

Cerebrotendinous Xanthomatosis in Three Siblings from a Chinese Family

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ABSTRACT

Cerebrotendinous xanthomatosis (CTX) is exceptionally rare in the Chinese population. We reported a 31-year-old Chinese male in Hong Kong, who has the characteristic features of cerebrotendinous xanthomatosis including the multiple xanthomas of tendons, mental retardation, bilateral cataracts, cerebellar ataxia and spasticity of the left arm, high concentrations of plasma phytosterols and abnormal MR of brain. On screening the family, two other siblings of 27 and 29 respectively, have tendon xanthomas and high plasma phytosterols. An extensive search of the international medical literature, including the Medline, has revealed only one other case report of cerebrotendinous xanthomatosis in Taiwan. CTX is a potentially treatable disease. It is hoped by alertness, early diagnosis and treatment can be made, and hence prevent further progression of the disease.

Keywords: Chinese, cerebrotendinous xanthomatosis, familial, xanthomas, mental insufficiency

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INTRODUCTION

Cerebrotendinous xanthomatosis (CTX) is an inborn error of bile acid metabolism⁽¹⁾. It is extremely rare in the Chinese population⁽²⁾. The presenting features of the disease include multiple xanthomas of tendons and other tissues, cataract, dementia, slowly progressive cerebellar ataxia, spasticity, peripheral neuropathy and chronic diarrhoea. Early detection of cerebrotendinous xanthomatosis is crucial, as the plasma phytosterols can be normalized by pharmacological therapy. Early treatment prevents irreversible damage of the nervous system due to the metabolic abnormalities⁽³⁾.

CASE REPORT

A 31-year-old waiter in a fast-food restaurant, who had attended school education only up to primary 5, began to have multiple xanthomas since 16. The xanthomas

Table I. The laboratory measurement of the plasma cholestanol and cholesterol of the affected siblings.

Sibling	Normal values	M/31	M/29	M/27
Plasma phytosterols				
Cholestanol	0.2 + 0.2	2.0%	1.6%	2.1%
Cholesterol	99.6 + 0.2	97.4%	97.6%	97.3%
Campesterol	0.05 + 0.04	0.6%	0.8%	0.6%
Cholesterol (mmol/L)	<5.5	2.9	4.6	3.6
Triglycerides (mmol/L)	<2.0	1.11	0.96	0.89
LDL-Chol (mmol/L)	<3.5	1.8	2.8	2.2
HDL-Chol (mmol/L)	>0.9	0.55	1.33	0.9

appeared over many of the finger tendons and web spaces, both Achilles tendons, and lower thighs. One of the xanthomas over the left Achilles tendon was excised a few years ago but reappeared later. His plasma cholesterol and triglycerides once checked were within normal limits. He was admitted into the orthopaedic ward for an infection of a xanthomas over his left ankle. Bacterial culture yielded Lancefield Group G streptococci. The infection responded to treatment with penicillin, incision and drainage. When physicians were consulted, in addition to the xanthomas, he was detected to have mild mental insufficiency with subnormal Mini-Mental Status Score, impaired heel toe walking, mild spasticity of the left arm and bilateral cataracts; otherwise, the rest of the physical examination was normal.

Laboratory tests gave normal total plasma cholesterol, LDL-cholesterol and triglycerides levels, but high concentration of plasma cholestanol, diagnostic of cerebrotendinous xanthomatosis (Table I). Electroencephalogram showed a moderately abnormal record with an increase in diffuse theta waves and short runs of irregular delta activity of 2-3 Hz, whereas MRI showed periventricular T₂ hyperintensities in the cerebral hemispheres but normal findings of the spinal cord.

The proband's father died of lung cancer at the age of 72, while his mother aged 66 was demented over the last few years, but had no tendon xanthomas. There was no known consanguinity in the family. The proband

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has got 3 sisters and 6 brothers, whose age range from 27 to 48, and all are from the same parents. On physical examination, only two other brothers, aged 29 and 27 respectively, were found to have tendon xanthomas. They were also detected to have high plasma cholestanol levels. Their magnetic resonance images of brain were normal.

All the 3 affected siblings were treated with HMG-CoA reductase inhibitor simvastatin 10 mg daily, and their plasma cholestanol levels became normal within a month. They have been followed up at the clinic for more than two years. Basically their mental scores and sizes of xanthomas remained the same, though the plasma cholestanol remained normalized.

DISCUSSION

Cerebrotendinous xanthomatosis is a rare autosomal recessive lipid storage disease with prominent neurological features. The disease was first described by Van Bogaert et al in 1937⁽⁴⁾. Its unique chemical feature, deposition of cholestanol, a derivative of cholesterol, within the nervous system, was uncovered only in 1968 by Menkes et al⁽⁵⁾.

