Cerebrotendinous Xanthomatosis as a Very Rare and Treatable Disease Frequently Overlooked: A Case Series

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ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is a very rare autosomal recessive lipid storage disorder affecting bile acid biosynthesis. It is manifested by neurologic and non-neurologic symptoms due to abnormal tissue lipid deposition. One of the early symptoms of CTX is juvenile cataract formation. Diagnosis is usually delayed but early diagnosis and replacement therapy can prevent devastating neurologic sequelae. Three patients with bilateral juvenile cataracts from same family were reviewed in this case series.The present case series aims to draw attention to the importance of early diagnosis for patients with CTX and to increase the awareness of physicians who have the potential to treat patients with CTX. Early diagnosis has vital importance in the prognosis of these patients.

Key Words: Cerebrotendinous xanthomatosis, Juvenile cataract, Cholestanol.

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare inborn error of lipid metabolism, including bilateral juvenile cataracts. CTX is classified as a bile acid synthesis disorder caused by the underlying genetic mutation that causes deficiency in an important enzyme in the bile acid synthesis pathway, sterol 27-hydroxylase. Bile acids (chenodeoxycholic and cholic acid) are important components of bile and have a role in the absorption of fats during intestinal passage. The disorder can also be classified as a lipid storage disorder (due to fat deposition in various tissues of the body) or a leukodystrophy (due to the involvement of central nervous system white matter).

The estimated incidence ranges from 1:134,970 to 1:461, 358 in Europeans, 1:71,677 to 1:148,914 in Americans, and 1:64,267 to 1:64,712 in East Asians.[1] Despite the published incidence rates, according to findings in the current literature, approximately three hundred individuals affected by CTX have been described worldwide. This suggests that many cases may go undiagnosed or are misdiagnosed.

CTX is an autosomal recessive disease caused by mutations in the CYP27A1 gene on chromosome 2q33-qter.[2] CYP27A1 plays a pivotal role in cholesterol side chain oxidation during the synthesis of chenodeoxycholic acid (CDCA), which is a bile acid.[1] Therefore, perturbations in the CYP27A1 gene result in reduced enzymatic activity causing impairment of cholesterol side chain oxidation, finally culminating in excessive production and abnormal deposition of cholestanol in various tissues.[3]

The classic triad of the syndrome consists of juvenile bilateral cataracts, tendon xanthomas (predominantly involving the Achilles tendon), and various neurologic abnormalities.[4] Other common pediatric manifestations of CTX include intellectual disability or developmental delay (60% of patients, mean age of 6 years at diagnosis) and epilepsy (33% of patients, mean age of diagnosis 10 years).[5] Chronic diarrhea may begin in infancy and continue into adulthood.[6]

CDCA has been demonstrated to decrease the levels of serum cholestanol and urinary bile alcohols in patients with CTX.[7] Treatment with CDCA can stabilize or even reverse some symptoms in most patients with CTX.[8] Initiating

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CDCA treatment during childhood or earlier is believed to be more beneficial than treatment during adulthood.[9]

In order to stress the importance of early diagnosis and early treatment for CTX, the following three cases are discussed.

CASE REPORT

Case #1

Patient 1 was a 6-year-old male who had been followed with a diagnosis of juvenile cataract since the age of 2 years. A cataract operation was planned at a different eye clinic but his neurologic examination revealed unfavorable outcomes for induction of anesthesia. The patient was followed up by a metabolic diseases specialist in line with the patients' symptoms; however, an ophthalmic operation was not tried.

