Cerebrotendinous Xanthomatosis: A Treatable Neurodegenerative Disease

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Abstract

Cerebrotendinous xanthomatosis is one of the rare forms of treatable hereditary neurodegenerative disorders. It is due to a defect in hydroxylation of cholesterol side chain that impairs oxidative cleavage of cholesterol leading to excess accumulation of cholesterol. Here we present such a case which presented to us with recurrent generalized tonic clonic seizures. He is under treatment for the same and has not neurologically deteriorated since then.

Introduction

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive disease characterized by formation of xanthomatous lesions in many tissues, in particular the brain and tendons.1 The diagnosis of CTX before neurologic deterioration is crucial to prevent brain damage that leads to severe mental and neurologic dysfunction and death.1 It is due to a deficiency of the mitochondrial enzyme 27-sterol hydroxylase (CYP27).2 This causes an impairment of the metabolic pathway of cholesterol, resulting in an excessive production of cholestanol, which then accumulates in many tissues.3 The classical triad of the disease consists of premature bilateral cataracts, tendon xanthomas and neurologic abnormalities. Chenodeoxycholic acid alone or in combination with 3-hydroxy-methylglutaryl coenzyme A reductase inhibitors has been shown to slow or even reverse the progression of the disease.4 Here we report a rare case of cerebrotendinous xanthomatosis which presented to us with all the florid features of this disease.

Case Summary

Thirty-one year old male patient presented to us with history of several episodes of generalized tonic clonic convulsions since the age of nine months. He had delayed motor and social milestones of development and showed deterioration of fine motor skills by the age of five years. He had below average scholastic performance and discontinued schooling at the age of nine years. By the age of twelve years he developed difficulty in walking due to swaying to either sides. He developed several swellings over the tendons on the back of the elbow, over the patella and Achilles tendons by the age of fifteen years which has progressively increased in size over the years. He became chair bound by the age of 25 years due to weakness of lower limbs and contractures. He developed emotional lability, drooling of saliva and difficulty in speech. He has progressive diminution of vision over the last five years.

Examination revealed bitot spots in both eyes, suggestive of vitamin A deficiency, bilateral immature cataract, kyphoscoliosis, tendon xanthomas over the back of the elbow, both achilles tendons and patellar tendons. Neurological examination revealed bilateral pendular nystagmus, reduced visual acuity, wasting of muscle groups of upper and lower limbs, bi-pyramidal signs, pseudobulbar palsy and truncal ataxia.

Routine investigations including fasting lipid profile were normal. Fine needle aspiration from the swellings revealed foam cells and macrophages in a background of cholesterol crystals suggestive of xanthoma. MRI of the brain revealed T2 hyper-intensities in the pyramidal tracts and dentate nucleus and adjacent deep white matter of the cerebellum consistent with cerebrotendinous xanthomatosis. He was started on carbamazepine 200 mg twice daily and sodium valproate CR preparation 300 mg once daily for his seizures and chenodeoxycholic acid for the disease. He is under follow up and has not deteriorated neurologically since then.

Discussion

Cerebrotendinous xanthomatosis is a rare inborn disorder of bile acid synthesis in which hepatic conversion of cholesterol to cholic and chenodeoxycholic acids is impaired.2 A defect in hydroxylation of the cholesterol side chain that impairs oxidative cleavage has been identified. This disorder is due to a deficiency of the mitochondrial enzyme 27-sterol hydroxylase (CYP27) which plays a key role in bile acid synthesis.2 This leads to an excessive production of cholestanol, which then accumulates in many tissues.1 This is depicted in the illustration given below.

Clinical signs and symptoms include cataracts, tendon xanthomas, neurologic abnormalities, and premature atherosclerosis.5 These findings represent the consequences of the accumulation of cholesterol and cholestanol in affected tissues.

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"Illustration of the metabolic defect in Cerebrotendinous Xanthomatosis"

Due to the defect in 27-sterol dehydrogenase cholestanol is not converted to bile acids but gets converted to cholestanol and bile alcohols. The cholestanol gets deposited in tissues. By providing chenodeoxycholic acid exogenously, there will be a negative feedback effect which reduces bile acid synthesis. Further cholestanol accumulation is thus prevented.
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. Association of bilateral cataracts with chronic diarrhea may represent the earliest clinical manifestation of CTX.

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 two xanthomatous disorders.

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. Plasma cholesterol levels and lipoprotein profile remain within or below normal range. In patients with CTX, several studies with use of conventional MR imaging have shown diffuse and focal abnormalities of the white matter, cerebral and cerebellar atrophy, and a typical abnormal MR signal intensity change of the dentate nuclei and the surrounding white matter. Brain MT (magnetization transfer) ratio histograms are said to be better in quantification of neurological damage in CTX.

Bile acid therapy (cheno-deoxycholic acid, 250 mg three times daily) is effective, affordable, and safe. Further neurological deterioration can be prevented. Cheno-deoxycholic acid given exogenously inhibits the bile acid synthesis by negative feed back and thus further accumulation of cholestanol in tissues is prevented. Early detection and treatment of CTX significantly reduces the complications of the disease. Role of statins is controversial. Thus this entity becomes one of the rare forms of treatable hereditary ataxias.

References