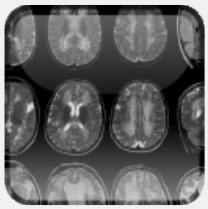

Inherited Metabolic Disease in Adults: A Clinical Guide

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Cerebrotendinous Xanthomatosis

Chapter: Cerebrotendinous Xanthomatosis

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Introduction

Since the description of the first cerebrotendinous xanthomatosis (CTX) patient by van Bogaert et al in 1937,[1] more than 300 patients have been described worldwide. The prevalence of CTX is estimated to be 3 to 5 per 100,000.[2] Early diagnosis of CTX is important, as an early start of treatment can prevent severe neurological disease.

Metabolic Pathway

Biochemistry: Normal Bile Acid Synthesis

Normal hepatic bile acid synthesis is shown in Figure **40.1** (outside the dashed boxes). Cholesterol is metabolized within hepatic mitochondria. The rate-limiting enzyme in bile acid synthesis is 7α-hydroxylase. There

are two main routes for 27-hydroxylation of cholesterol.[3] In the "auxiliary" pathway, which is exclusively hepatic, the substrate 5β-cholestane-3α,7α-diol is metabolized into chenodeoxycholic and cholic acid by sterol 27-hydroxylase. The second pathway is the acidic or regulatory pathway, in which both hepatic and extrahepatic cholesterol is metabolized directly into 27-hydroxycholesterol by the sterol 27-hydroxylase.[3] The acidic pathway is probably the most important pathway in bile acid synthesis, because of the significant amount of extrahepatic cholesterol that is metabolized and the regulatory effects of 27-hydroxycholesterol, which has a strong negative feedback on the activity of β-HMG CoA reductase, the rate-limiting enzyme in cholesterol synthesis. The acidic pathway is thought to be an important oxidative mechanism for eliminating intracellular cholesterol in humans.[4]

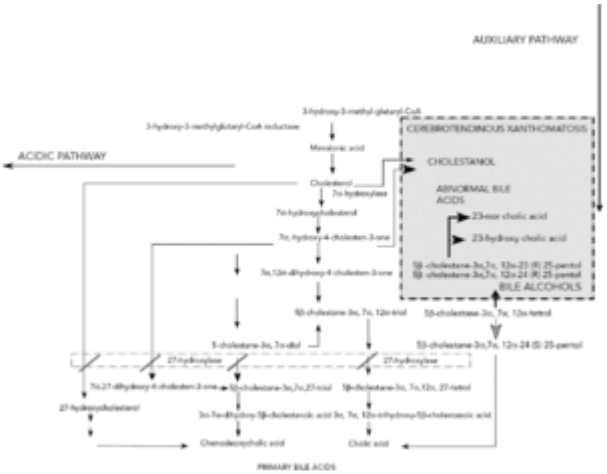

Figure 40.1
Normal bile acid synthesis and biochemical derangement in cerebrotendinous xanthomatosis.

Pathophysiology

The biochemical derangement in cerebrotendinous xanthomatosis is also shown in Figure **40.1**. The deficiency of 27-hydroxylase (CYP 27A1), shown by the clear box, leads to several processes (shown in the shaded box). Due to the absence of negative feedback on 7α-hydroxylase caused by the absence of chenodeoxycholic acid, cholesterol is converted into cholestanol.[5] In CTX patients cholesterol is converted into cholestanol in the liver, mainly via the 7α-hydroxycholesterol pathway. In healthy persons, small amounts of cholestanol are produced via cholesterol and 4-cholesten-3-one. In CTX

patients, about 80% of the excessive amount of cholestanol is synthesized via the conversion of 7α-hydroxycholesterol into 7α-hydroxy-4-cholesten-3-one. This metabolite is further converted into cholesta-4,6-dien-3-one and via 4-cholesten-3-one into cholestanol.

