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Egypt J Neurol Psychiatry Neurosurg (2023) 59:52
https://doi.org/10.1186/s41983-023-00644-4

The Egyptian Journal of Neurology, Psychiatry and Neurosurgery

REVIEW

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Case of cerebrotendinous xanthomatosis with giant xanthomas and literature review

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Abstract

Introduction Cerebrotendinous xanthomatosis (CTX) is a rare autosomalrecessive disease that occurs as result of mutation in the CYP27A1 gene. Theclinical presentation of the disease is quite wide. We planned to brieflyreview the literature with this case diagnosed as a CTX.

Case A 50-year-old male patient was admitted to the neurologyoutpatient clinic complaining of progressive worsening of his walking, andswelling in his legs. Mild mental retardation was detected in our patient. Inaddition to the visual impairment that would be explained by cataracts, he hadxanthomas in both lower extremities. Signs related to bilateral cataractsurgery and intraocular lens were detected during an eye examination. Therewere no abnormal findings in electroencephalography, electroneuromyography, andbrain magnetic resonance imaging of the patient, whom we learned that hervisual impairment started in childhood. The Mignarri Suscipion Index index wascalculated as 275. A genetic examination was requested and the CYP27A1 gene wasp.A216P (c.The mutation 646G>C) (CM044609) was detected as homozygous.

Conclusion Due to the lowawareness of CTX and the variability of its clinical findings, its diagnosis maybe delayed for years, as in our patient. When diagnosed, most patients may havesevere, often irreversible neurological damage. With the early recognition ofthe CTX and the start of treatment, patients can have a chance to quality life.

Keywords Cerebrotendinous xanthomatosis, Xanthomatosis, Cholestanol, Osteoporosis, Juvenile bilateral cataract, CYP27A1 gene

Introduction

Cerebrotendinous xanthomatosis (CTX) is a rare autosomal recessive disease that occurs as a result of a mutation in the nine-exon CYP27A1 gene on the long arm of the second chromosome; CTX is an autosomal recessive disorder with an adjusted global prevalence of about 1:86,000 [1].

The clinical presentation of the disease is quite wide. Even if the diagnosis is delayed until adulthood, many clinical symptoms with age can make many diseases come to mind in differential diagnosis; jaundice, refractory diarrhea, cholestasis, juvenile cataracts, tendon xanthoma, osteoporosis, coronary heart disease, mental retardation, pyramidal, cerebellar and extrapyramidal signs, epilepsy, progressive myelopathy are located in the rich symptomatology of the disease [2]. CTX is one of the rare diseases, whose progression can be significantly prevented by starting treatment early [3]. We planned to briefly review the literature with this case diagnosed as a CTX.

Case

A 50-year-old male patient was admitted to the neurology outpatient clinic complaining of progressive worsening of his walking, and swelling in his legs. In the patient's family history, it was learned that his grandfathers were siblings. Three of the five brothers had died

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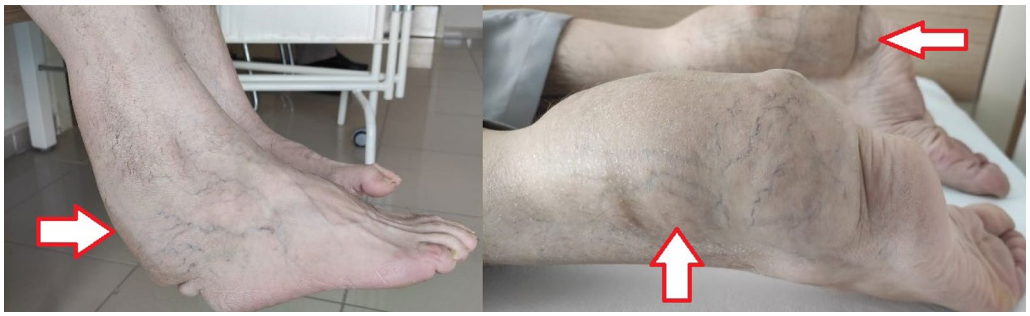

Fig. 1 Distal xanthomas of the bilateral lower extremities

in middle age. Therefore, we could not perform the necessary examinations and tests the other siblings of the patient. We were able to learn the findings of the other siblings based on the information that we received from the first brother. It was learned that the first sibling was 60 years and healthy. The second brother had died due to sepsis at the age of 40. According to the information received, it was learned that he had mental retardation, cataracts in both eyes, and swelling in the distal lower extremities, as in our patient. The third sibling was our

