

# **CEREBROTENDINOUS XANTHOMATOSIS**

**Nivedita Patni, MD**, Division of Pediatric Endocrinology, Department of Pediatrics UT Southwestern Medical Center, Dallas, Texas. nivedita.patni@utsouthwestern.edu

**Don P Wilson, MD, FNLA**, Diplomate, American Board of Clinical Lipidology, Endowed Chair, Cardiovascular Health and Risk Prevention, Pediatric Endocrinology and Diabetes, Cook Children's Medical Center, Fort Worth, Texas. don.wilson@cookchildrens.org

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#### ABSTRACT

Cerebrotendinous xanthomatosis is a rare autosomal recessive disorder caused by homozygous or compound heterozygous mutations in the CYP27A1 gene. These patients lack mitochondrial sterol 27hydroxylase enzyme, which is responsible for conversion of cholesterol to cholic acid and chenodeoxycholic acid (CDCA) in bile acid synthesis pathway. CYP27A1 mutation leads to decreased synthesis of bile acid, excess production of cholestanol, and consequent accumulation of cholestanol in tissues, including brain, leading to progressive neurological dysfunction marked by dementia, spinal cord paresis, and cerebellar ataxia. Deposition in other tissues causes tendon xanthomas, premature atherosclerosis, and cataracts. The clinical manifestations usually start at infancy and develop during the first and second decades of life. The diagnosis of CTX is based on clinical findings, biochemical testing, and neuroimaging. Molecular genetic analysis although not necessary for initiation of treatment, provides definitive confirmation of CTX. Early initiation of CDCA is the treatment of choice for

neurological and non-neurological symptoms of CTX and treatment with cholic acid has also been shown to be effective for non-neurological symptoms.

#### INTRODUCTION

Cerebrotendinous xanthomatosis (CTX; OMIM#213700) is a rare autosomal recessive disorder of bile acid metabolism and lipid storage characterized by abnormal deposition of cholestanol and cholesterol in multiple tissues. It is caused by homozygous or compound heterozygous mutation in the CYP27A1 gene located on chromosome 2q33-gter. CYP27A1 gene encodes sterol 27-hydroxylase which is involved in bile acid synthesis. Over 100 different mutations (missense, deletions, insertions, splice site, and nonsense mutations) of the CYP27A1 gene have been reported worldwide in patients of different ethnic origin (1,2). About 50% of these mutations were found in the region of exons 6-8 of the CYP27A1 gene, however here is no genotype phenotype correlation (3,4). The metabolic pathway for bile acids synthesis is shown in the figure 1.



Figure. Bile acid synthesis in Cerebrotendinous Xanthomatosis (CTX).

Figure 1. Bile acids are synthesized from cholesterol in the liver through two pathways: the classic pathway and the alternative pathway. The bile acid synthesis mainly produces two primary bile acids, cholic acid and chenodeoxycholic acid (CDCA). In the classic pathway, the mitochondrial sterol 27-hydroxylase (CYP27A1) catalyzes the steroid side-chain oxidation in both CA and CDCA synthesis. In the alternative pathway, CYP27A1 catalyzes the first step to convert cholesterol to 27-hydroxycholesterol which eventually is converted to CDCA.

CTX was first described by Van Bogart, Scherer and Epstein in 1937 as a condition characterized by early development of cataracts and large tendon xanthomas and later by progressive neurologic impairment (5,6). The incidence of CTX is estimated to be 3 to 5 per 100,000 people (1,7). The prevalence is estimated to be highest in Asians (1:44,407-93,084), intermediate in Europeans, Americans, and Africans/African Americans (1:70,795-233,597) and lowest in the Finnish population (1:3,388,767) (8).