Due to the absence of 27-hydroxylated products, and therefore the lack of negative feedback, β-HMG CoA reductase activity is increased, leading to higher cholesterol synthesis.[5] In CTX patients, bile alcohols (5β-cholestane-3α,7α,12α,24-tetrol, 5β-cholestane- 3α,7α, 12α,25-tetrol [predominant], 5β-cholestane-3α,7α,12α, 23,25 pentol, and 5β-cholestane-3α,7α,12α,24,25 pentol) are produced via the 24- and 25-hydroxylation pathways, which normally play a minor role in this part of metabolism. Via the same pathway, abnormal bile acids (23-norcholic acid, 23-hydroxycholic acid) and small amounts of cholic acid are produced.[5]

Cholestanol is excreted in bile and enters the circulation by resorption in the terminal ileum (enterohepatic circulation). It accumulates, together with cholesterol, in many tissues, especially in the eye lenses, the central nervous system, and muscle tendons. The exact mechanism of accumulation is still unknown.[6] Bile alcohols are excreted in bile and resorbed in the gut. After glucuronidation they are excreted in urine, but elevated serum levels of these bile alcohols are found in CTX.

Clinical Description

CTX is a slowly progressive and variable disease, with symptoms and signs increasing with age in untreated patients. The earliest presentations are with neonatal cholestatic jaundice (“hepatitis of infancy”).[7] During the early childhood stage I of CTX, more typical clinical features such as premature cataracts (one of the clinical hallmarks of the disease), diarrhea, and global developmental delay may develop. Tendon xanthomas (Figure **40.2**) and neurological symptoms (stage II disease) are characteristic of advancing disease in the second or third decade of life.[8,9] Premature arteriosclerosis,[10] osteoporosis,[11] and pulmonary involvement[12] have also been reported. The cataracts are not congenital but may be diagnosed by the age of 10 years in nearly half of patients, some of whom present without visual complaints.[13] Chronic diarrhea is a key symptom of CTX at all ages.[8] It disappears within a few days after starting chenodeoxycholic acid (CDCA) therapy, but the pathogenesis of this symptom is still unknown. The presence of tendon xanthomas is not required for the diagnosis of CTX.[8] Stage III of the disease, after the age of 30 years, is characterized by severe neuropsychiatric symptoms and signs.

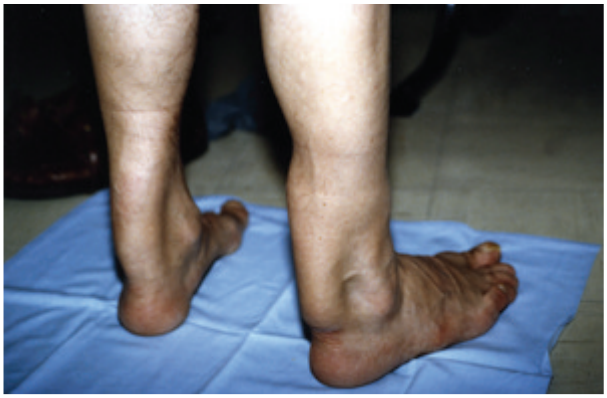

Figure 40.2
Large tendon xanthomas in a 50-year-old male patient with cerebrotendinous xanthomatosis.

Clinical Presentation in Adults

The adult clinical presentation of CTX is of a neuropsychiatric disorder. Neurological symptoms that may occur are pyramidal and cerebellar signs, mental deterioration, epilepsy, and a predominantly axonal polyneuropathy.[8,9] Psychiatric disturbances such as dementia, depression, aggression, agitation, and hallucinations may occur.[14,15]

Because this presentation is not specific, CTX patients are often misdiagnosed initially, especially when tendon xanthomas are not present or remain unnoticed.[8,15,16,17,18]

Some adult CTX patients present with a slowly progressive, mainly spinal cord syndrome that remains the sole expression of CTX for many years. This so-called “spinal xanthomatosis” is a clinical and radiological variant of CTX.[16,19] An unexplained finding in CTX patients between the age of 20 to 40 years is the presence of an increased speech velocity (tachylalia).[20]

The diagnosis of CTX should be considered in all patients with premature cataracts and in patients with neurological signs of spasticity, early-onset dementia, ataxia, and Parkinsonism.[21] Patients should be asked about symptoms of chronic diarrhea, and xanthomas—particularly of the Achilles tendons—should be carefully sought.