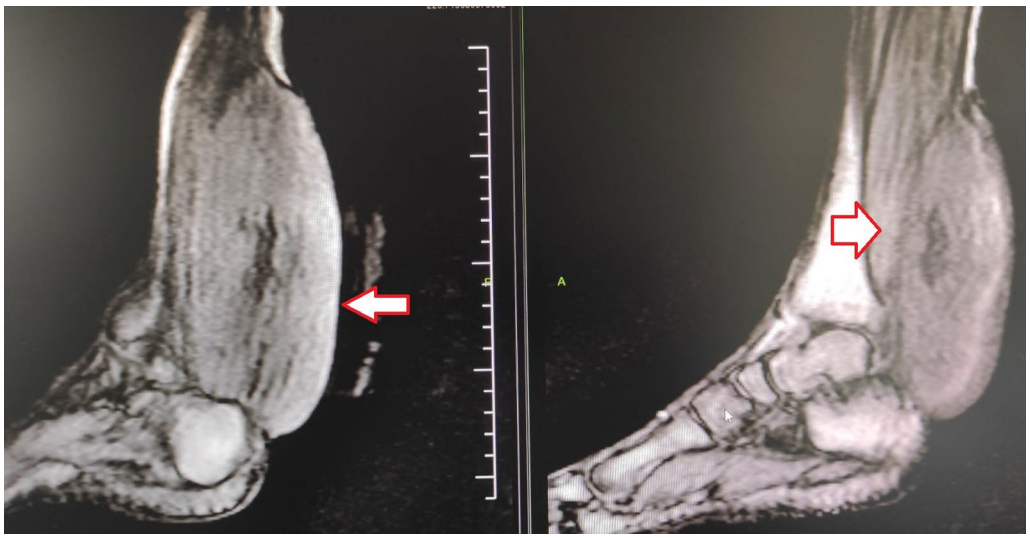

Fig. 2 Xanthomas on MRI of the lower extremities

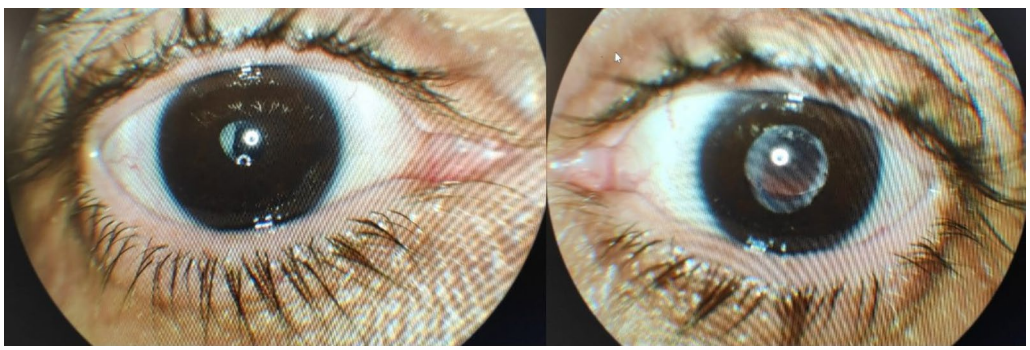

Fig. 3 Signs of bilateral cataract surgery and intraocular lens

patient. The fourth sibling had died at the age of 50 due to a traffic accident. This sibling had bilateral cataracts, xanthoma in both lower extremities, gait imbalance (ataxia), a history of generalized tonic–clonic seizures and had used antiepileptic treatment for epilepsy. The fifth sibling had a history of cataracts in both eyes, mental retardation, epilepsy, and xanthomas in both lower extremities. According to the anamnesis taken from the family, was learned that he died due to status epilepticus. Three brothers with symptoms had a Mignarri Suscipion Index (MI) score above 200. However, since these brothers died, the necessary diagnostic tests could not be performed. The intellectual and socioeconomic level of the family was very low, so it was very difficult for us to get an anamnesis.

The Wechsler Adult Intelligence Scale-R (WAIS-R) test results of our patient were between 76 and 89 and were consistent with the lower limit intelligence deficiency and mental retardation in our patient had been detected since childhood. On Physical examination of the patient, he had xanthomas in both lower extremities (Fig. 1). Xanthomas were detected on magnetic resonance imaging (MRI) of the lower extremities (Fig. 2). Signs related to bilateral cataract surgery and intraocular lens were detected during eye examination (Fig. 3). No abnormal findings were detected in the electroencephalography and electroneuromyography, pelvic and abdominal ultrasound, routine blood test, brain MRI of the patient. Bone mineral density was consistent with osteoporosis, more prominent in the lumbar region. The T score in the lumbar region was significantly lower with a value of -2.8. The MI index was calculated as 275. A genetic examination was requested and the CYP27A1 gene p.A216P (c.The mutation 646G > C) (CM044609) was detected as homozygous. After diagnosis, kenodeoxycholic acid (CDCA) was started at a dose of 500 mg/day. The rehabilitation and medical treatment process of the patient continues. A brief summary of all siblings with clinical features of the disease is shown in the table (Table 1).

