Cerebrotendinous xanthomatosis: a rare and multisystemic disease still little known. When should we suspect?

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ABSTRACT
Cerebrotendinous xanthomatosis (CTX) is a rare, multisystemic autosomal-recessive disease of biliary acid metabolism that leads to accumulation of cholesterol intermediates in multiple tissues. Its primary presentation is progressive and irreversible neurological damage, beginning in childhood and progressing to neurological dysfunction in adulthood. There also are characteristic non-neurological symptoms, including tendinous xanthomas, cataracts beginning in childhood, and chronic infantile diarrhea. In Brazil, there is no available treatment for CTX. The primary therapeutic approach to slow disease progression is a palliative one, with multidisciplinary team. While CTX symptoms begin in childhood, most patients are diagnosed at approximately age 16, when neurological damage is extensive and therapeutic approaches are no longer effective. Here, we report a case of a 47-year-old female patient with CTX with symptoms beginning in childhood, with neurological worsening at the age of 38 and diagnosis at 44, at which neurodegeneration was already severe and irreversible. Laboratory tests and magnetic resonance imaging indicated characteristic symptoms. It is important to consider CTX as a differential diagnosis in the presence of a progressive, wide, and varied neurological picture, with tendinous xanthomas and other specific symptoms. Because it is a chronic and degenerative disease, early diagnosis is essential to establish measures to improve the quality of life.

Keywords: Neurology, Neuromuscular diseases, Neurodegenerative diseases, Rare diseases.

INTRODUCTION
Cerebrotendinous xanthomatosis (CTX) is an autosomal-recessive disease involving biliary acid metabolism, caused by mutations in the gene encoding the cytochrome P450 sterol 27-hydroxylase, CYP27A1). Mutations lead to reduced production of quenodesoxicholic acid and accumulation of cholestanol and cholesterol in multiple tissues, especially in the nervous system, eyes, and tendons. There is no consensus from available data on the prevalence of CTX, but best estimates are less than 5/100,000 worldwide. However, the incidence of CTX may be substantially higher than current estimates, due to the difficulty of diagnosis and the lack of knowledge of societal and health professionals.

Patients with CTX present with a wide variety of neurological and non-neurological symptoms that can occur in childhood, youth, or adulthood. Neurological symptoms are the most common; they include changes in both the central (CNS) and peripheral (PNS) nervous systems. In addition to neurological manifestations, CTX may have more systemic symptoms, with primary non-neurological presentations including tendinous xanthoma, infantile cataracts, and chronic, childhood-onset diarrhea. It is necessary to recognize these characteristics because early diagnosis is important for improving both treatment and prognosis.

As CTX is a rare disease, there a limited number of cases are encountered in most health centers. Therefore, it is essential that clinicians analyze case reports and literature reviews. Therefore, our objective is to provide a CTX case report and provide a brief review on the clinical characteristics and possible pathological mechanisms of other reported cases. Because it is a rare disease, CXT is often ne-
glected and patients may undergo unnecessary tests and treatments.

**CASE REPORT**

A 29-year-old female patient presented with progressive parkinsonism. At the age of 38, she had been diagnosed with Parkinson’s disease and treated with levodopa with little response. After a few months, the patient evolved with spastic tetraparesis and dementia, this time being made the diagnosis of multiple system atrophy.

In the following 6 years, the patient suffered from aphasia, dementia, cervical dystonia, behavioral control, and sphincter control, needing diapers. She also suffered from severe oropharyngeal dysphagia, causing significant weight loss. She had earlier presented with infantile cataracts and multiple seizures. There was no history of consanguinity and similar symptoms in the family.

The physical exam revealed severe cachexia, cervical dystonia, sialorrhea that hindered eating, and bilateral xanthomas in the Achilles tendons (Figure 1). The neurological exam showed global arreflexia, except for bilateral tricipital. Paresis was slightly worse in the left dimidium. It was not possible to test for cognitive impairment, due to the severe dysarthria and an inability to write or extend the neck. The patient also presented with paresis of the bilateral eye orbicularis, but ocular motricity was preserved.