Acute Decompensation in Adulthood

In the untreated state, most CTX patients deteriorate slowly. Acute decompensation is likely to be psychiatric in nature with acute

psychosis or attempted suicide. Because of the development of premature atherosclerosis, acute myocardial infarction may occur.[22]

Table 40.1 Key Clinical Features, Complications and Associated Conditions in Cerebrotendinous Xanthomatosis

Key clinical features	Complications	Follow-up investigations	Management
Chronic diarrhea	Weight loss		Disappears soon after start of CDCA treatment
Premature bilateral cataracts			Cataract extraction if symptomatic Minimal cataract is stable after start of CDCA treatment
Neurological signs and symptoms	Epilepsy, walking disturbances with frequent falling	Cerebral MRI, EEG	Stable disease after start treatment
Psychiatric signs and symptoms	Depression, anxiety, mental deterioration		Antidepressive drug or psychological treatment Institutionalization
Tendon xanthomas	Pressure ulceration		Stable xanthoma size after start treatment. Sometimes orthopedic surgery.
Premature arteriosclerosis	Cardiovascular disease	ECG, blood pressure, general physical examination	Standard treatments

Other	Elevated serum cholestanol Elevated excretion of urinary bile alcohols	Serum and urine samples	Adapt dose of CDCA treatment

CDCA, chenodeoxycholic acid

Clinical Complications During the Course of Disease

In untreated patients the disease progresses relentlessly. In the early stages, most patients have intractable diarrhea and bilateral cataracts, which are not always symptomatic. From the age of 10 years, most patients develop progressive neurological signs and symptoms. In the Dutch adult patient group, almost two-thirds of the patients did not develop tendon xanthomas.[8] Neurological deterioration can be stopped with chenodeoxycholic acid and statin therapy[23,24] (see below). If started early enough in the disease, before the onset of neurological signs, therapy can prevent the development of neurological disease.[25,26] In moderate and severe disease stages, drug therapy is less effective. In a retrospective study (unpublished data) we investigated 32 patients of whom 13 started therapy before the age of 21 at an early stage of the disease. Nineteen patients started their therapy at a later stage and had more advanced disease. The duration of treatment in patients varied from 8 months to 27 years (mean 11.4 years). We saw improvement or stabilization of clinical manifestations in all but one of the younger patients. The older patient group (21 years and older) developed some additional symptoms and showed progression of preexistent symptoms and signs, especially cognitive decline and gait disturbances.

Investigations

Diagnostic Tests

Three diagnostic tests with increasing specificity can be used: elevated serum cholestanol levels (gas chromatography–mass spectrometry), elevated bile alcohol excretion in urine (mass spectrometry), and identification of pathogenic *CYP27A1* mutations by genetic analysis. In one unique patient with cerebrotendinous xanthomatosis, Hansson et al.

found evidence for the presence of a defect in a gene that is not identical to sterol 27-hydroxylase.[27]

Other Investigations

Magnetic resonance imaging (MRI) of the brain has replaced the CT scan and may reveal nonspecific findings such as cerebral and cerebellar atrophy. In more advanced disease stages, typical findings are symmetrical high signal lesions in the globus pallidus and in the deep cerebellar white matter, together with low signal lesions in the dentate nucleus on T2-weighted MRI (Figure **40.3**).[28] The cerebellar lesions, particularly those in and surrounding the dentate nuclei, are the most constant radiological feature of CTX.[29] Once these lesions are found, they are often stable in time.[30] There is no correlation between the clinical, biochemical, and neuroimaging findings.[31] In patients with spinal xanthomatosis the spinal cord MRI scans may show extensive, poorly delineated bands of increased signal on T2-weighted images restricted to the lateral and dorsal columns.[19] MR imaging of tendon xanthomas may show intermediate signal intensity comparable to muscle on T1-weighted images, and a patchy appearance with a mixed intermediate/high signal on T2-weighted images.[28]

