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Progressive ataxia of cerebrotendinous xanthomatosis with a rare c.255 + 1G > T splice site mutation in the CYP27A1 gene: a case report

A case report and review of the literature

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Abstract

BACKGROUND

Cerebral xanthomatosis (CTX) is an autosomal recessive disorder of lipid metabolism caused by the mutation of the *CYP27A1* gene encoding sterol 27-hydroxylase, an essential enzyme for the conversion of cholesterol to chenodeoxycholic and cholic acids. CTX is a rare neurological disease with a wide range of clinical symptoms that are easily misdiagnosed.

CASE SUMMARY

Here we report the clinical, biochemical, and molecular characterization of a 33-year-old female patient with CTX. The patient developed ataxia and had the typical symptoms of juvenile cataracts, tendon xanthomata, and progressive nervous system dysfunction. Magnetic resonance imaging of the brain revealed bilateral dentate nucleus lesions and white matter abnormalities. This patient was misdiagnosed for two years resulting in severe neurological complications. After two years of chenodeoxycholic acid treatment, she still presented with ataxia and dysarthria. The pathogenic sites of *CYP27A1* were identified as c.255+1G > T and c.1263+1G > T, which were both caused by shear denaturation.

CONCLUSION

Cerebrotendinous xanthomatosis requires a multidisciplinary diagnosis that must be made early to avoid progressive neurological degeneration. c.1263 + 1G > T is a known mutation but c.255 + 1G >T is a rare mutation site.

Key Words: Cerebrotendinous xanthomatosis (CTX); *CYP27A1* gene; Ataxia; Juvenile cataracts; Tendon xanthoma; Lipid metabolism

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Core Tip: Our study was to screen in a case delayed diagnosis to result in severe neurological impairment with CTX for CYP27A1 gene mutation, and detected one rare mutation and one known mutation. Cerebrotendinous xanthomatosis is a multidisciplinary diagnosis that must be made early to avoid neurologic injury and worsening. This finding also provides new data for further revealing the pathogenesis of xanthomatosis, enriching the pathogenic mutation spectrum of CYP27A1 gene and molecular diagnosis of the disease, which is of great significance for fertility guidance and prenatal diagnosis of this patient in the future.

³ INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disorder of lipid metabolism caused by mutation of the CYP27A1 gene encoding sterol 27-hydroxylase. Sterol 27-hydroxylase is vital to the rate-limiting step in bile acid synthesis, which when deficient results in insufficient production of chenodeoxycholic acid [1]. Therefore, cholesterol¹ accumulates in plasma and precipitates into various lipophilic tissues, such as the brain (with a preference for the cerebellum), eyes, and tendons. This results in the characteristic cataracts and tendon xanthomata. CTX can occur in infants, adolescents, and adults. The clinical symptoms are diverse, with 85% of patients developing bilateral cataracts in childhood, 90% presenting with intelligence lower than other children of the same age, 80% with pyramidal tract abnormalities, 73% with the typical signs of cerebellar ataxia and about half of the patients having seizures. Tendon xanthomata is the most common symptom, present in 90% of patients. Other symptoms include osteoporosis, arterial disease, and early atherosclerosis. The rarest symptoms include Parkinson and xanthoma of the spine [2]. CTX is easily misdiagnosed as a treatable disease. While patients with early detection show good treatment effect [3], patients with

severely impaired neurological function have poor treatment effect, and are prone to sequelae. In this article, we share the clinical misdiagnosis and genotypic manifestations of a CTX patient, and report a rare pathogenic mutation site for clinical reference.

CASE PRESENTATION

Chief complaints

5 The patient, a female with non-consanguineous parents, came to clinical attention at age 33.

History of present illness

She reported having poor stress tolerance, attention deficits, a “weird personality”, and poor learning ability during childhood. When she was 9, she was diagnosed with cataracts in both eyes and subsequently underwent cataract surgery. At the age of 27, she developed symptoms of nervous system damage such as ataxia and episodes of bilateral foot dystonia with falls with no easily observable cause. She had difficulty walking: her walking speed slowed and raising her right leg was laborious, with her right foot dragging on the floor. She needed assistance descending the stairs and easily fell when traversing slopes. She went to the hospital repeatedly but did not receive adequate treatment. Her symptoms progressively intensified, leading to multiple falls. Since the age of 31, she has reported the onset of difficulty in speech without dysphagia.

History of past illness

Human body health

Personal and family history

There were no known consanguineous marriages in the family.

Physical examination

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Finally, in a neurological examination at the age of 33, the patient presented with spastic paraparesis, progressive gait ataxia, mild dysarthria, clonic knee reflexes, bilateral Babinski sign, and abnormal proprioception, vibration, and temperature sensation in both feet.

