Cerebrotendinous Xanthomatosis with Cerebellar Ataxia as the Chief Symptom

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Introduction

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive lipid storage disease caused by a deficiency of the mitochondrial enzyme sterol 27-hydroxylase (CYP27). The clinical characteristics of CTX are diarrhea, cataracts, tendon xanthomas and neurological manifestations including dementia, psychiatric disturbance, pyramidal and/or cerebellar signs, and seizures. We report a 46-year-old female having CTX with cerebellar ataxia as the chief symptom.

Case Report

A 46-year-old female presented with the chief complaint of unsteady gait.

From August 1995, the patient noticed a tumor on the right Achilles tendon, which was enucleated in 1996. The biopsy diagnosis was xanthoma. Since 2002, the patient tended to lose balance and stumble frequently while walking on level ground. Her hands began to tremble when trying to pick up an object. The patient also became aware of a light-headed feeling accompanied by dizziness, and visited the Department of Neurology at our hospital in July 2002. Her cranial MRI showed abnormal signal intensity in both cerebellar hemispheres.

Medical and family history: The present patient had chronic diarrhea during childhood, cataract since age 20 and amenorrhea from 29 years of age.

Her family history was unremarkable, with no history of consanguineous marriage.

In the general physical examination, cataracts were identified in both eyes. Xanthomas were noted in both periorbital regions, subcutaneously in the left metacarpal and abdominal regions, and at the left Achilles tendon. There was no other abnormality.

Neurological findings: She was alert. Mental function was indicative of low intelligence; she scored 28 in the Mini Mental State Examination, and her WAIS performance IQ was 76. The manner of speech was ataxic, but she was capable of carrying out a conversation. Neurologically, there was no disturbance in the field of vision. Eye movement was normal, saccadic movement was not observed, nystagmus was absent and the light reflex was also normal. There was no other appreciable abnormality. The patient’s dominant hand was the right. Grip strength was 28 kg and 24 kg for the right and the left hands, respectively. Ataxia was observed in the upper and lower limbs, with similar severity. Dysfunction in the torso was mild. Diadochokinesis was poor. In a finger-to-nose test, both sides exhibited dysmetria and the emergence of an intention tremor was identified. Dysgraphia was also observed. In a knee-heel test, the heel could not be placed over the knee in an orderly fashion for either of the lower limbs, and a straight, smooth movement could not be obtained.Decreased muscle tone was observed, but there was no clear loss of muscle strength. Although a mild increase in the deep tendon reflex was apparent in both upper and lower limbs, no pathological reflex was observed. Maintenance of upright and seated postures was possible, but when both lower limbs were kept together while in an upright position, the patient tended to fall over easily. Assistance was required for the patient to be able to walk. Nevertheless, Romberg’s sign was negative, suggesting that the condition was not due to clear sensory impairment or vesicorectal disorders. The autonomic system was unremarkable.

Laboratory tests: Serum cholestanol was elevated to 8.9 μg/ml (about four-fold the reference value). Cholesterol was normal. The sitosterol level was 2.9 μg/ml, the lactic acid level was 10.9 mg/dl (there was no decrease in lactic acid), the blood-alcohol concentration was measured as 0.0, blood bile acid level was 7.8 nmol/ml and urinary bile acid was negative. In the apoprotein fraction, apolipoprotein B was elevated. Immunoserological examinations were negative for antinuclear antibody and anti-Yo autoantibody. In abdominal ultrasound examination, fatty liver and splenomegaly were identified. Neurophysiologic examinations, including electromyography, showed normal nerve conduction velocities. Cerebrospinal fluid examination was also within the normal range.

Genetic analyses indicated that SCA-1, SCA-2, SCA-6 and MJD were all normal. The CYP27A1 gene showed no abnormal finding in the regions from exon 1 through exon 9. The analysis was conducted with the reference value of 255 base pairs (bp) for the exon length and 322 bp for the
Figure 1. This is the head MRI T2-weighted image taken 4 years after the initial diagnosis. On the left is the image at the cerebellar hemisphere level, and on the right is that at the cerebral hemisphere level. Hyperintensive signals were observed on both sides of the cerebellar hemisphere, but no abnormality was observed at the cerebral hemisphere level.

