

Cerebrotendinous xanthomatosis with a novel mutation in CYP27A1 gene in a Turkish patient

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Abstract

Cerebrotendinous xanthomatosis (CTX) is a rare genetic metabolic disorder that inherited in an autosomal recessive trait, characterized by abnormal lipid storage. CTX is characterized by infantile or early childhood onset of chronic diarrhea, tendon xanthomas (especially in the achilles tendon), cataracts, and neurological symptoms such as cognitive impairment, pyramidal, extrapyramidal and cerebellar signs, seizures, peripheral neuropathy that appear in the second or third decades of life. A thirty-nine years old Turkish female patient admitted to the Neurology outpatient clinic with the complaint of increasing dizziness and walking difficulty in recent years. She had an operation for both achilles tendon xanthomas and juvenile cataract. Her neurological symptoms and cranial magnetic resonance imaging (MRI) findings were consistent with cerebrotendinous xanthomatosis. A novel homozygous splicing site mutation (IVS8+2T>C, c.1476+2T>C, NM_000784.3) in CYP27A1 gene was detected. This is the first CTX related mutation reported in the literature.

Keywords: Cerebrotendinous xanthomatosis (CTX); CYP27A1; cholestanol; novel mutation

INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive lipid storage disorder. CTX is caused by a mutation in the CYP27A1 gene, which encodes the sterol-27-hydroxylase enzyme, which converts cholesterol to cholic acid and chenodeoxycholic acid (CDCA) (1). This mutation causes an increase in serum cholesterol and cholestanol. Cholestanol accumulates in blood and organs such as central nervous system, eyes, tendons and vessels due to this enzyme deficiency. CTX is characterized by early childhood onset chronic diarrhea, tendon xanthomas that especially in the achilles tendon, cataracts, and neurological symptoms such as cognitive impairment, pyramidal, extrapyramidal, cerebellar signs, seizures, and peripheral neuropathy (2). We present clinical and radiological findings of a late diagnosed a Turkish female CTX patient with a novel mutation in CYP27A1 gene.

CASE REPORT

The 39 years old female Turkish patient with non-consanguineous parents was admitted to Neurology outpatient clinic with the complaints of dizziness and walking difficulty. There was no family history of this disorder. She was capable of self-care until the last year, with the exception of basic requirements like drinking, eating and using the toilet. Painless masses on her Achilles tendons were detected and operated two times at the age of 37. She had a juvenile cataract operation at the age of 11. Her physical examination was normal other than tuberous xanthomatosis and operation scars for xanthomas on her achilles tendons. She has high arc palatine. Beck Depression Inventory (BDI; 32/63), mini mental state examination (MMSE; 23/30), Kent Emergency Scale (Kent E-G-Y; IQ score 70-80) and Addenbrooke's Cognitive Examination Revised (ACE-R; 60/100) were performed. ACE-R scores were as follows:

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attention/orientation (17/18), memory (11/26), fluency score (5/14), language (20/26), visuospatial (7/16) domain. These tests indicated limited intelligence, major depression and cognitive impairment. Neurological examination revealed 4/5 quadriparesis, bilateral rigidity in both upper and lower extremities, rest tremor in the left hand, mask face, increased deep tendon reflexes, bilateral extensor plantar reflex, bilateral dysmetria, dysdiadochokinesia and positive heel-knee-shin test. She is able to rotate in bed from lying to sitting without support. She needs assistance to stand up while in sitting position. She is able to walk for a short distance with assistance. Her functional capacity is limited according to the Berg balance scale (9/56) and functional ambulation scale (1/5). The functional independence scale (56/126) was also limited.

Laboratory tests were normal other than serum cholestanol level of 3.319 mg/dL (0.045-0.375). Electromyography was consistent with sensorimotor polyneuropathy in the lower extremities. Cranial MRI revealed bilateral symmetrical hyperintense lesions in flair sequence in the cerebral deep white matter bilaterally, and in the dentate nucleus of the cerebellum (Figure 1). Dual energy x-ray absorptiometry findings (lumbar total T score: -1.4, Z score: -1.2, femur neck T score: -1.4, Z score: -1.1) were consistent with osteopenia.

