Case Resolution

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DIAGNOSIS

Cerebrotendinous xanthomatosis.

DISCUSSION

Cerebrotendinous xanthomatosis (CTX) also known as van Bogaert-Scherer-Epstein disease is a rare autosomal-recessive inborn disorder of the bile acids metabolism caused by mutations in the *CYP27A1* gene (located on chromosome 2q33-qter); this gene codes for the mitochondrial enzyme sterol 27-hydroxylase. This enzyme is involved in the cholesterol and other sterols metabolism, and especially in the bile acid synthesis. It catalyzes the initial step in the side-chain oxidation of sterols which are intermediates in the formation of bile acids. A *CYP27A1* functional mutation determines decreased levels or deficiency of the enzyme activity, which leads to decreased synthesis of bile acid (mainly of chenodeoxycholic acid [CDCA]), and accumulation of cholesterol and cholestanol in plasma and multiple tissues.

CTX patients present diverse manifestations with multi-organ involvement and a broad range of neurological and non-neurological symptoms. Childhood-onset diarrhea and psychomotor retardation are common and often coexisting clinical features of CTX. The mean age at onset of symptoms in CTX patients is 19 years, but the average age at the time of diagnosis is 35 years, thus representing a diagnostic delay of 16 years (range 2–34).

Central nervous system symptoms and signs commonly constitute the initial manifestations in CTX patients. Epilepsy and Parkinsonism may be found as the initial neurological features of CTX. Neurological manifestations may be divided into two main clinical subgroups, the classic form (cerebellar and supratentorial symptoms) and the spinal form (chronic myelopathy). The range of neurological features of CTX is broad, including intellectual disability, dementia, psychiatric symptoms (i. e., behavioral changes, depression, agitation, hallucination, and suicide attempts), pyramidal signs, progressive ataxia, dystonia, and palatal myoclonus.

MRI imaging in CTX patients may show diffuse and focal abnormalities of the white matter (WM), and different degrees of cerebral and cerebellar atrophy. These MRI findings are non-specific as they can be found in many neurometabolic disorders. However, abnormal MRI signals on T2 and FLAIR around the dentate nuclei and in the surrounding WM may suggest a CTX diagnosis. Differential diagnoses for bilateral dentate nucleus T2 hyperintensity include metronidazole toxicity and acutely decompensated maple syrup urine disease.

Long WM lesions in the lateral corticospinal tracts and the gracile tracts are characteristic MRI findings of the rare spinal form.

Childhood-onset cataract is a typical sign of CTX. This has been emphasized as an early symptom that may even precede neurological signs and tendon xanthomas, and is considered useful for early diagnosis. Cataracts and optic disk paleness are also the common ocular features in adults with CTX.

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Premature atherosclerosis and cardiovascular disease have been reported among the multiple clinical manifestations of CTX. Blood lipid analysis in patients with CTX commonly reveals high levels of 27-hydroxycholesterol and low levels of high-density lipoprotein cholesterol, which place CTX patients at a high risk of suffering from cardiovascular diseases.

Bronchoalveolar lavage fluids and lung biopsy of CTX patients may present accumulations of foamy and giant cells engorged with cholestanol. However, CTX patients with pulmonary involvement may have no clinical pulmonary symptoms and no disturbance in pulmonary function tests.

Between 50-90% of patients suffer chronic and intractable diarrhea, which begins in childhood. However, the gastrointestinal examinations in many of the patients with diarrhea are normal.

Up to 75% of CTX patients may show peripheral nerve abnormalities; features of axonal degeneration, including demyelination and remyelination, can be found. It is also possible to observe mild myopathic changes and mitochondria ultrastructural abnormalities in muscle lesions.

Tendon xanthomas commonly appear in the second or third decade of life and are usually located on the Achilles tendon, extensor tendons of the elbows and hands, and the patellar tendons. These xanthomas consist of connective tissue and foamy and giant cells containing mainly cholestanol and cholesterol.

The diffuse reticulated pattern in transverse sections has been described as a characteristic MRI finding of tendon xanthoma. The areas of low signal intensity are likely to represent residual collagen fascicles of the tendon bundles, visualized as round structures in the axial plane and linear trabeculations in the sagittal plane. The reticulated low signal intensity is also made up of free cholesterol and cholesterol esters that produce an MRI signal that is hypointense relative to skeletal muscle. The surrounding higher signal intensity between the collagen fibers represents the infiltrating triglycerides. Interfascicular edema or inflammation in response to the infiltrative cholesterol deposition is also thought to contribute to the reticulated MRI appearance and areas of high signal on STIR, T2-weighted and T2*-weighted images. The presence of an associated inflammatory reaction is supported by contrast enhancement on post gadolinium T1-weighted images.