Laboratory tests showed high serum levels of beta-cholestanol, 7-dehydrocolesterol, and 8(9)-cholesterol, whereas serum cholesterol concentrations were normal. Magnetic resonance imaging (MRI) showed intense cerebral and cerebellar atrophy (Figure 2), as well as hyper-signal foci on T2-weighted and FLAIR sequences without contrast uptake in the semioval center, corona radiata, periventricular/periaqueductal white matter, external capsule, midbrain and cerebellar parenchyma, including the dentate nuclei (Figure 3).

There was a suspicion of inherited metabolic disease, with the diagnosis confirmed by detection of a mutation in the CYP27A1 gene. Although treatment with 3α,7α-dihydroxy-5β-cholan-24-oic acid (chenodeoxycholic acid, CDCA) has been recommended, it is not available in Brazil. Therefore, symptomatic therapy with L-dopa was maintained and anticonvulsant treatment initiated. We also performed multidisciplinary evaluation and therapy in collaboration with a nutritionist, phonoaudiologist, neuropsychologist, psychologist, and physiotherapist.

**DISCUSSION**

Patients with CTX have mutations in the gene that encodes sterol 27-hydroxylase, an enzyme expressed in nearly all cells and is essential in both the classical and alternative pathways of biliary acid synthesis\(^1\). This deficiency leads to decreased CDCA production and increased 7α-hydroxylase cholesterol levels. This in turn increases levels of 7α-hydroxylated cholesterol metabolites, particularly 7αhydroxy-4-cholesten-3-one, which is converted to cholestanol and bile alcohols\(^1\)\(^-\)\(^5\).

Neurological signs and symptoms are the most common clinical manifestations of CTX\(^3\). They can be divided into two main subgroups: classical, with cerebellar and supratentorial symptoms, and spinal, with symptoms of chronic myelopathy\(^4\)\(^-\)\(^5\). Our patient presented with the classical form, including epilepsy, parkinsonism, cognitive deficits, dementia, psychiatric symptoms, pyramidal signs (paresis, hyperreflexia, Babinski sign, and spasticity), dystonia, and peripheral neuropathy (motor sensory abnormalities, arreflexia, and paresis)\(^3\)\(^-\)\(^7\)\(^,\)\(^8\). Her clinical condition was quite characteristic, although she did not present with most of the pyramidal signs and dystonia. We were unable to determine whether she had psychiatric symptoms or sensory changes. Her initial neurological symptoms were seizures beginning in childhood, followed by parkinsonism in adulthood, findings compatible with those described in the literature\(^1\)\(^-\)\(^7\).

In addition to neurological manifestations, CTX symptoms involving ocular, cardiovascular, skeletal, pulmonary, hepatic and muscular enterrum systems. The most typical non-neurological symptoms are tendinous xanthomas and infantile cataracts, which our patient exhibited, as well
as chronic childhood diarrhea². It is also important to check for other manifestations including osteoporosis, which together with gait alteration predisposes the patient to recurrent bone fractures; neonatal jaundice; severe and premature atherosclerosis; pulmonary failure; and cardiovascular disease, despite normal serum cholesterol concentrations¹.

Biochemical abnormalities in CTX include plasma cholestanol concentrations 5–10-fold higher than normal (330 ± 30 μg/dL), urinary bile alcohol concentration of 14,000 ± 3,500 nmol/L, and plasma bile alcohol concentration 500–1000 times higher than normal (8.5 ± 3.7 nmol/L), with normal or low plasma cholesterol concentrations.

MRI is an essential part of CTX diagnosis. The T2-weighted and FLAIR sequences of our patient showed hyperintensity in the dentate nuclei, one of the main findings associated with CTX, together with cortical and/or cerebellar atrophy¹. This may occur due to the vulnerability of the dentate nuclei to ischemic, metabolic, and inflammatory injury⁹.

Other MRI findings in our patient included hyperintense T2-weighted and FLAIR lesions in the periventricular white matter, internal capsule, midbrain, anterior region of the bridge and cerebellar parenchyma, consistent with published MRI CTX findings³. These signs occur due to the accumulation of lipids in nerve cells with demyelination and axonal degeneration, especially late in disease progression³,⁹,¹⁰.

