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Case Report
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Adult-Onset Treatable Leukodystrophy: Cerebrotendinous Xanthomatosis

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ABSTRACT

Cerebrotendinous xanthomatosis is a leukodystrophy resulting from sterol 27-hydroxylase enzyme deficiency caused by CYP27A1 gene mutations. It is characterized by diarrhea and cataract in children, xanthomas in adolescents, and progressive neurologic symptoms in adults. This study presented a 39-year-old woman who had progressive difficulty in talking, clumsiness in the hands, and imbalance for 2 years. She was able to walk on her toes but was unable to perform activities of daily living or simple housework. Speech difficulty was present since disease onset. Neurologic examination revealed mild mental retardation, hyperactive deep tendon reflexes, bradykinesia prominent on right, and ataxia. She had bilateral cataract surgery at the age of 15 years. There was no parental consanguinity. Routine biochemical tests, vitamin levels, viral serology, autoimmune antibodies, vasculitis, tumor, and paraneoplastic markers were negative. Brain magnetic resonance imaging showed hyperintensities in cerebellar dentate nuclei in T2-weighted/Fluid Attenuated Inversion Recovery (FLAIR) images. Patient benefited from early levodopa therapy given for dystonia-Parkinsonism. Genetic analysis demonstrated homozygote 1476+2T>C mutation in CYP27A1 gene. Chenodeoxycholic acid replacement therapy was started gradually twice but discontinued due to side effects. Cerebrotendinous xanthomatosis may present with neurologic symptomatology in adults, but the presence of chronic diarrhea, juvenile cataract, and xanthomas at earlier ages should be kept in mind. Early diagnosis and treatment have beneficial results in preventing the emergence of neurologic symptoms as it is a treatable leukodystrophy. Rarely, intolerance to the drug may occur. Early levodopa therapy in patients having dystonia-Parkinsonism will increase patient's quality of life.

Keywords: Cerebrotendinous xanthomatosis/Serebrotendinöz ksantomatozis, leukodystrophy/lökodistrofi, Parkinsonism/parkinsonizm, side effects/yan etki

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is a rare genetic disease with autosomal recessive inheritance. It was first described in 1937. It is a defect in bile acid synthesis caused by mutation of the mitochondrial CYP27A1 gene, a member of the cytochrome 450 gene family which leads to the deficiency of sterol 27-hydroxylase that has a role in bile acid synthesis.[1] This enzyme works in the synthesis of bile acids from cholesterol, especially chenodeoxycholic acid, a process through which the bile acids that help in lipid digestion are produced and cholesterol is excreted from the body. In the deficiency of this enzyme, cholesterol remnants and waste products accumulate in parts of the body such as tendons, lenses, arteries, neurons of medulla spinalis, and brain.[2] It can be classified as both a lipid

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storage disease due to the accumulation of lipids in several organs and a leukodystrophy due to its effects on the white matter of the central nervous system.

The average time of diagnosis is in the fourth decade. The affected individuals have early onset cataracts and diarrhea during childhood and have lipid tumors (xanthomas) on the tendons during adolescence. If the disease is not diagnosed and treated at an early stage, it can lead to progressive neurological signs such as seizures, cognitive complaints, and ataxia. This study presented a 39-year-old patient who was not diagnosed at the time of cataract onset and presented to the clinic with neurological symptoms, which led to the diagnosis of CTX by genetic testing.

CASE PRESENTATION

A 39-year-old female presented to our neurology clinic with complaints of speech difficulty, clumsiness of hand and imbalance that started to progress in the last 2 years. Upon questioning, the history of complaints was discovered to have started at age 22 during which the patient expressed that she had feelings of pulling and contracting on her legs, often leading to falls. The contractions that were causing the falls increased over the years leading to difficulty in walking, causing the patient to use walking aids on one side since age 33 and being able to walk only on fingertips for the last 2 years. Following the interview, it was discovered that in addition to speech difficulty, the patient also had similar contractions on her fingers and elbows leading to clumsiness which were quickly worsening, making the patient unable to perform her daily activities.

Upon neurological examination, mild mental retardation was observed which was expressed to be present since birth. Patient was alert, cooperating, and oriented. The speech was dysarthric and difficult to understand. Retrognathia and elevated palate were observed. Muscle strength in the extremities was normal. Deep tendon reflexes were hyperactive and the plantar reflexes were extensor on both sides. On inspection of face, there was bradymimia accompanied by a need to keep the mouth slightly open and some teeth were visible, leading to a dystonic expression. There was bilateral synkinetic rigidity and bradykinesia on right upper extremity. Foot tapping amplitude decreased on both sides, being more apparent in the right extremity. There was a marked elevation of the longitudinal arc of the feet and the patient could walk only on fingertips, leading to steppage gait and the steps were narrow and slow, without associating arm movements. The gait was observed to be ataxic and dystonic. Postural instability was present. There was no complaint of sphincter dysfunction or constipation. There were no tendon xanthomas on inspection.