#### **ETIOLOGY AND PATHOGENESIS**

Patients with CTX lack mitochondrial sterol 27hydroxylase, which is an important enzyme in both the alternative and classic bile acid synthesis pathways (9). The biochemical defect prevents the synthesis of chenodeoxycholic acid (CDCA) and cholic acid (10).The absence of the negative feedback mechanism of CDCA on 7a-hydroxylase, the rate limiting step, leads to the accumulation of cholestanol and its precursor  $7\alpha$ -hydroxy-4-cholesten-3-one (Figure 1) (9-11). Bile acid alcohols are glucoronidated and can be found in significantly increased amounts in blood, urine, and feces of untreated CTX subjects. It has been hypothesized that the increased bile alcohol levels may lead to disruption of the blood–brain barrier (BBB), and that increased permeability of BBB may be caused by circulating bile alcohol glucuronides (12). Cholestanol and cholesterol accumulate in many tissues, including brain (primarily white matter), leading to progressive neurological dysfunction marked by dementia, spinal cord paresis, and cerebellar ataxia. Deposition in other tissues causes tendon xanthomas, premature atherosclerosis, and cataracts (13).

## **CLINICAL FEATURES**

Patients with CTX present diverse manifestations with multi-organ involvement and a broad range of neurological and non-neurological symptoms (Table 1). The clinical manifestations usually start at infancy and develop during the first and second decades of life. Neonatal cholestatic jaundice and infantile-onset diarrhea with failure to thrive may be the earliest clinical manifestation (14-16). Childhood-onset cataracts are a common early symptom, described in 92% patients with CTX. Cataracts precede neurological signs and tendon xanthoma, and if present, are considered useful for early diagnosis (14, 16, 17).Tendon xanthomas have been documented in 71% patients with CTX and can appear in first, second or third decade. They are common in Achilles tendon, but can also be seen in fingers, tibial tuberosity, and triceps (17,18). Pes cavus deformity has also been described (19,20). Neurological dysfunction is almost always present in patients with CTX and usually occurs in late adolescents and early adulthood. The range of symptoms are wide and include intellectual disability; dementia; psychiatric symptoms (i.e., behavioral changes, depression, hallucination, and suicide attempts); agitation. pyramidal signs (spasticity, hyperreflexia, extensor plantar responses); cerebellar signs (progressive ataxia, dysarthria); movement disorder (parkinsonism, dystonia, myoclonus, postural tremor); seizures; and peripheral neuropathy (1,4,21-23). Osteoporosis, heart involvement, and premature atherosclerosis have also been described later in life (19,24-26).

Table 1. Clinical Features of Cerebrotendinous Xanthomatosis
Early childhood
Neonatal cholestatic jaundice
Chronic diarrhea
Cataracts
Developmental Delay
Late childhood
Tendon xanthomas
Psychiatric disorders
Adulthood
Neurological dysfunction
Pyramidal signs (spasticity, hyperreflexia, extensor plantar responses)
Cerebellar signs (ataxia, dysarthria)
Movement disorder (parkinsonism, dystonia, myoclonus, postural tremor)
Seizures
Dementia
Pes Cavus
Osteoporosis
Premature atherosclerosis

#### DIAGNOSIS

The diagnosis of CTX is mainly based on clinical features, biochemical testing, neuroimaging, and molecular genetic analysis. Since clinical presentation can be variable in type, severity, and timing, diagnosis is often delayed. Patients with CTX include having high plasma cholestanol concentration (five- to tenfold greater than normal), normal-to-low plasma cholesterol concentration, elevated urine bile alcohol concentration. elevated plasma bile alcohol concentration, decreased CDCA level, and increased levels of cholestanol and apolipoprotein B in cerebrospinal fluid (10,17). Cholesterol concentration in tissue is increased but plasma cholesterol levels are low to normal (27). Brain MRI features are strongly suggestive of diagnosis and include bilateral hyperintensity of the dentate nuclei, diffuse cerebral and cerebellar atrophy, and white matter signal abnormalities. Brain MRI spectroscopy shows decreased n-acetylaspartate and increased lactate signals, suggestive of widespread axonal damage and