The disease is associated with mutations in CYP27, which encodes mitochondrial sterol 27-hydroxylase, an enzyme that catalyses the oxidation of sterol intermediates during bile acid synthesis⁽¹⁾. The loss of this enzyme results in accumulation of cholestanol in many tissues, particularly in the brain. As a result, it leads to multiple xanthomas of tendons and other tissues, dementia, premature cataracts, progressive cerebellar ataxia, spinal cord paresis, peripheral neuropathy and chronic diarrhoea.

Onset of the disease usually occurs toward the end of first decade of life, and most individuals live beyond middle age. Progression is generally slow, and in many instances, the illness does not interfere with a normal life span. The triad of progressive spinocerebellar ataxia, pyramidal signs, and mental retardation is seen, in the large majority of patients with cerebrotendinous xanthomatosis, and mental retardation is seen in over 90%. Cataracts are present in 76% and are generally seen as early as 5-6 years. Seizures are encountered in 40-50%, and can be the presenting symptom⁽⁶⁾. Intractable diarrhoea can be a major manifestation during childhood⁽⁷⁾. A sensori-motor neuropathy has also been documented⁽⁸⁾. Xanthomas usually develop in adult life on the Achilles or other tendons. The cholesterol and triglycerides concentration in serum are normal, but cholestanol levels in serum and erythrocytes are elevated. Bile acid production is reduced, although the activity of the rate-limiting enzyme of bile production is elevated. CT reveals the presence of hypodense nodules in the cerebellum, and

diffuse white matter hypodensity. MRI demonstrates demyelination in cerebral and cerebellar white matter⁽⁹⁾.

Gross examination of the brain usually reveals mild cortical atrophy, especially of the frontal lobes. Atheromas are not common. No other gross abnormalities of the hemispheres are apparent. Gross examination of the cerebellum reveals granulomatous lesions in the white matter and atrophy of adjacent cerebellar folia. Microscopic examination of the cerebellum reveals profound demyelination; in some areas, cystic spaces of varying size may contain mononucleated cells with vacuolated eosinophilic, foamy cytoplasm. Needlelike clefts are present in some of the cystic spaces, which do not stain with oil red O but appear to be birefringent under polarized light, suggesting the presence of cholesterol⁽¹⁰⁾. Other studies of the cerebellum have revealed marked loss of Purkinje cells.

This well-defined disease has a predilection for Sephardic Jews of Moroccan ancestry. Orientals can be affected rarely, and the disease has been reported in the Japanese population⁽¹¹⁾. The occurrence in the Chinese population is exceptionally rare. In 1992, Chang et al⁽²⁾ reported cerebrotendinous xanthomatosis in three siblings from a Taiwanese family, whose clinical features consisted of tendinous xanthomas, cataracts, mental defects, pyramidal signs, cerebellar ataxia, peripheral neuropathy and renal stones, and biochemical findings included normal serum cholesterol levels, high serum cholestanol levels and elevated serum cholestanol to cholesterol ratios. An extensive search of the international medical literature, including the Medline, did not reveal other cases in the Chinese population.

In this communication, we have described 3 siblings from a Chinese family in Hong Kong, and their plasma cholestanol were normalized by a HMG-CoA reductase inhibitor simvastatin 10 mg daily within a month. They have been followed up for more than two years, and their mental scores and xanthomas remained the same. The long-term clinical outcome warrants further evaluation.

Treatment with chenodeoxycholic acid (CDCA) has been reported to be beneficial in some patients with cerebrotendinous xanthomatosis who showed a correction of biochemical abnormalities, a reversal of neurological symptoms, and an improvement in somatosensory evoked potentials and in the MRI scan⁽³⁾. The combined use of chenodeoxycholic acid and pravastatin was thought to be a good treatment, based on the improvement of serum lipoprotein metabolism, the suppression of cholesterol synthesis, and the reductions of cholesterol and plant sterol levels⁽¹²⁾. In a recent study, a combination of 750 mg chenodeoxycholic acid (CDCA) and 40 mg simvastatin

daily is effective to further reduce serum cholestanol, LDL cholesterol, and lathosterol in adult cerebrotendinous xanthomatosis patients treated with long-term CDCA⁽¹³⁾. In our patients, the cholestanol levels returned promptly to normal levels after treatment with simvastatin, but the mental scores and xanthomas remained the same. The place of simvastatin in the treatment of cerebrotendinous xanthomatosis requires further evaluation.

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