Laboratory examinations

Her laboratory data were as follows: Triglyceride (TG): 0.83 mmol/L (0-1.7), cholesterol-9 (TC): 3.92 mmol (0-5.2), high-density lipoprotein (HDL-C): 2.02 mmol/L (1.04-1.90), and low-density lipoprotein (LDL-C): 1.77 mmol/L (1.63-3.81).

Imaging examinations

MRI

Genetic confirmation

FINAL DIAGNOSIS

Cerebral xanthomatosis (CTX)

TREATMENT

At the age of 33, she started the chenodeoxycholic acid (CDCA) regimen.

OUTCOME AND FOLLOW-UP

She had been treated with CDCA (750 mg/day) orally for ≥ 2 year, but still presented with spastic paraparesis, progressive gait ataxia, mild dysarthria, clonic knee reflexes, and tendon xanthomata.

DISCUSSION

CTX is a rare disease of lipid deposition which characteristically deposits lipids in the tendons, resulting in tendinous xanthomatosis. Typical clinical manifestations of

CTX include diarrhea, bilateral cataracts in childhood, progressive neurologic dysfunction, tendon xanthomata, and atherosclerosis in adolescence and early adulthood. There are also some cases where ⁴ the spinal form has a milder clinical manifestation, presenting primarily with adult-onset paraparesis similar to hereditary spastic paraparesis [4]. Juvenile cataracts occur in up to 90% of patients, and signs of cerebellar dysfunction are the most common features in CTX patients, accounting for about 68%. Childhood diarrhea and juvenile cataracts are the primary non-nervous system manifestations [5]. However, Abdel-Hamid *et al.* (2017) reported a case of CTX with tendon xanthomatosis and neurological impairment without obvious cataracts [6]. Brain MRI typically reveals symmetrical lesions in the cerebellar white matter, especially the cerebellum. The classic neurological dysfunction form predominantly displays with cerebellar ataxia, dementia, tendon xanthoma formation, and early-onset peripheral polyneuropathy. In the case of the present patient, juvenile cataracts were present early, followed by progressive xanthoma of the tendon, which progressed to neurological impairment (ataxia). These classic features of xanthomatosis presented without significant childhood diarrhea. A brain MRI showed the characteristic focal lesions appearing as xanthomata in cerebellum.

The CTX median age at diagnosis is 24.5 years old [7]. The onset of symptoms for the present patient began at 9 years old with cataracts, and by the age of 27, she reported symptoms of nervous system damage such as ataxia, with her symptoms progressively worsening. She repeatedly visited doctors, but did not receive a clear diagnosis. On May 28, 2019, she was admitted to our department with ataxia, and finally diagnosed with CTX at the age of 33 with serious neurological involvement. She had been treated with CDCA (750 mg/day) orally for ≥ 2 year, but still presented with spastic paraparesis, progressive gait ataxia, mild dysarthria, clonic knee reflexes, and tendon xanthomata. While CTX can be treated, it is very easy to misdiagnose. Once there is severe nervous system damage, it is likely to leave serious disability, affecting the patient's quality of life.

The *CYP27A1* gene contains nine exons and eight introns. Of the 108 variants of *CYP27A1* that have been reported, over 50 are considered pathogenic or likely pathogenic according to the Human Gene Mutation Database. Several studies have reported *CYP27A1* mutations including nonsense (22%), splice site (20%) and small deletion and insertion (18%) mutations [8]. According to a recent nationwide survey on CTX in Japan, the most frequent mutations in the *CYP27A1* gene were c.1214G > A, c.1421G > A, and c.435G > T [9]. In the Chinese population, we found that the most frequent mutations were c.410G > A, c.379C > T, and c.1435C > T. The pathogenic mutations (c.389 T > A and c.571C > T, c.379C > T, c.435G > T, c.1016C > T, c.1214G > A, c.1263 + 1G > A, c.1420C > T, and c.1435C > T) were also identified [10]. The genotype of the patient included c.435+1G > T and c.1263+1G > T as well as the rare mutation site c.255+1G > T.

Mutation c.1263+1G>T has been reported previously, but the pathogenicity of c.255+1G >T has rarely been reported. Stelten *et al* (2021) reported four cases of CTX in a South African family that showed multiple xanthomata on the Achilles tendons. Despite this, their neurological examinations were all normal, their brain MR spectroscopies were unremarkable, and even their ophthalmology evaluations showed no signs of cataracts. However, the diagnosis of CTX was confirmed through genetic analysis, identifying the mutations c.2T > C and c.255+1G > A [11-12]. The latter mutation is shared with the current case, suggesting that the same genotype but different clinical manifestations may be caused by different races.

CONCLUSION

Our paper reports a case of delayed cerebrotendinous xanthomatosis diagnosis resulting in severe neurological impairment. The CTX diagnosis was confirmed by detection of *CYP27A1* gene mutations, which comprised one rare mutation (c.255+1G > T) and one known mutation (c.1263+1G > A). Cerebrotendinous xanthomatosis requires a multidisciplinary diagnosis and must be made early to avoid progressive neurological impairment.

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