Early diagnosis and multidisciplinary treatment are crucial to prevent disease progression and irreversible neurological dysfunction¹¹. However, what typically occurs with CTX is late diagnosis. Bilateral cataracts, mental retardation, and chronic diarrhea appear in childhood, but they are often neglected until neurological symptoms appear, leading to delayed diagnosis and treatment³. Pilo de la Fuente and coworkers showed that the mean age at onset of symptoms is 19 years, whereas the mean age at diagnosis is 35 years, representing a 16-year delay⁴. Our patient had bilateral cataracts and seizures from childhood, with worsening symptoms at 38 years and CTX diagnosis only at 44 years; by this time, the patient already had severe and irreversible neurological deficits.

CTX diagnosis is challenging due to its remarkable heterogeneity in clinical presentation and age of onset³. To facilitate this process, Mignarri and coworkers developed a scoring system to provide earlier diagnosis of CTX, with clinical suspicion, imaging findings, and family history components (Table 1)¹². This index, together with serum cholestanol and molecular genetic analysis, provides a reliable diagnostic tool in earlier stages of the disease¹². CTX should be suspected and plasma cholestanol tested in all patients presenting with spasticity, early-onset dementia, ataxia, and parkinsonism of uncertain cause, particularly when associated with tendinous xanthomas, cataracts in infancy, and/or chronic diarrhea⁸.

The recommended treatment for patients with CTX is administration of 250mg chenodeoxycholic acid (CDCA) 3 times per day¹¹. This bile-acid supplementation produces negative feedback and inhibition of biliary acid production, decreasing endogenous production of cholesterol intermediates¹¹. This improves or stabilizes most symptoms. However, early treatment is essential, as most neurological symptoms become irreversible over time. This occurs because the disease progresses from cholesterol deposition to irreversible apoptosis³. Our patient was unable to receive CDCA because it is not available in Brazil. Moreover, at the time of diagnosis the patient was already in a severe and late stage, at which CDCA treatment would have little or no efficacy. Faced with this situation, the best approach was symptomatic treatment to improve parkinsonism and to reduce seizures, as well as multidisciplinary monitoring and therapy to slow the progression of the disease.

CONCLUSION

CTX is a rare autosomal recessive disease that leads to the accumulation of cholestanol and cholesterol metabolites in several tissues. Despite being manageable through multidisciplinary monitoring, its rarity and variability result in diagnostic delays that prevent the beginning of treatment and lead to irreversible progression of neurological symptoms. CTX should be sus-
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Expected in a broader neurological frame, bringing together syndromes including parkinsonism, dementia, epilepsy, and first motor neuron syndrome. The neurological symptoms can be associated with non-neurological manifestations such as tendon xanthomas, early osteoporosis, and severe and early atherosclerosis. A clinical history of neonatal jaundice, infantile cataracts, and chronic childhood intractable diarrhea signals CTX, which should be confirmed through genetic analysis. Measurements of serum cholesterol and its metabolites and MRI will help with diagnosis. Thus, clinicians should be aware of the earliest and most common characteristics of CTX so that it can be diagnosed earlier, to allow the institution of measures that improve quality of life.

REFERENCES


REQUISITOS DE AUTORIA

1- Contribuição substancial no esboço do estudo ou na interpretação dos dados; EGG, FRCF, DSS, RSS, MBH, KLP
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**FIGURE 1:** Female patient with Cerebrotendinous Xanthomatosis. A and C demonstrate cachexia and cervical dystonia. B and D present left (b) and right (d) tendon xanthomas.

**FIGURE 2:** Magnetic Resonance Imaging on T2-weighted FLAIR in sagittal section of the patient with Cerebrotendinous Xanthomatosis showing cerebral and cerebellar atrophy.
FIGURE 3: T2-weighted MRI FLAIR in axial section of the patient with Cerebrotendinous Xanthomatosis showing cerebral and cerebellar atrophy and foci of hypersignal without contrast uptake in the semi oval center, corona radiata, periventricular and periaqueductal white matter, external capsule, midbrain and cerebellar parenchyma, including the dentate nuclei.

TABLES

Table 1
Clinical Suspicion Index of Mignarri et al.

<table>
<thead>
<tr>
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<th>Systemic Symptoms</th>
<th>Neurological Symptoms</th>
<th>A: Very Strong (100 pts)</th>
<th>B: Strong (50 pts)</th>
<th>C: Moderate (25 pts)</th>
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<tr>
<td>Siblings with CTX</td>
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