On history of past illnesses, the patient who was dependent on her family for daily activities was said to have mental retardation, hypertension, and vitamin B12 deficiency which were constantly treated. There was a history of bilateral cataract surgery at age 15. There was neither history of cigarette or alcohol consumption nor a history of drug abuse. On examining the family history, the parents were expressed to be from the same village, but there was no familial relation. There was no history of similar disease in any family member on both sides.

Upon laboratory tests, the patient's hemogram and blood biochemistry were within normal ranges. The serum cholesterol levels were normal but serum cholestanol levels could not be evaluated. Vitamin E level was observed to be normal with a value of 1.68 mg/dL with a normal range of 0.5-1.8 mg/dL. Although serum copper and 24-hour urine copper levels were slightly high, they were below the levels that could indicate Wilson's disease (2 µg/mL [0.75-1.45 µg/mL] and 84 µg [<100 µg], respectively). On detailed evaluation, the viral serology was negative. Extensive vasculitis panel, paraneoplastic panel, and tumor markers were measured and autoimmune antibodies were screened; the results for all of them were not determined to be positive. With all these findings, low vitamin B12 levels (369.5 pg/mL under constant replacement), early onset cataracts, dystonia, ataxia, and Parkinsonism could be signs of hyperhomocysteinemia , but under evaluation, there were no supportive findings for such a diagnosis.

On patient's electroencephalography, there was mild-medium bioelectrical disruption. On brain magnetic resonance imaging (MRI), there was hyperintensity on bilateral cerebellar dentate nuclei on T2-weighted and FLAIR imaging (Figures 1 and 2). Mesencephalon was observed to be normal, cerebellar folliae and cerebral sulci were marked relative to patient's age, and the fourth ventricle was observed to be wide (Figure 3).

With a preliminary diagnosis of sporadic Friedrich's ataxia, a genetic analysis was ordered, but the polymerase chain reaction method for the Frataxin gene showed a normal length of GAA repeat sequence. For other preliminary diagnoses of spinocerebellar ataxia, dopa-responsive dystonia, and cerebrotendinous xanthomatosis, whole-exon sequencing, bioinformative analysis, and Sanger sequencing tests were ordered. CYP27A1 gene showed a homozygous 1476+2T>C mutation. The same mutation was observed to be heterozygous in both parents. The family tree is shown in Figure 4.

For the extrapyramidal symptoms, early levodopa+benserazide treatment started at 100 mg/25 mg dose in tablet form, titrated slowly to 3 times a day. Under said treatment, the patient's dystonic posture

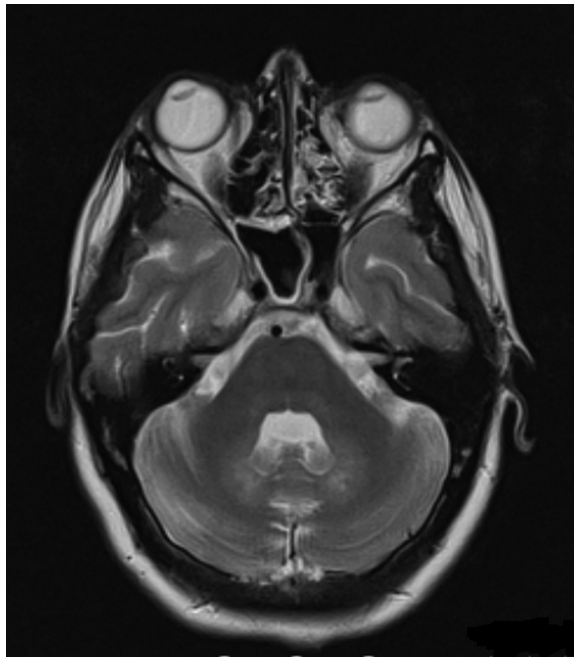

Figure 1. Increased signal in both cerebellar dentate nuclei in T2-weighted examination in cranial magnetic resonance imaging.

