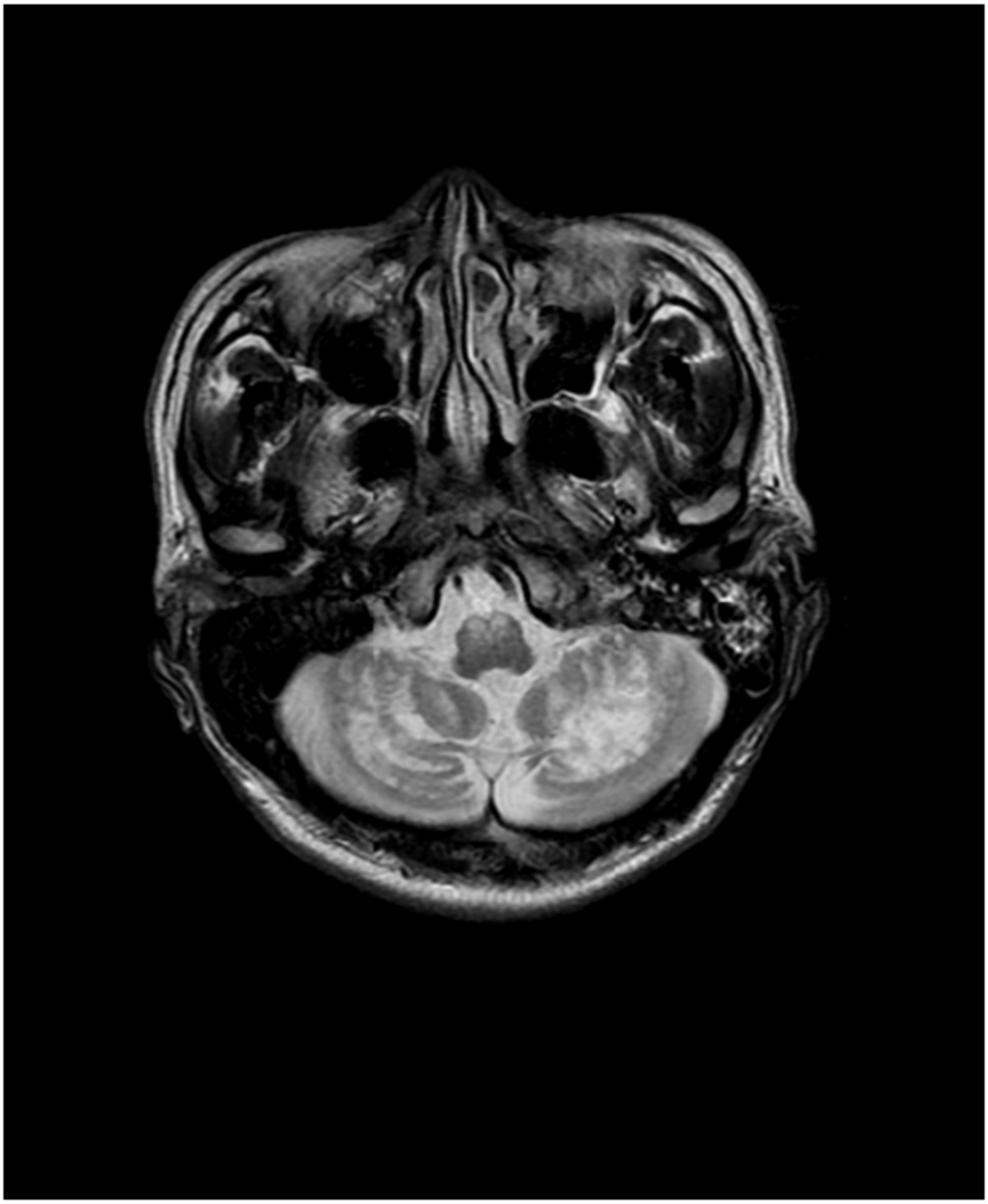


Figure 1

Brain MRI. Axial T2-weighted image shows symmetric hyperintensity of the cerebellar dentate nuclei and cerebellar atrophy.