Discussion

The pathogenesis of CTX is related to mutations in the CYP27A1 gene, which can decompose the original sterol-27 hydroxylase, reduce the activity of cholesterol synthesis of bile acids, and cause cholesterol metabolism disorders in different tissues [4]. A genetic epidemiological study (ExAC) found different incidence rates on different continents [5]. In a multicenter study conducted in Turkey, CTX was diagnosed in 7 of 452 patients (1.55%) with bilateral juvenile cataracts [6]. In addition to the suspicion of the disease with MI, the detection of mutations in the CYP27A1 gene confirms the diagnosis of CTX. The MI was revealed in 2014. In addition to early diagnosis with this index, early initiation of treatment positively affects the prognosis. The MI facilitates the diagnosis with ratings given to very strong, strong, and moderately strong markers. In this index, a total score $\geq$ 100 warranted serum cholestanol assessment. Elevated cholestanol or a total score $\geq$ 200, with one very strong or four strong indicators, warranted CYP27A1 gene analysis [7]. In addition to many clinical signs, the high MI, and the presence of family history made it easier for us to confirm our definition with a genetic test. The family had not previously been evaluated in detail for possible genetic diseases, and the other siblings had been followed up with symptomatic treatments. Although genetic testing is the gold standard, the primary biochemical test used to diagnose CTX is to look for cholestanol in the blood. The fact that the plasma cholestanol level is 5–10 times more

Table 1 Brief summary of all siblings with clinical features of the disease

Case	Age of death	Clinical features	Mignarri Suscipion Index	Genetic test
Second brother	40	According to the information received, it was learned that he had mental retardation, cataracts in both eyes, and swelling in the distal lower extremities	350	There had been no genetic testing
Our case	He is alive	He had xanthomas in both lower extremities,bilateral cataracts,osteoporosis and he was mental retardation	275	A genetic examination was requested and the CYP27A1 gene p.A216P (c.The mutation 646G > C) (CM044609) was detected as homozygous
Fourth brother	50	This sibling had bilateral cataracts, xanthoma in both lower extremities, gait imbalance (ataxia), a history of generalized tonic–clonic seizures	375	There had been no genetic testing
Fifth brother	48	This sibling had a history of cataracts in both eyes, mental retardation, epilepsy, and xanthomas in both lower extremities	375	There had been no genetic testing

than normal is highly specific for the diagnosis of CTX [8]. Apart from this, among the biochemical findings in patients; significantly low CDCA and cholic acid levels, high bile fatty alcohols and conjugates in bile, urine, and plasma, elevated cholestanol and apolipoprotein b levels in cerebrospinal fluid can be detected due to the deterioration in primary bile acid synthesis [9–11]. Due to the presence of a genetic diagnosis, these examinations did not need to be performed for our patient. Due to the low awareness of the CTX and the variability of its clinical manifestations, the diagnosis may extended until the third decade or, as in our patient, to the fifth decade [8]. We believe that the quality of life can be significantly improved with treatment and that the awareness of this disease by clinicians should increase.

The clinical features of the disease can be studied in a wide range with systemic involvement.

Gastrointestinal system: chronic diarrhea in the infantile and neonatal period and cholestasis in the neonatal period are early clinical manifestations [12, 13].

Ocular manifestations: ocular manifestations include palpebral xanthelasmas, juvenile bilateral cataracts, optic nerve atrophy and proptosis, optic disc pallor, retinal vascular sclerosis and premature retinal senescence, cholesterol-like deposits along vascular and myelinated nerve fibers [14]. Three other brothers of our patient also had a history of cataracts.

Xanthomas and skeletal system ınvolvement: xanthomas generally appear in the second or third decade. Tendon xanthomas most often affect the achilles tendon, although xanthomas may also develop on the fingers, tibial tuberosities, triceps, and plantar surfaces of the feet. Xanthomas also have been reported in the lung, bones, and central nervous system [15].

Osteoporosis and increased bone fractures are CTX-associated systemic manifestations. Teenage CTX patients could have early osteoporosis and a history of bone fracture. Skeletal deformities including kyphosis, pectus excavates, pes equinovarus, and pes cavus was found in CTX patients [8, 16]. All other siblings, except the first sibling, had a history of xanthomas, but it was learned that these xanthomas were not as large as our patient.