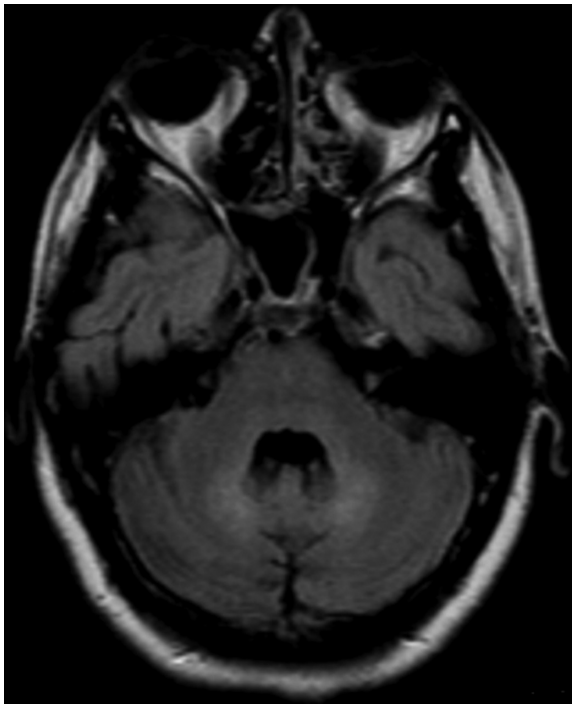

Figure 2. Increased signal in both cerebellar dentate nuclei in FLAIR examination in cranial magnetic resonance imaging.

on hands, bradykinesia, and ataxia were improved by up to 50% of original levels and the speech became understandable. The patient became semi-independent, being able to eat, sit, stand, brush her teeth, and wash her hands without assistance. With the confirmation of cerebrotendinous xanthomatosis diagnosis via genetic testing, the patient was to be started on chenodeoxycolic acid replacement of 750 mg/day and statin group 3-hydroxy 3-methyl glutaryl CoA (HMG-CoA) reductase inhibitor 20 mg/day, but the patient did not accept the second medicine. Chenodeoxycolic acid was started at 1 tablet per day dosage, but the family reported via phone call the complaints of confusion and agitation on the second day of treatment, leading to the decrease in dosage to half a tablet per day. These symptoms persisted and increased to aggression, shouting, and intolerability, and the patient was admitted to psychiatry emergency department. Upon examination, the psychiatric doctor discontinued

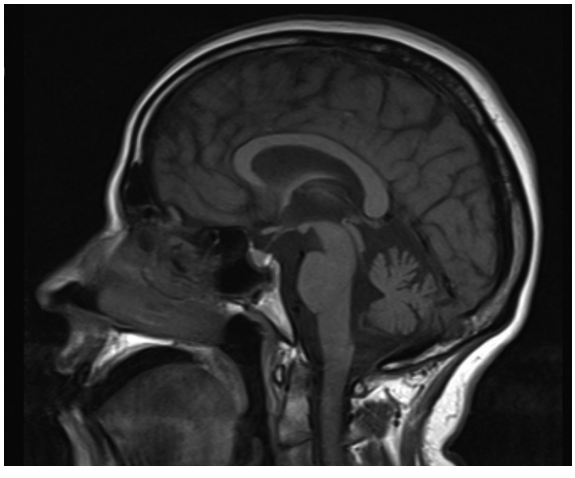

Figure 3. Large fourth ventricle with cerebellar and cerebral atrophy.

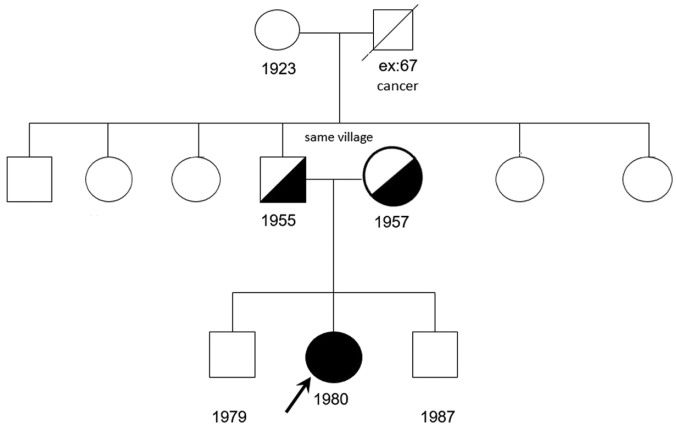

Figure 4. Family tree.

the levodopa+benserazide and chenodeoxycolic acid treatments and started the patient on aripiprazole 10 mg/day. The family discontinued aripiprazole due to sedation side effects. Following this, the treatment of chenodeoxycolic was restarted at quarter tablets and then reduced to quarter tablets every other day, but similar side effects were present in even such small doses. Despite being efficient in decreasing patients' contractions and dystonia, chenodeoxycolic treatment could not be continued due to side effects. The patient was restarted on levodopa+benserazide treatment and it was reported that there were no side effects and that it was the most efficient treatment for the patient and so it was continued.

DISCUSSION

Genetic leukodystrophies, especially those presenting in adulthood, comprise a different group of neurodegenerative diseases.[3] It should be known that patients who demonstrate cerebral and cerebellar white matter lesions and present with cognitive decline, ataxia, and movement disorders have many significant and treatable diseases. The overlap of majority of the clinical findings may cause difficulty in diagnosing, but a well-constructed differential diagnosis approach makes it possible to diagnose rare white matter diseases. Thus, the early diagnosis of treatable genetic diseases can prevent the emergence of additional complaints and permanent neurological damage.