cerebral mitochondrial dysfunction (20). Although not necessary for initiation of treatment, molecular testing provides definitive confirmation of CTX. Various mutations in all nine exons and in introns 2,4,6,7 and 8 of the CYP27A1 gene have been described worldwide (8). Mignarri et al (22) developed a suspicion index to be used by clinicians to calculate CTX prediction score. They proposed using family history, systemic and neurologic features as diagnostic indicators, classified as very strong (score of 100; e.g., tendon xanthoma or, sibling with CTX); strong (score of 50; e.g., juvenile cataract, chronic diarrhea, prolonged neonatal cholestasis, ataxia, MRI alterations, intellectual disability and/or psychiatric disturbances); or moderate (score of 25; e.g., early osteoporosis. epilepsy. parkinsonism or polyneuropathy. A total score  $\geq$  100 warrants serum cholestanol assessment, and elevated cholestanol or total score  $\geq$  200, with one very strong or four strong indicators, warrants CYP27A1 gene analysis (22). Quantification of bile acid precursor 7a-hydroxy-4cholesten-3-one has been proposed to be a rapid,

convenient diagnostic test for CTX (28). Early detection of ketosterol bile acid precursors can play important role in early detection through newborn screening (29).

## MANAGEMENT

Early initiation of oral chenodeoxy-cholic-acid (CDCA) therapy at a dose of 250 mg given 3 times daily for adults and 15 mg/kg/d for children is the treatment of choice for neurological and non-neurological symptoms such as diarrhea (30-32), however it still does not have U.S. Food and Drug Administration approval for CTX. FDA has granted it an orphan drug designation for use in CTX. CDCA has been approved in the European Union to treat adults and children with CTX over 1 month of age. This treatment suppresses synthesis of cholesterol, cholestanol, bile alcohols, and bile acids and alleviates clinical symptoms if started at an early age (33,34); however it has not been shown to improve bone mineral density in affected patients (35). The treatment is most effective when started early (31), and patients diagnosed later in life with significant neurological disease may progress despite CDCA therapy. A retrospective cohort study in 79 Dutch patients with CTX showed that the MRI brain remained normal even after 25 year of follow-up treatment if therapy was started in young patients with a normal MRI at diagnosis. Treatment with cholic acid has also been shown to be effective, especially in patients with side effects to CDCA therapy (36,37). HMG-CoA-reductase-inhibitors along with CDCA can improve lipoprotein metabolism, inhibit cholesterol synthesis, and reduce plasma levels of cholestanol (38). Surgical excision of bilateral tendon may worsen the gait imbalance and cannot prevent the deterioration of neurologically affected patients (39). Lumbreras et al (40) showed that adenoassociated virus (AAV) vectors expressing CYP27A1 restored bile acid metabolism

and normalized the concentration of most bile acids in plasma in a CTX mouse model, making gene therapy a feasible option.

### SCREENING

Screening of all first-degree relatives, when feasible, should be considered as early detection and treatment are the most important aspects for preventing morbidity and mortality (41). A recent pilot study has also shown promising option of screening for CTX as part of newborn screening (42). A recent study on deidentified dried blood spots of 20,076 newborns from the 2019 cohort of the biobank of the Dutch newborn screening program (Dutch National Institute for Puublic Health and the Environment, Bilthoven, The Netherlands) showed that metabolite ratios bile alcohol cholestanetetrol glucuronide (GlcA-tetrol)/ tauro-chenodeoxycholic acid (t-CDCA) to be informative biomarker, paving way for introduction of CTX newborn screen (43).

## CONCLUSIONS

Cerebrotendinous xanthomatosis is a rare autosomal recessive disorder of bile acid metabolism and lipid storage characterized by abnormal deposition of cholestanol and cholesterol in multiple tissues. Clinical manifestations include neonatal cholestatic jaundice, infantile-onset diarrhea with failure to thrive, childhood-onset cataracts, tendon xanthomas, and progressive neurological dysfunction including intellectual disability, dementia, and psychiatric symptoms. Treatment with CDCA is treatment of choice, however cholic acid, HMG-Co-A reductase inhibitors, and surgical excision also play a role in management. Timely detection and treatment are the key to prevent severe morbidity and mortality in these patients.

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