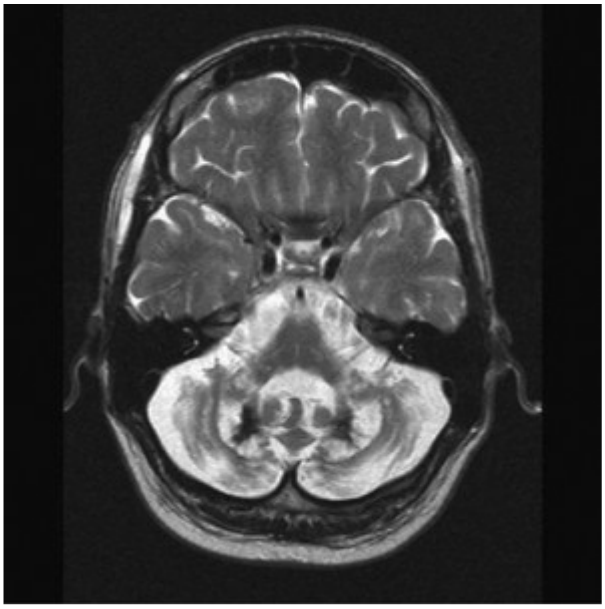

Figure 40.3
T2-weighted MRI of a 53-year-old male patient with cerebrotendinous xanthomatosis showing the typical symmetrical low-signal lesions in the dentate nucleus and the high-signal lesions in the deep cerebellar white matter on T2-weighted MRI.

An EEG before therapy shows the nonspecific characteristics of a metabolic encephalopathy in most patients, with theta and delta activity as the dominating background rhythm. Paroxysmal high-voltage delta and theta discharges may occur spontaneously or during hyperventilation, with or without seizures.[26] Electromyography in CTX patients may detect a peripheral, predominantly axonal, neuropathy.[32]

Management

Specific Treatment

Cerebrotendinous xanthomatosis is a treatable disease. The treatment consists of chenodeoxycholic acid in three divided oral doses of 250 mg daily.[23]

Simvastatin should be added in a daily dose of 40 mg daily.[24] In the first 6 months of therapy, serum transaminases and serum creatine kinase must be monitored each 2 months. During the first 2 years of therapy serum cholestanol levels and urinary bile alcohol excretion must be determined each 6 months. After these 2 years, biochemical monitoring once a year is

sufficient. Therapy with ursodeoxycholic acid does not restore the negative feedback on 7α-hydroxylase and therefore does not inhibit the production of cholestanol and other unwanted metabolites. It is contraindicated in CTX patients.[33,34,35]

Pregnancy

To date it is still unknown whether pregnancy in women with CTX represents a higher risk for the fetus and neonate. Berginer et al. described the outcomes of 18 children, born to 9 CTX mothers. Two were mentally retarded, 12 were apparently normal, and no information was available on four children. The 11 children of seven CTX fathers were normal.[36] Chenodeoxycholic acid is potentially teratogenic and is considered contraindicated in pregnancy.[37]

Neonatal Period

In a cohort of 50 Dutch CTX patients (out of 26 families), of 26 pregnancies (out of 18 families) we had reliable information in only nine cases on the pregnancy and the neonatal outcome.

Six of these 9 patients had prolonged, self-limiting (cholestatic) jaundice in the neonatal period. The family histories of the 44 CTX families revealed four fetal deaths among siblings of the affected individuals.[7]

Recommendations

The presence of two of the four clinical hallmarks of CTX (premature cataracts, intractable diarrhea, progressive neurological signs, and tendon xanthomas) should prompt thorough metabolic screening for CTX. As therapy is available, the early recognition of CTX is important. The biochemical diagnosis can be established easily and reliably. As affected relatives may be asymptomatic, and because of the intrafamilial phenotypic heterogeneity, biochemical examination of all siblings of a CTX patient is indicated because an effective treatment is available. The typical pattern of cerebral and spinal MR findings should prompt the diagnosis of CTX.

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