Case Report

A Rare Case of Cerebrotendinous Xanthomatosis Associated With a Mutation on COG8 Gene

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Abstract

Cerebrotendinous xanthomatosis (*CTX*) is a rare hereditary disease described by a mutation in the *CYP27A1 gene*, which encodes the sterol 27-hydroxylase enzyme involved in the synthesis of bile acid. Accumulation of cholesterol and its metabolite, cholestanol, in multiple body organs causes the symptoms of this disease. In addition, a mutation in the *COG8 gene*, which encodes a subunit of conserved oligomeric Golgi (COG) complex, causes another rare disorder attributed to type IIh of congenital disorder of glycosylation (*CDG*). We described a rare case of *CTX disorder* associated with a mutation on *COG8 gene*, which presented by unusual symptoms.

Keywords

CTX disorder, *CDG type IIh*, *CYP27A1 gene*, *COG8 gene*

Introduction

Cerebrotendinous xanthomatosis (*CTX*) is a rare autosomal recessive lipid storage disorder caused by a mutation in the *CYP27A1 gene* that is located on chromosome 2q35 and encodes the sterol 27-hydroxylase enzyme.[1] In the absence of this enzyme, cholesterol cannot be transformed into bile acid, chenodeoxycholic acid (CDCA), which results in abnormal accumulation of cholestanol and cholesterol in many tissues, most notably the brain and tendons.[2-4] Cerebrotendinous xanthomatosis is often characterized by frequent diarrhea, neurological problems, tendon xanthomas, and cholestasis in infancy, which is seen as prolonged jaundice and bilateral cataracts in childhood.[3,5-7] However, *CTX* patients may not experience all the symptoms which complicates its diagnosis.

Congenital disorder of glycosylation (*CDG*) type II is a result of defects in the genes that affect processing of the protein-bound oligosaccharides in the endoplasmic reticulum and Golgi. Congenital disorder of glycosylation type IIh is a rare hereditary disease described by a mutation in the *COG8 gene*, which encodes a subunit of conserved oligomeric Golgi (COG) complex and results in disruption of glycoprotein synthesis. Congenital disorder of glycosylation type IIh results in severe psychomotor retardation and hypotonia.[8]

Herein, we describe a patient with non-palpable xanthomas in tendons and a normal cholesterol plasma level who is found to have apparent homozygous variants in both *CYP27A1* and *COG8 genes*.

Case Presentation

A 17-year-old intellectually disabled boy was admitted to our neurology clinic due to an abnormality in his hand and difficulty in walking. He had a feeling of fear and trembling of his legs when climbing the stairs. His symptoms had begun when he was 4 years old and worsened until his parents noted and brought him to the clinic.

He had diarrhea and jaundice during infancy and underwent phototherapy 3 times until the jaundice was completely resolved. Also, he had bilateral cataracts at the age of 12. At

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Figure 1. Patient's right hand with flexion and extension in the joints.

the age of 14, he had a car accident that caused a fracture in his skull. He had no history of cardiovascular or pulmonary diseases, and there was no genetic disorder in his family history. He was the fourth child of the third-degree consanguineous marriage and was born at term after a normal pregnancy, and his development was normal.

At the time of admission to the clinic, his weight was 54 kg (11.70 percentile), height was 158 cm (1.07 percentile), and head circumference was 56 cm.

Physical examination revealed ataxia, dysarthria, and spastic paraparesis with pyramidal signs more prominent on the right lower extremity. Eye examination and other neurological tests were performed because of his symptoms such as visual impairment, peripheral neuropathy, hallucinations, depression, and delusion and yielded negative results. There was no sign of palpable xanthoma in any of his tendons even in Achilles tendon. In the examination of his right hand, the fourth and fifth interphalangeal joints were flexed, and the third and fifth metacarpophalangeal joints were extended, which was found to be the result of presence of small xanthoma in the tendons of the right hand (Figure 1).

Electromyography and nerve conduction velocity (EMG/NCV) revealed no evidence of myopathy or neuropathy, and the motor and sensory conduction velocities were normal. Laboratory tests showed a normal cholesterol level in the serum (162 mg/dL) and a normal total serum bile acid level (10 µmol/L). Other laboratory test results are shown in Table 1.

