Cerebrotendinous Xanthomatosis

A Rare Disease With Diverse Manifestations

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This mini-review deals with a new appraisal of cerebrotendinous xanthomatosis. In addition to neurologic symptoms, patients with cerebrotendinous xanthomatosis develop cataracts, diarrhea, Achilles tendon xanthoma, atherosclerotic vascular disease, and many other abnormalities. Although the pathophysiology of the disease is not completely understood, excess production and consequent accumulation of cholestanol in tissues may play a crucial role. Chenodeoxycholic acid is the most effective therapy. The causative role and detrimental effects (at a low plasma level) of cholestanol merit further investigation.

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disease characterized by formation of xanthomatous lesions in many tissues, in particular the brain and tendons. The diagnosis of CTX before neurologic deterioration is crucial to prevent brain damage that leads to severe mental and neurologic dysfunction and death. In this regard, specific biochemical abnormalities include elevated plasma and bile cholestanol levels and increased urinary excretion of bile alcohols associated with diminished biliary concentrations of chenodeoxycholic acid. In children unexplained bilateral cataracts with chronic diarrhea are the features that suggest this diagnosis before the onset of neurologic disease.

Cerebrotendinous xanthomatosis is potentially treatable with improvement in neurologic function. Replacement therapy with chenodeoxycholic acid inhibits abnormal bile acid synthesis and is most effective in reducing elevated plasma cholestanol concentrations, and eliminating bile alcohols.

NEW INSIGHTS

Cerebrotendinous xanthomatosis is a rare inborn disorder of bile acid synthesis in which hepatic conversion of cholesterol to cholic and chenodeoxycholic acids is impaired. A defect in hydroxylation of the cholesterol side chain that impairs oxidative cleavage has been identified. Thus, laboratory findings include elevated plasma levels of cholestanol and bile alcohols and increased urinary excretion of bile alcohol glucuronides with diminished biliary concentrations of chenodeoxycholic acid. Clinical signs and symptoms include cataracts, tendon xanthomas (particularly of the Achilles tendon), neurologic abnormalities, and premature atherosclerosis. These findings represent the consequences of the accumulation of cholesterol and cholestanol in affected tissues. An increase in hepatic cholesterol and bile acid synthesis with up-regulation of the rate-controlling enzyme activities has been reported in patients with CTX. Plasma cholesterol levels and lipoprotein profile remain within or below normal range.

Cerebrotendinous xanthomatosis shares some clinical manifestations such as xanthomas and coronary atherosclerosis with other lipid storage disorders including familial hypercholesterolemia and sitosterolemia. However, cataracts, progressive neurologic symptoms, and mild pulmonary insufficiency are unique features that distinguish CTX from these 2 xanthomatous disorders. The Table summarizes the clinical, biochemical, and molecular features of these lipid disorders.

It is believed that massive deposition of cholesterol and cholestanol in affected organs leads to dysfunction and clinical development of the disease because only trace amounts of cholestanol are normally found...
in mammalian tissues. Several lines of evidence support the hypothesis that increased levels of plasma and tissue cholesterol arise endogenously and that cholestanol is a degradation product of cholesterol.5

Association of bilateral juvenile cataracts with chronic diarrhea may represent the earliest clinical manifestation of CTX. Tendon xanthomas and neurologic symptoms lend additional support to the diagnosis of CTX in children. The presence of bile alcohol glucuronides in plasma and/or urine in association with elevated cholestanol levels in young individuals confirms CTX. Early diagnosis and treatment with chenodeoxycholic acid contribute to a better prognosis by preventing the progression of this disabling disease.6 The Figure shows the metabolic background of CTX and the mechanisms for chenodeoxycholic acid therapy.

Accumulation of cholestanol in the brain and cerebrospinal fluid is of particular importance. Cholestanol is exclusively synthesized in the liver and not in the nervous system. How specifically cholestanol accumulation produces functional abnormalities is unknown and should be investigated further. The presence of apolipoprotein B in cerebrospinal fluid indicates penetration of low-density lipoprotein particles from plasma through the blood-brain barrier.7 These lipoprotein particles may carry cholestanol as well as cholesterol. Future experimental and/or clinical investigations may answer the question of whether increased cholestanol biosynthesis and its accumulation causes neurologic dysfunctions by itself or through other mechanisms. Because most patients with CTX have brain atrophy, it can be postulated that the adverse effects of cholestanol may be caused by increased apoptosis pathways. Treatment with chenodeoxycholic acid reestablished selective permeability of the blood-brain barrier and normalized cerebrospinal fluid sterol and apolipoprotein concentrations.7

Most patients with CTX have normal lipoprotein profiles despite increased cholesterol synthesis. Chenodeoxycholic acid replacement therapy is usually associated with normalization of cholesterol synthesis and also with the significant reduction in plasma cholestanol levels which then leads to improvement in the clinical symptoms of the disease. This plus the absence of neurologic dysfunction in other lipid disorders such as familial hyper-

### Table: Characteristic Features of Cerebrotendinous Xanthomatosis (CTX) Along With Those of 2 Other Lipid Disorders With Certain Similarities in Clinical Course