Cardiovascular system and pulmonary involvement: coronary artery disease, mitral valve insufficiency, myocardial infarction, abdominal aortic aneurysm, lipomatous hypertrophy of the atrial septum, atherosclerotic changes in the coronary and carotid arteries can be seen in CTX patients [2, 8].

Elevated levels of cholestanol in bronchoalveolar lavage fluid as well as in serum have been reported in CTX patients without pulmonary symptoms, or radiological and pulmonary function abnormalities [17]. No abnormal findings related to the cardiovascular and respiratory systems were detected in the examinations performed on our patient.

Neuropsychiatric manifestations: intellectual disability is the most common neurological symptom in CTX patients. Developmental, mental retardation, and learning difficulties in childhood are important in the early diagnosis of CTX. A progressive decline in cognition may begin in adolescence and early adulthood [18–20]. In the second and third decades, pyramidal and cerebellar signs begin to appear. Clinical manifestations are manifested by the involvement of the corticospinal tract, subcortical white matter, and dentate nuclei. Pyramidal findings often accompany cerebellar findings. Among the cerebellar findings seen are ataxia, dysarthria, and nystagmus [21, 22]. Extrapyramidal manifestations can be considered a late disease manifestation, with parkinsonism the most frequently reported, followed by dystonia, myoclonus, and postural tremor [8]. Asymptomatic or severe polyneuropathy symptoms are observed in CTX patients. When we examined the literature, it was observed that motor findings prevailed more predominantly [23–25). There were no abnormal findings in electrophysiological tests in our patient.

MI is one of the diagnostic clues in epilepsy. Different rates of epilepsy have been detected in CTX patients. Although it often starts in the early stages of the disease, it can occur at any stage of the CTX patient's life [1, 18, 20]. Although his brothers had epilepsy, our patient had no history of epileptic attacks.

MRI is one of the key parts of the diagnostic process. Many anatomical areas have been reported to be affected by MRI for CTX, and it may be useful to explore these findings thoroughly to identify typical and common MRI features of CTX. The most distinctive neuroradiological findings are signal hyperintensities on T2-weighted and/or FLAIR images in the dentate nuclei and adjacent cerebellar white matter [2]. MRI also gives an idea of the prognosis. Cerebellar vacuolation has been recently indicated as a marker of a poor prognosis in CTX, while the absence of dentate nuclei signal alteration is considered an indicator of a better prognosis [26]. The fact that imaging examinations were normal in our case may explain why the prognosis was better than that of his brothers.

The diagnosis of CTX is mainly based on clinical suspicion, laboratory and imaging findings, and molecular genetic analysis. Differential diagnosis of CTX differs substantially according to presenting symptoms. In differential diagnosis, familial hypercholesterolemia, sitosterolemia, cerebellar ataxia, spinocerebellar atrophy, multiple system atrophy, and Marinesco–Sjögren syndrome are clinical conditions that should be kept in mind [27–29].

CDCA has been approved as a first-line treatment for CTX. Assessment of cholestanol levels may be useful in monitoring patient adherence to treatment. However, it should be noted that a decreased level of cholestanol does not necessarily suggest a good prognosis [30]. Early treatment is essential to reverse neurological symptoms. A retrospective cohort study showed that CDCA was generally effective and acceptable for safety, with disease signs and symptoms improved, alleviated, or stabilized in most patients an average of 9.9 months after treatment [31, 32].

Conclusions

Due to the low awareness of CTX and the variability of its clinical findings, its diagnosis may be delayed for years, as in our patient. When diagnosed, most patients may have severe, often irreversible neurological damage. With the early recognition of the CTX and the start of treatment, patients can have a chance to quality life.

Abbreviations

CTX	Cerebrotendinous xanthomatosis
MRI	Magnetic resonance imaging
CDCA	Chenodeoxycholic acid
MI	Mignarri Suscipion Index

Acknowledgements

Not applicable.

Author contributions

SE analyzed and interpreted the patient data regarding the emg and laboratory findings, collecting data, and analyzing data. GC was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

No funding was received for this research.

Availability of data and materials

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its additional files.

Declarations

Ethical approval and consent to participate

This review conducted by following STROBE guidelines for reporting observational studies (www.strobestatement.org) and the Declaration of Helsinki. Ethical approval is not required for this literature review in Turkey. Participant gave his informed consent for this study.

Consent for publication

All authors gave their informed consent for publication of the article.

Competing interests

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non financial interest in the subject matter or materials discussed in this manuscript. There is no competing interests.

Received: 29 July 2022 Accepted: 10 March 2023
Published online: 18 April 2023

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