Brain magnetic resonance imaging (MRI) demonstrated diffuse and focal cerebral and cerebellar white matter abnormalities (Figure 2).

The genetic study was performed by the next-generation sequencing (NGS) method, and the results were confirmed by the Sanger sequencing method. The apparent homozygous variants in the *NM_000784.4(CYP27A1)*: *c.803G>A (p.Trp268*)* and *NM_032382.5(COG8)*: *c.1073G>A (p.Arg358Gln)* in the *CYP27A1* and *COG8 genes* were found which are pathogenic based on American College of Medical Genetics (ACMG) classification.[9,10] Therefore, our patient was diagnosed with *CTX* and a mutation on *COG8 gene*. In due course, we started CDCA 810 mg daily (15 mg/kg/day).

Table 1. Laboratory test results.

Variable	Result	Normal range
WBC ($\times 10^9$/L)	7.6	4-11
Hb (g/dL)	16.7	12.5-16
Platelets ($\times 10^9$/L)	256	140-450
FBS (mg/dL)	96	70-100
ALT (U/L)	16	10-55
AST (U/L)	19	10-40
ALP (U/L)	333	45-115
BUN (mg/dL)	19	6-24
Serum bile acid (µmol/L)	5	0-6
Cr (mg/dL)	0.9	0.5-1.5
ESR (mm/h)	1	<20
CRP (mg/L)	1.20	<0.9
25-OH Vitamin D_3 (ng/mL)	35.7	50-70
TSH (mU/L)	1.1	0.7-6.4
Ca (mg/dL)	10.4	8.5-10.5
Phosphorus (mg/dL)	3.8	2.5-4.5
Serum albumin (g/dL)	4.5	3.1-4.3
Magnesium (mg/dL)	1.5	1.5-2
CPK (U/L)	10	24-195
Tg (mg/dL)	145	40-150
Chol (mg/dL)	162	<200
Total bilirubin (mg/dL)	1.5	0.0-1.0
Direct bilirubin (mg/dL)	0.4	0.0-0.4
LDH (U/L)	116	60-170

Abbreviations: WBC, white blood cell count; Hb, hemoglobin; FBS, fasting blood sugar; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; Cr, creatinine; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; TSH, thyroid stimulating hormone; Ca, calcium; CPK, creatine phosphokinase; Tg, triglycerides; Chol, cholesterol; LDH, lactate dehydrogenase.

In a 3-month follow-up, he had a cholesterol level of 96 mg/dL and a bile acid level of 4 µmol/L which both were normal, and the symptoms had been under control. Due to the absence of seizures, he did not receive any additional treatment. Since then, he was followed every 3 months with a physical examination and laboratory tests including cholesterol level. In addition, the patient's family was consulted on how to respond correctly to his needs, due to his intellectual disability.

Discussion

Cerebrotendinous xanthomatosis is a rare hereditary disorder which was first described by Von Bogaert in 1937.[11] The condition is caused by a hereditary genetic mutation in the *CPY27A1 gene*, which results in a lack of the mitochondrial enzyme sterol 27-hydroxylase. This enzyme involves the pathway that breaks down the cholesterol to CDCA. Due to the lack of enzyme activity, the alternative