PCR product length using primers 1F2 and 1R2 for exon 1; 199 bp for the exon length and 252 bp for the PCR product length using primers 2F and 2R for exon 2; 200 bp for the exon length and 292 bp for the PCR product length using primers 3F and 3R for exon 3; 198 bp for the exon length and 296 bp for the PCR product length using primers 4F and 4R for exon 4; 173 bp for the exon length and 286 bp for the PCR product length using primers 5F and 5R for exon 5; 167 bp for the exon length and 263 bp for the PCR product length using primers 6F and 6R for exon 6; 79 bp for the exon length and 266 bp for the PCR product length using primers 7F and 7R for exon 7; 213 bp for the exon length and 293 bp for the PCR product length using primers 8F and 8R for exon 8; and 344 bp for the exon length (of which the coding region was 120 bp) and 200 bp for the PCR product length using primers 9F and 9R for exon 9. All results were negative.

The cranial MRI findings were as follows (Fig. 1). There was no appreciable abnormality found in the T1-weighted images at the cerebral hemisphere level, but a hyperintensive signal was observed at the cerebellar hemisphere level. FLAIR and T2-weighted images showed high signal intensity areas in the white matter of both cerebellar hemispheres, but no abnormal signal intensity in any other region, including the cerebral white matter.

**Discussion**

Cerebrotendinous xanthomatosis (CTX) is a rare genetic disorder of metabolism with an autosomal recessive inheritance, in which patients develop multiple xanthomas, including Achilles tendon xanthoma, and juvenile cataract, with progressive impairment of the central nervous system, such as dementia, mental illness, pyramidal tract symptoms and cerebellar symptoms, in adulthood (1). About 200 cases have been reported to date, of which about half were in Japan. Central nervous system symptoms are variable. Nakamura et al (2) reported a case of CTX complicated by extrapyramidal symptoms. According to a study conducted by Verrips et al (3) who studied 32 cases of cerebrotendinous xanthomatosis (CTX), the frequency of concurrent occurrence of intermarriage was 3%, xanthomas 41%, cataracts 97% and childhood chronic diarrhea 50%. Furthermore, the frequencies of occurrence of various neurological symptoms were 66% for cognitive dysfunction, 81% for extrapyramidal symptoms, 56% for cerebellar symptoms, 31% for peripheral neuropathy, 50% for convulsive seizure and 3% for Parkinsonism. Missense mutations in CYP27A1 were reported to be found in 99% of the cases, including carriers, although sporadic cases could also be found. Barkhof et al (4) reported nearly identical results to those of Verrips et al (3) regarding the frequencies of concurrent occurrence of various clinical signs among 24 cases of CTX. However, the present case is extremely rare in that during the course of several years of observation, the patient mainly exhibited symptoms of cerebellar ataxia, but did not exhibit or only minimally exhibited other neurological symptoms, including extrapyramidal symptoms, which are reported to show the highest frequency of occurrence among observed neurological symptoms. As far as we know, this is the first report of a case in Japan in which almost all of the clinical signs considered as the principal signs consist only of cerebellar
symptoms. Even several years after onset, our patient has developed only cerebellar ataxia, without other central nervous symptoms except for mild cognitive impairment.

Cranial MRI images are known to be helpful for the diagnosis of CTX. For example, Federico and Dotti (5) reported that most cases showed lesions affecting the internal capsule at the level of the medial thalamus (including the pyramidal tract) optic radiation, deep temporal lobe, etc. in addition to the cerebellar lesions. Swanson and Cromwell (6) reported that cranial MRI images showed lesions in the periventricular white matter. Therefore, it appears that the radiographic findings of this disease are as variable as the clinical symptoms. In the present case, cranial MRI findings were localized to the cerebellar hemispheres. According to a report by Nakamura et al (2), hyperintense signals in head MRI are thought to be white lesions due to accumulation of lipids, such as cholesterol. The appearance of hypointensive signals at the position that exhibits abnormality in the head MRI T2-weighted image suggests an accumulation of hemosiderin, while the presence of hypointensive signals in the T1-weighted image and hyperintensive signals in the T2-weighted image suggests the presence of necrotic tissue. However, the current case exhibited hyperintensive signals in both T1- and T2-weighted images in head MRI at the cerebellar hemisphere level. Therefore, along with our diagnosis of CTX based on the observed clinical signs, we speculate that the hyperintense signal found in the cerebellar hemisphere was likely to be due to an accumulation of lipids, such as cholestanol, as in the case reported by Nakamura et al (2).

Based on their autopsy findings of CTX cases, Okada et al (7) reported that the progressive changes in head MRI findings appear to be associated with secondary demyelination and gliosis caused by sterol infiltration. Similar changes were seen in the present patient.

In summary, the present case is most unusual in that cerebellar ataxia was almost the only clinical symptom, and the lesions were localized in the cerebellar hemispheres, based on head MRI findings.

References


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