<table>
<thead>
<tr>
<th>Lipid Disorder</th>
<th>Molecular Defect</th>
<th>Metabolic Background</th>
<th>Laboratory Findings</th>
<th>Clinical Manifestations</th>
<th>Differential Diagnosis</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>CTX</td>
<td>Mutations in sterol 27-hydroxlyase</td>
<td>Decreased bile acid formation and excess production and tissue accumulation of cholesterol</td>
<td>Increased plasma levels of cholestanol and bile alcohols and normal or low plasma cholesterol levels</td>
<td>Childhood chronic diarrhea, bilateral cataracts, low intelligence, and several other neurologic dysfunctions; massive Achilles tendon xanthomas; other types of xanthomas; atherosclerosis; and osteoporosis and bone fracture</td>
<td>Progressive neurologic symptoms, chronic diarrhea, and bilateral cataracts (particularly in childhood); extensive tendon (Achilles) xanthomas; and pulmonary insufficiency</td>
<td>Chenodeoxycholic acid</td>
</tr>
<tr>
<td>Familial hypercholesterolemia</td>
<td>Deficiency or defects in low-density lipoprotein receptor activity</td>
<td>Decreased clearance of apolipoprotein B containing lipoproteins and their consequent tissue accumulation</td>
<td>Elevated plasma low-density lipoprotein cholesterol level</td>
<td>Coronary heart disease and tiberosus tendon xanthomas</td>
<td>No neurologic symptoms or diarrhea</td>
<td>Various cholesterol-lowering strategies</td>
</tr>
<tr>
<td>Sitosterolemia</td>
<td>Mutations in ABCG5 and ABCG8*</td>
<td>Increased absorption and decreased excretion of plant sterols</td>
<td>Extremely high plasma phytonserol levels and normal or slightly elevated plasma cholesterol level</td>
<td>Extensive tiberosus and tendon xanthomas, accelerated atherosclerosis, and thrombocytopenic purpura</td>
<td>No neurologic symptoms or diarrhea</td>
<td>Low plant sterol diet, bile acid resins, and/or ileal bypass</td>
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*ABC indicates adenosine triphosphate–binding cassette, a transporter family that includes GS and G8 among its members.
percholesterolemia or sitosterolemia further support the hypothesis that cholestanol itself impairs brain function.

Several patients with CTX who develop premature atherosclerosis have been described. Atherosclerosis and consequent cardiac events are a serious concern in subjects with CTX. Segev et al. reported a myocardial infarction in a patient who had very low plasma cholesterol levels (138 mg/dL [3.57 mmol/L]). Another case report described atherosclerotic aneurysms in coronary arteries of a patient with CTX. Whether aneurysmal rather than obstructive coronary artery disease is more characteristic of CTX is unknown. Therefore, it is strongly recommended that in all 3 lipid disorders (familial hypercholesterolemia, sitosterolemia, and CTX) the presence of cardiovascular disease should be investigated even in asymptomatic patients. Unlike familial hypercholesterolemia, in both CTX and sitosterolemia there is an increased low-density lipoprotein receptor activity. Extensive tendon xanthomas in the presence of low plasma cholesterol levels are clues for differentiation of CTX from the 2 other disorders.

Osteoporosis and repeated fractures are also features of patients with CTX. The underlying mechanisms for this association are unexplained. One possibility is that the excess accumulation of cholestanol and cholesterol may render bones more fragile. Unsteady gait due to neurologic impairment and subsequent frequent falls may further increase the chance of bone fracture. Normal serum calcium, phosphate, and vitamin D metabolite levels are reported in patients with CTX who suffered bone fractures; however, impaired absorption of radiolabeled calcium in patients with CTX has been reported. The latter observations raise the question whether cholic acid and chenodeoxycholic acid can affect calcium absorption? A recent study reported an imbalanced calcium distribution in advanced atherosclerotic lesions and bone tissues in individuals with hypercholesterolemia. Such a situation may also exist in patients with CTX.

Bile acid therapy is effective, affordable, and safe. A female Canadian patient with CTX who has been taking chenodeoxycholic acid for many years is free of CTX symptoms, particularly neurologic signs. While receiving chenodeoxycholic acid treatment, she gave birth to 2 healthy children (Jean Davignon, MD, oral communication, October 21, 2000). The major adverse effects of chenodeoxycholic acid therapy may be diarrhea, restlessness, and impatience. Although statins have been used, their effectiveness is controversial. One major concern with using statins is the possibility of worsening the condition owing to increased low-density lipoprotein uptake as the result of augmented low-density lipoprotein receptor activity. Removal of the Achilles tendon xanthomas may be considered for cosmetic reasons, but it may worsen the gait in neurologically affected patients.

CONCLUSIONS

Cerebrotendinous xanthomatosis is a familial disorder of bile acid synthesis. It may present with chronic diarrhea and bilateral cataracts in early childhood. Patients usually develop tendon xanthomas and neurologic symptoms after the second decade of life. Elevated plasma and bile cholesterol levels, increased urinary excretion of bile alcohol glucuronides associated with diminished biliary concentrations of chenodeoxycholic acid, plus neurologic impairments (mental retardation, pyramidal and cerebellar signs along with an abnormal electroencephalogram, brain computed tomographic scans, or magnetic resonance images), cataracts, and tendon xanthomas confirm its diagnosis. In most cases CTX can be effectively treated by the administration of chenodeoxycholic acid (250 mg, 3 times daily). Early detection and treatment of CTX significantly reduces the complications of the disease. Laboratory assessment of plasma cholesterol levels and the urinary excretion of bile alcohol glucuronides along with sensory evoked potentials can provide a sensitive objective index of improved neurologic and biochemical function during chenodeoxycholic acid treatment. This coincides with the normalization of plasma and cerebrospinal fluid cholesterol levels to normal values during chenodeoxycholic acid treatment.

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