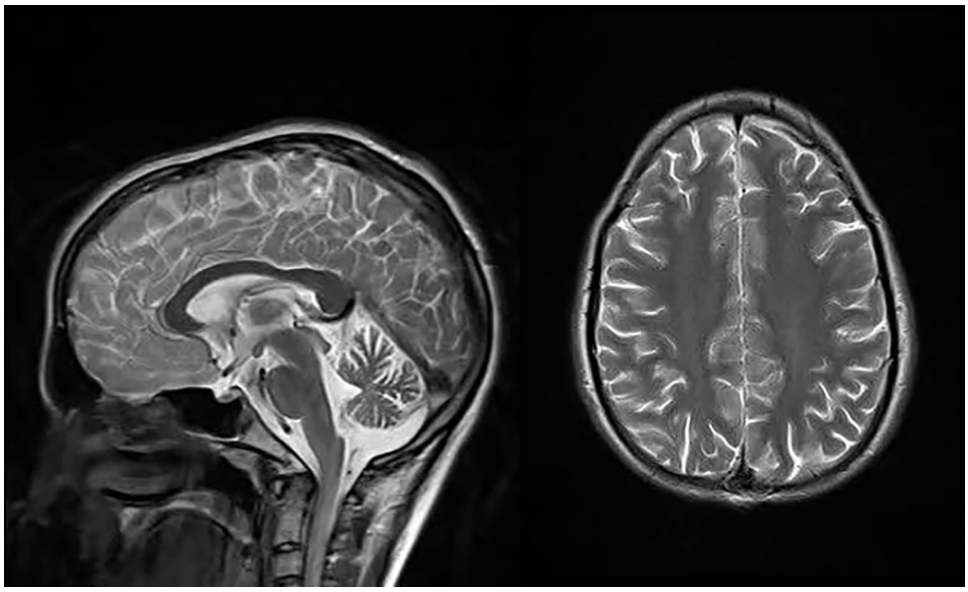

Figure 2. Brain magnetic resonance imaging (MRI) showing diffuse and focal cerebral and cerebellar white matter.

pathway produces some other substances, such as cholestanol and bile alcohols.[12,13] Accumulation of cholestanol and bile alcohols, as well as cholesterols in multiple body organs, creates xanthomas, especially in the brain and tendons which leads to the symptoms of this disease.[6,3,12] Varying *CTX* symptoms in people of different ages make diagnosis difficult. Our patient lacked a palpable xanthoma in the tendons, resulting in delayed diagnosis. In addition, the patient described in this article had intellectual disability, jaundice in infancy, and bilateral cataracts at 12 years of age, all of which were compatible with the clinical symptoms of *CTX*. To confirm the *CTX* diagnosis, genetic analysis is essential. In addition to a mutation in the *CPY27A1 gene* in our case, he had another mutation in the *COG8 gene*, which makes this case valuable for consideration; the *COG8 gene* encodes a component of the COG complex which is involved in membrane trafficking and modifying the glycosylation of proteins.[14] Therefore, a mutation in this gene leads to a rare disorder called *CDG* type IIh, which is described by under glycosylated proteins of serum and mostly involves nervous and skeletal systems.[8,15] This mutation explained other signs and symptoms of our patient, including failure-to-thrive, intellectual disability, microcephaly, ataxia, hypotonia, and dysarthria.

For distinguishing *CTX* from other disorders with xanthomas such as dyslipidemias including sitosterolemia or familial hypercholesterolemia, increased cholestanol concentration in serum and tissues, normal to low level of cholesterol, reduced CDCA levels, and elevated levels of bile alcohols could be helpful.[16-18] Combining biochemical and genetic test results allowed us to make a definitive diagnosis for our case.

At the time of diagnosis, severe neurological symptoms are associated with a poorer prognosis for patients diagnosed with *CTX* who were at least 25 years old.[6] There was evidence of diffuse and focal cerebral and cerebellar white matter issues in brain MRI of our case. Recently, some studies have shown that the cerebellar vacuolation on MRI could be a marker related to the poor prognosis of *CTX* patients.[19,20]

Because of the positive effects of long-term consumption of CDCA in patients with *CTX*, as detailed in a study by Berginer in 1984, CDCA has been approved for use as a first-line treatment for *CTX*.[21] According to studies, the prognosis of *CTX* patients is affected by the age at diagnosis and the initiation of CDCA treatment. [6,22,23]

Patients should be evaluated by the detection of plasma cholestanol levels and through neurologic tests.[24] But, additional studies are required to discover the most effective methods for monitoring the disease's progression throughout treatment.

Conclusion

This example demonstrates that homozygous variants in the *CYP27A1* and *COG8 genes* can present with uncommon symptoms such as non-palpable xanthomas in tendons. In addition, as a clinician dealing with a patient exhibiting these symptoms, we should continue to follow-up laboratory values with being required to administer treatment.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author.

Declaration of Conflicting Interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series. All of the authors declare that confidentiality of the patient was respected.

Informed Consent

Written informed consent was obtained from a legally authorized representative(s) for anonymized patient information to be published in this article.

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Supplemental Material

Supplemental material for this article is available online.

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