Upon referral to our clinic, a physical examination was performed and uncorrected visual acuity (30/80) was reported in each eye. Manifest refraction was observed +0.75+2.75*5 in the right eye and +0.25 +3.25*10 in the left eye. A complete dilated examination showed that the eyes were normal other than the cataracts, which were described as wedge-shaped on slit lamp examination, with mild cortical opacifications (figure:1).The axial length of the right eye was observed as 22.46 mm and 22.56 mm for the left eye. Central macular thickness (CMT) was observed as 236 and 230 µm, in the right and left eyes, respectively. The retinal nerve fiber layer (RNFL) was measured as 84 µm in the right eye and 80 µm in left eye. Central cornea thickness was measured as 560 µm and 563 µm in the right and left eye, respectively. Consanguineous marriage was reported for the parents. Epilepsy and nonverbal learning disorder was reported for this patient according to the previous medical records. As a result of the overall evaluation, right eye cataract surgery was performed and no complications were observed.

Due to the presence of bilateral idiopathic cataract and history of epilepsy and nonverbal learning disorder, which resulted in a possible diagnosis of CTX, serum cholestanol testing was planned and performed. The patient's plasma cholestanol was observed about ten times higher than normal ranges (2.86 mg/dL; normal, 0.23±0.12 mg/dL). The diagnosis was confirmed by the identification of previously reported compound heterozygous mutations in the CYP27A1 gene (p.R127W:c.379C>T and p.R474W:c.1420C>T). The patient was put on 125 mg CDCA treatment on a daily basis. Visual acuity in the left eye declined rapidly one month after his first cataract surgery

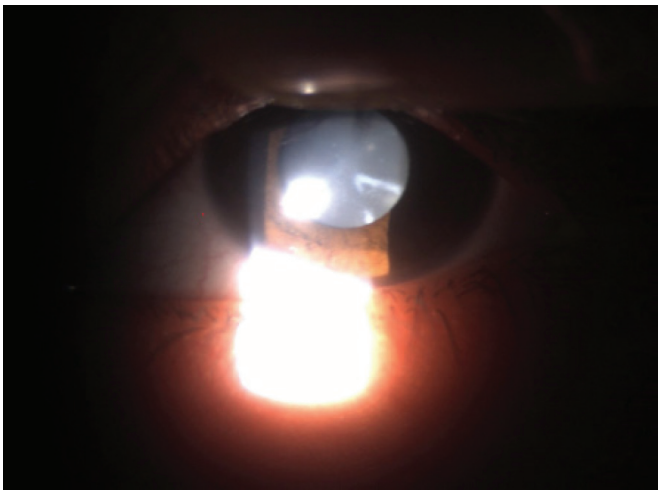

Figure 1. *The left eye cataract.*

and the patient underwent cataract extraction and had an intraocular lens implant for the left eye. Postoperatively, visual acuity improved from 30/80 to 20/25 for both eyes.

Case #2

This female patient was the sibling of the parents of the first case, was aged 14 years at the time of our initial examination, and was previously followed by a metabolic disease specialist due to progressive ataxia, epilepsy, and cognitive decline. She underwent surgery for bilateral juvenile cataracts 4 years earlier; however, the patient's left eye was eviscerated after a trauma two years after the cataract operation. The patient was wearing a prosthetic eye at the time of the examination, visual acuity was 80/80 with -0.75+1.75*180 refraction. In the dilated fundus exam, the right eye showed optic disc drusen. CMT was observed as 555 µm and the axial length of right eye was measured as 22.16 mm. A metabolic examination indicated that plasma 5α-cholestanol was markedly elevated to 3.7 mg/dL (normal < 0.2 mg/dL). The diagnosis was confirmed by the identification of previously reported compound heterozygous mutations in the CYP27A1 gene (p.R127W: c.379C>T and p.R474W: c.1420C>T). The patient was started treatment with 125 mg CDCA on a daily basis.