CYP27A1 gene sequence analysis calculation was performed for diagnosis by using MiSeq next generation sequencing (NGS) platform which is a FDA approved

diagnostic system (Illumina, San Diego, CA, USA). Genomic DNA was isolated according to the commercial kit procedure from blood sample (QIAamp DNA Blood Midi Kit, Germany). We have been amplified all nine exons of the CYP27A1 gene and their flanking splice site junctions with PCR primers, by using PRIMER® – Primer Designer software package v.2.0 . (Scientific & Educational Software program). After the PCR, libraries were performed by using the NexteraXT kit (Illumina Inc.). Next-gene sequencing was carried on MiSeq (Illumina Inc.). Sequences were aligned to the hg19 genome within MiSeq Reporter software (Illumina Inc.). Data was documented with IGV 2.3 (Broad Institute) software. Sequence data revealed a novel homozygous splicing site mutation (IVS8+2T>C, c.1476+2T>C, NM_000784.3) in CYP27A1 gene (Figure 2). In silico analysis software like mutation taster and human splicing finder revealed a very close relationship with the disease.

The patient was treated chenodeoxycholic acid 1000 mg/day, calcium and vitamin D for both treatment of primary disorder "CTX" and osteopenia, in addition to levodopa (400 mg per day) and baclofen (30 mg per day) for extrapyramidal and pyramidal symptoms. Physical therapy and rehabilitation improved the patient's functional capacity. She got started to walk for a short distance without assistance, her functional ambulation scale (3/5), functional independence scale (94/126) and Berg balance scale (42/56) increased, extrapyramidal signs decreased and self-care improved after 1 year follow-up.