The differential diagnosis of this punctate appearance includes traumatic or degenerative tendinopathy, which may have a similar appearance. However, thickened tendon of an Achilles tendinopathy may be differentiated by a more non-uniform, heterogeneous pattern with geographic regions of intermediate signal intensity on T1-weighted images. Partial tendon tears may be differentiated by geographic regions of linear high signal intensity within the tendon substance, focal discontinuity of the tendon, or edema within Kager's fat pad. Achilles tendon tumors and infections are rare. These diagnoses are actually often dismissed in the presence of these xanthomas. When in presence of bilateral and symmetrical involvement of the tendon, with a typical reticulated pattern, cholesterol deposition disease should be considered and its diagnosis is usually simple.

It should be highlighted that the presence of tendon xanthomas is not necessary for diagnosing CTX, as not all patients present clinically evident tendon xanthomas. On the other hand, their presence is not pathognomonic for CTX, because they may be present in other lipid storage diseases, such as familial hypercholesterolemia or sitosterolemia. These are the differential diagnoses based on imaging findings. However, in spite of the increased cholesterol synthesis in CTX patients, the cholesterol plasma levels do not usually increase. This feature may help in differentiating CTX from other lipid storage diseases. Thus, the biochemical abnormalities that distinguish CTX from other diseases with xanthomas include high plasma cholestanol concentration, normal-to-low plasma cholesterol concentration, decreased CDCA level, and increased levels of cholestanol and apolipoprotein B in cerebrospinal fluid.

The involvement of the skeletal system may also include Osteoporosis and repeated bone fractures. Serum calcium, phosphate, and vitamin D metabolites in CTX patients are normal, but the total body bone mineral density is low and intestinal calcium absorption is decreased, which underlying pathogenesis is still unknown. There is no correlation between the severity of osteoporosis and biochemical parameters.

Neurophysiological examinations may reveal visual evoked potential, somatosensory evoked potential, brainstem auditory evoked potential, and nerve conduction velocity.

The mainstay for treatment of CTX is CDCA, which provides negative feedback for the bile acid biosynthesis pathway, thereby suppressing the production of cholestanol and bile alcohols. Inhibitors of 3-hydroxy 3-methyl glutaryl coenzyme A reductase are also effective. The earlier this treatment is started, the more effective it is at preventing neurologic damage and deterioration. Patients who start treatment after 25 years of age have a worse outcome than those who start treatment early, and their condition may continue to clinically deteriorate.

ABSTRACT

CTX is a rare autosomal-recessive disorder characterized by an abnormal deposition of cholestanol and cholesterol in multiple soft tissues, caused by defective bile acid synthesis.

The underlying mutation is in the *CYP27* gene, which codes for sterol 27-hydroxylase, a key enzyme in the conversion of cholesterol to the primary bile acids, cholic acid and CDCA. The diagnosis of CTX is based on high plasma cholestanol concentration and elevated urine bile alcohol concentration.

Clinical manifestations include childhood-onset cataracts, progressive neurological dysfunction, tendon xanthomas, aterosclerosis, and chronic diarrhea.

The most frequent neuroimaging findings in patients with CTX are nonspecific and include cerebral and cerebellar atrophy and periventricular WM lesions. More characteristic lesions are seen in the basal ganglia, cerebral peduncles, and dentate nuclei. Hyperintensity of the bilateral dentate nuclei and surrounding deep cerebellar WM may be seen.

Tendon xanthomas may be present in other lipid storage diseases, such as familial hypercholesterolemia or sitosterolemia. These are the differential diagnoses that are based on standard radiology and MRI scans.

CTX pathophysiology is well defined and therapeutic options are available. Replacement therapy with CDCA has shown to cause negative feedback on cholestanol synthesis. Though somatic symptoms subside, early diagnosis and treatment is of utmost importance as there is a poor response of psychomotor symptoms to treatment once developed.

Thus, early diagnosis is vital in this rare disease, for which 300 cases have been reported worldwide. Hence the importance of radiologists being aware of CTX and its radiologic main features, as diagnosis may involve linking multisystem imaging findings. The features seen at brain and ankle imaging pose multiple differential diagnoses when considered separately; however, the combination of the findings may lead to the diagnosis of CTX and more so when it correlates with the biochemistry panel. Genetic studies will be of benefit for affected families, as it provides chances for stopping the disease progression and achieving a normal life expectancy. In untreated patients, life expectancy is 50 to 60 years; however, premature deaths have been reported as early as childhood.

Conflict of interest: Authors claim they do not have any conflict of interest.

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