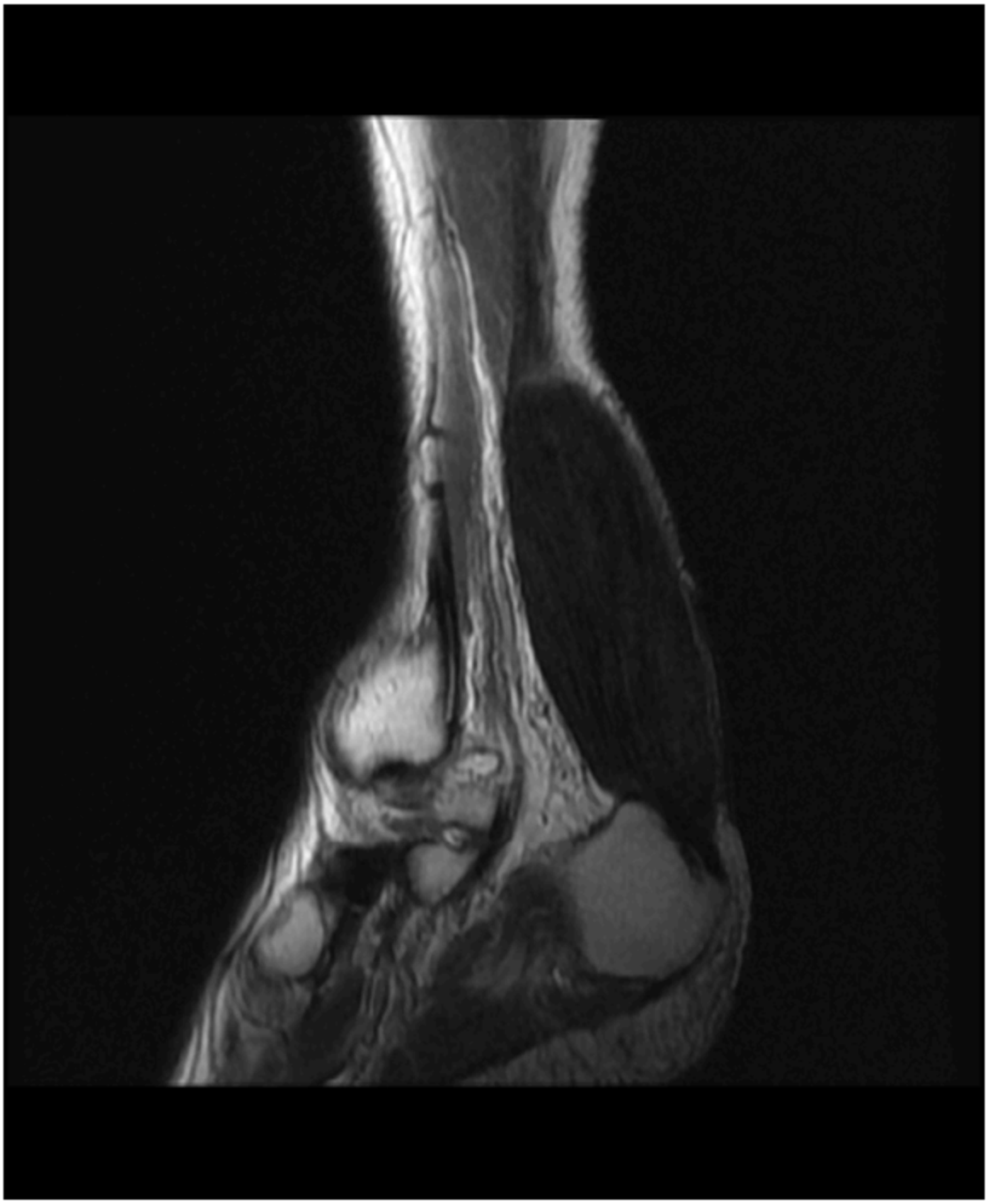


Figure 2

Left ankle MRI. Sagittal T2-weighted image shows fusiform swelling of the Achilles tendon with a convex anterior border and low signal intensity on T2-weighted imaging.