In patients with white matter involvement, the exclusion of acquired leukodystrophies is a must. Routine biochemical tests and infectious markers must be evaluated, such as human immunodeficiency virus, syphilis, hepatitis B, hepatitis C, and tuberculosis. In immunocompromised patients, the cerebrospinal fluid (CSF) should be examined for John Cunningham (JC) virus. Vasculitides (such as systemic lupus erythematosus) or drug and substance abuse should be investigated. Tumors, use of chemotherapeutics (such as 5-fluorouracil or methotrexate), history of radiotherapy, and paraneoplastic syndromes must be excluded.[4]

Following the exclusion of acquired leukodystrophies, priority must be placed on hereditary metabolic diseases. The number of hereditary metabolic leukodystrophies that begin in adulthood and can be easily diagnosed with clinical tests is few; these being very long chain fatty acids (for the diagnosis of X-linked adrenoleukodystrophy in males), specific leukocyte enzyme activities (for diagnosis of Krabbe's disease [galactocerebrosidase] and metachromatic leukodystrophy [arylsulphatase-A]), serum cholestanol and urine bile

alcohols (for CTX), and serum aminoacid levels (for the diagnosis of methylenetetrahydrofolate reductase deficiency, hyperhomocystei nemia, and homocystinuria).

CTX is a disease that is caused by the accumulation of cholestanol in serum and tissues due to loss of function of sterol-27-hydroxylas e enzyme as a result of CYP27A1 gene mutation and is characterized by chronic diarrhea, bilateral juvenile-onset cataracts, tendon xanthomas, and neurologic dysfunction findings.[5] The most common symptoms are mental retardation, early onset dementia, autistic behaviors, behavioral and psychiatric problems, ataxia, movement disorders, and seizures. In our case, symptoms typical of CTX, chronic diarrhea, and tendon xanthomas were not present. However, bilateral juvenile cataracts and mental retardation were present. Movement disorders that are markedly present in our case were reported as being seen in CTX and were associated with postsynaptic iron accumulation.[6] There are positive examples in literature regarding the efficiency of levodopa treatment[7] and it was seen to be effective in our case as well.

Typically, in CTX, there are elevated levels of cholestanol in plasma, CSF, and bile, along with xanthomas. The increase in bile alcohol can also be used as a secondary diagnostic tool. In CSF studies, the levels of cholesterol, cholestanol, apolipoprotein B, apolipoprotein A1, and albumin are elevated.[5] In brain MRI, the most diagnostic finding is the bilateral hyperintensity of the cerebellar dentate nuclei and the surrounding white matter in T2-weighted and FLAIR MRI. Additionally, cerebral and cerebellar atrophy and spinal white matter lesions may be present. In our case, while the serum cholestanol and urine bile alcohols could not be evaluated, the typical MRI findings were present.

Cerebrotendinous xanthomatosis is of importance among leukodystrophies due to its possibility of treatment. It is possible to prevent many neurological symptoms with early diagnosis and early treatment. After the neurological symptoms have developed, according to the severity of the illness, it may still be possible to halt the progression of the disease and sometimes even reverse some of the symptoms.[8] Chenodeoxycholic acid is the preferred treatment method as it inhibits the 7α-hydroxylase enzyme.[9] The use of HMG-CoA reductase inhibitors (statins) along with chenodeoxycholic acid can be more efficient in reducing cholestanol levels. Our patient did not have access to statins due to normal blood cholesterol and the use of chenodeoxycholic acid was not possible due to overwhelming and extraordinary psychiatric side effects. A rare disease was diagnosed, but the replacement treatment failed due to side effects. Serious side effects from this treatment are rare. Comparing the 2 retrospective cohort studies on CTX with 35 and 28 patients, there were 26 patients (74.3%) with side effects of which 7 were serious side effects and the other had 9 patients (32.1%) with side effects, with one of them being serious enough to stop the treatment.[9]
The aim of this case report was to emphasize the importance of investigating levodopa efficiency in early stages of the disease and the persistence of following with further diagnostic assessment in presence of ataxia accompanied by Parkinsonism and dystonia. Genome-wide association study(GWAS) is an important diagnostic method in selected cases in which the etiology could not be determined. The importance of following some MRI findings in leukodystrophy suspicion to lead toward persistent evaluation to find treatable causes is underlined. Cerebrotendinous xanthomatosis can present with adult-onset neurological symptoms, but the presence of chronic diarrhea, bilateral juvenile cataracts, and xanthomas should be kept in mind and questioned. The evaluation of plasma cholestanol levels can lead to the diagnosis and satisfying results can be achieved with chenodeoxycholic acid replacement therapy. In the presence of Parkinsonism, levodopa treatment must be tried.

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