Case #3

This patient was a distant relative of Case #1 and was a 21-year-old male at the time of our examination. Consanguineous marriage was reported for his parents. The patient had undergone cataract surgery for both eyes at the age of 10 years. His visual acuity was 0.6 to -1.75 +2.75*95 in right eye, and 0.9; 0.7 to -0.75 +1.75 *100 in left eye, and fully recovered with revision. The pupil of the right eye was slanted up slightly. Axial length was

measured as 22.68 mm and 22.78 mm in right and left eye, respectively. CMT was observed as 248 µm in left eye and 256 µm in left eye. RNFL was observed as 98 µm and 88 µm in the right and left eye, respectively. Central cornea thickness was measured as 507 µm in right eye and 496 µm in left eye. According to the physical examination outcomes, mild mental retardation and mild ataxia were reported. Osteoporosis was diagnosed earlier; however, the patient had no joint symptoms. A plasma cholestanol test was performed for a suspected diagnosis of CTX, which was found as 35.85 mg/mL, nearly ten times higher than the normal ranges (0.45-3.75 35.85 mg/mL). The diagnosis was confirmed by the identification of previously reported compound heterozygous mutations in the CYP27A1 gene (p.R270X:c.808C>T).

DISCUSSION

The diagnosis of CTX can be complicated by its pleiotropic clinical findings and variable age of onset of clinical manifestations.[10] Patients with CTX can present to pediatricians with diarrhea, an ophthalmologist for cataracts, a neurologist for neurocognitive impairment, ataxia, epilepsy, or symptoms of Parkinson's disease, or to a dermatologist for tendon xanthomas. Therefore, a multidisciplinary approach has critical importance for the diagnosis of these patients.

Earlier diagnosis is crucial for these patients in order that treatment can be initiated as early as possible. There are no certain strategies to improve diagnosis with a clinical suspicion index; moreover, most physicians are not even aware that they are facing a rare disease.[11] However, early diagnosis and treatment with CDCA can reverse metabolic derangement and may prevent or even improve the neurologic dysfunction associated with this disease.[12] Most importantly, treatment effects may diminish once neurologic symptoms are fully established, presumably due to the irreversibility of lesions, and therapy is considered more efficacious if started early in the disease course. Several studies have proved that early treatment of children with CTX is beneficial, because these patients showed an unequivocal clinical, neurophysiologic, and biochemical improvement after starting treatment. Early diagnosis and treatment also prevent irreversible neurologic damage.[13,14]

The lack of CDCA production in patients with CTX results in overproduction of cholestanol, with accumulations in the tendons and nervous system tissues of patients. Studies proved that CDCA represents the standard of care for treating patients with CTX and improving the clinical symptoms because administration of oral CDCA was shown to be the only treatment for the correction of the biochemical abnormality.[10,15] CDCA can help restore normal sterol, bile acid, bile alcohol, and cholestanol levels, and also appears to be generally effective in preventing adverse clinical manifestations of the disease from occurring or progressing if administered early enough.[15]

Alternative treatments have also been tried, including hydrophilic bile acids, cholestyramine, clofibrate, statins (alone or in combination with CDCA), and LDL apheresis, but have generally shown limited efficacy in inhibiting abnormal bile acid synthesis, reducing and maintaining reduced cholestanol levels. Cholic acid has shown some efficacy; however, it has not been widely tested and may not inhibit cholestanol formation to the same extent as CDCA.

Surgical removal of tendon xanthomas is not recommended, except when acute cord compression or pressure relief is needed for emergency therapy, because xanthomas can regrow rapidly in patients with uncontrolled CTX. [15]

CONCLUSION

As a conclusion, for the diagnosis of CTX, physicians must be aware that they are facing a rare disease and must suspect CTX in patients with juvenile cataracts. Ordering cholestanol tests should become routine practice for these kinds of cases and fellows also need to be imbued with the necessity of testing because they have the ability to change clinical practice. Early diagnosis has vital importance in the prognosis of these patients; therapy should be initiated at any stage of disease presentation and can be effective even when started at later stages of the disease.

Patient Consent

Written consents were obtained from all three patients for the publication of this case series.

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Conflicts of Interest

Author of this report has no financial disclosures.

Authorship

Author of this report attest that she meets the current ICMJE criteria for Authorship.

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