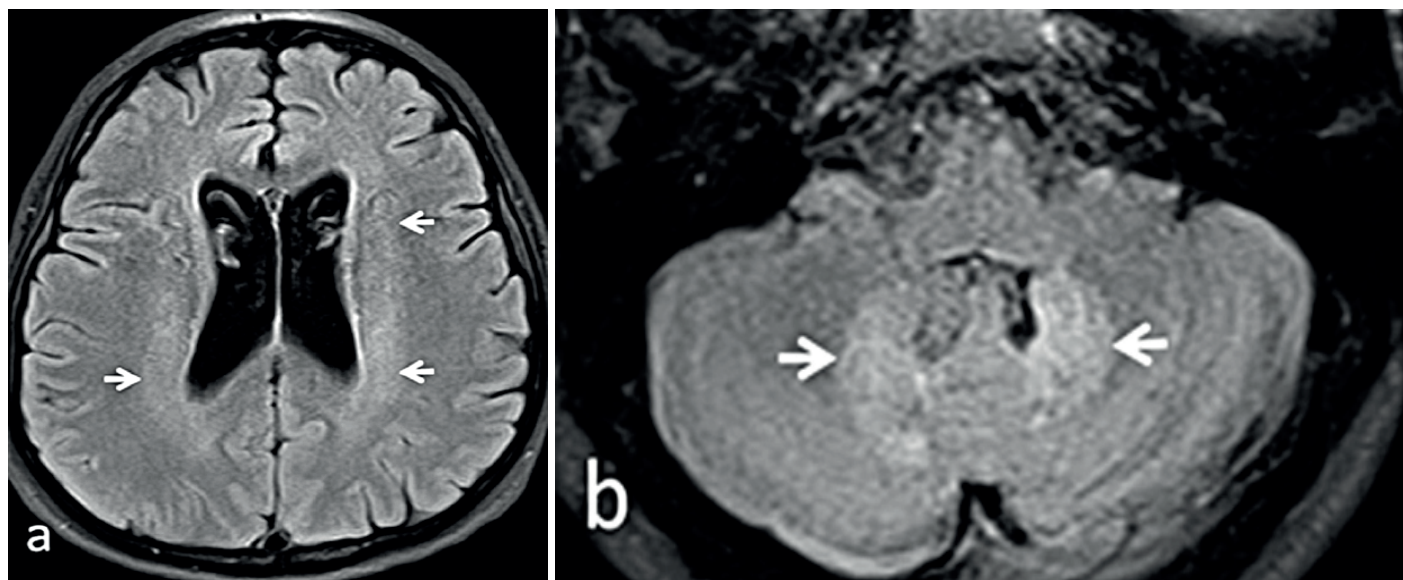


Figure 1. Axial FLAIR MR Image shows bilateral symmetrical hyperintense lesions in the frontal and parietal lobe deep white matter (a) and dentate nucleus of the cerebellum (b) consistent with cerebrotendinous xanthomatosis



Figure 2. A novel homozygous splicing site mutation (IVS8+2T>C, c.1476+2T>C, NM_000784.3) in CYP27A1 gene

DISCUSSION

CTX could be diagnosed with clinical features, biochemical tests, radiological findings and genetic analysis (3). Diagnosis could be difficult due to diversity in clinical presentation. Therefore, it is thought that epidemiological studies do not show the exact prevalence. CTX is more common in female individuals and its prevalence is estimated to be 3-5:100,000 in the USA (3). Some suggestions have been made to overcome CTX underdiagnosis. Metabolic screening was proposed to diagnose CTX in the presence of two of four clinical symptoms like premature cataracts, tendon xanthomas, intractable diarrhea, progressive neurological symptoms and signs such as pyramidal signs, low intelligence, cerebellar signs, and polyneuropathy (4). In another study, suspicion index based flow chart which could provide early diagnosis before neurological complications occur has been developed. The indicators are categorized such as very strong (e.g., family history), strong (e.g., juvenile cataract, child-onset chronic diarrhea, neurological and neuroimaging findings), moderated indicators (e.g. early osteoporosis, epilepsy, parkinsonism) and scored. Serum cholestanol level assessment is proposed if total score is ≥ 100 . CYP2A1 gene analysis, which is the diagnostic gold standard, is recommended in the presence of high cholestanol level or the score is ≥ 200 with one very strong or four strong indicators (5). One very strong (tendon xanthomas), 3 strong (juvenile cataract, dentate nuclei signal alterations at MRI, intellectual and psychiatric disturbances) and 2 moderate indicators (parkinsonism and polyneuropathy) were present in our patient and SI score calculated as 300. Then serum cholestanol level measurement and molecular genetic analysis were

performed. We observed an adult patient with a late-onset CTX harboring a novel mutation in the CYP27A1 gene. In various studies performed to date, different mutation types at different rates have been reported in all 9 exon of CYP27A1 gene (6,7). While approximately 50% of these mutations are located in exon 6-8 regions, and a smaller proportion of mutations are defined in exon 2 and 4 regions (6). A novel homozygous splicing site mutation (IVS8+2T>C, c.1476+2T>C, NM_000784.3) in CYP27A1 gene was detected in this patient. This is the novel CTX related mutation reported in the literature.

CTX is a rare etiology of osteoporosis (8). Although our patient was 39 years old, she has osteopenia. CTX could be diagnosed in adulthood although initial symptoms occur in childhood. As a result, in the presence of infantile onset diarrhea, juvenile cataract, tendon xanthomas and neurological symptoms in multiple areas such as cognitive, pyramidal, extrapyramidal, cerebellar, peripheral nerve CTX should be considered in the differential diagnosis, so delay in diagnosis, inadequate treatment and systemic complications that may occur in the future can be prevented.

Conflict of interest: The authors declare that they have no competing interest.

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Patient informed consent: The patient approval was received for this case report and she signed informed consent form.

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