A Japanese Adult Case of Megalencephalic Leukoencephalopathy with Subcortical Cysts with a Good Long-term Prognosis

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Abstract

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is a recently recognized neurological disease, and mutations in the MLC1 gene have been identified as the cause of the disorder. A 54-year-old Japanese woman with macrocephaly presented with progressive mental decline, gait disturbance due to spasticity and ataxia, and choreoathetotic movement in the left upper extremity. Brain magnetic resonance imaging (MRI) revealed characteristic subcortical cysts in addition to diffuse white matter involvement. Genetic analysis of the MLC1 gene identified an S93L mutation in a homozygous state. This case is particularly valuable because of the lack of knowledge on the long-term prognosis of MLC.

Key words: megalencephalic leukoencephalopathy with subcortical cysts, MLC1, adult, choreoathetosis, involuntary movement

(DOI: 10.2169/internalmedicine.51.6462)

Introduction

Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an autosomal recessive neurological disorder characterized by macrocephaly within the first year, gradual progressive motor dysfunction with cerebellar ataxia and spasticity, mental retardation, and epileptic seizures (1). In 2001, Leegwater et al reported that mutations in the MLC1 gene are responsible for this disease (2). Magnetic resonance imaging (MRI) findings including diffuse cerebral white matter lesions and subcortical cysts are diagnostic in MLC. The long-term prognosis of MLC remains unclear because the condition was only recently established as a disease, with the development of neuroimaging procedures. Here, we report a 54-year-old woman diagnosed with MLC, with an S93L mutation in the MLC1 gene.

Case Report

A 54-year-old woman visited our hospital with the chief complaint of slowly progressive gait disturbance. The patient was wheelchair-dependent at the time, and was the first child of consanguineous healthy parents. She was born without any complications, and had never experienced seizures. Mental deterioration was first noted in the pre-school year, and she attended a special school. At age 6, she experienced the onset of acute motor deterioration in the left lower extremity after an accidental falling, resulting in gait inability. The weakness in the left extremity gradually improved, and she was eventually able to walk independently. Although her cognitive decline progressed with age, the patient was able to take care of money for daily shopping in her late 20s. The patient delivered her second child at the age of 35, but experienced difficulty walking from this age onwards. The patient could not stand on her own by the age of 50.

Neurological examination revealed macrocephalus, with a head circumference of 63 cm. Eye movements were saccadic. The patient exhibited ataxia in the trunk and extremities, and spastic tetraparesis. Deep tendon reflexes were hyperactive, and ankle clonus was present in the right side. The patient exhibited choreoathetosis in the left upper extremity. The Mini-Mental State Examination score was 11/30.
Figure 1. Diffuse white matter involvement demonstrated by brain magnetic resonance imaging (MRI). T1-weighted (A), T2-weighted (B, D, E, and F) and fluid-attenuated inversion recovery (FLAIR) images (C).

Laboratory tests revealed that the patient suffered from hyperthyroidism. A diagnosis of toxic multinodular goiter was made on the basis of ultrasonography and scintigraphy using technetium-99 m. There was no reduction in the activity of β-galactosidase or arylsulfatase A, and the level of very long chain fatty acids in the blood was not elevated. An electroencephalogram revealed slow background activity without epileptic discharges.

Brain MRI examination, performed on a 3-Tesla MRI unit, revealed diffuse high intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the cerebral white matter, including U-fibers (Fig. 1). On the other hand, marked hypointensities were noted on T1-weighted images (Fig. 1). The corpus callosum was apparently intact, but abnormal hyperintensity was observed in the posterior limb of the internal capsules, cerebral and cerebellar peduncles, and pontine base on T2-weighted and FLAIR images (Fig. 1, 2). Subcortical cysts in the tips of the bilateral temporal lobes and the superior frontal gyrus were recognized clearly on FLAIR images (Fig. 2). Marked brain atrophy in the fronto-temporo-parietal lobes was obvious in the FLAIR images (Fig. 1). Cavum septi pellucidi and cavum vergae were present (Fig. 1). No contrast enhancement was observed. Proton MR spectroscopy using a 3-Tesla MRI unit did not reveal the presence of a lactate peak in the affected deep white matter lesion of the right posterior lobe in which abnormal hyperintensities were observed on T2-weighted and FLAIR images (Fig. 3). The metabolic peak area ratios of N-acetylaspartate to creatine (NAA/Cr) and choline to creatine (Cho/Cr) were 3.18 and 0.38, respectively.

After obtaining written informed consent from the patient’s brother, sequencing of MLC1 cDNA from peripheral leukocytes was performed, as previously reported (3, 4). This examination revealed the presence of a 393C>T mutation, resulting in a missense mutation of S93L. We confirmed a homozygous S93L mutation by sequencing the genomic fragment containing exon 4 of the MLC1 gene.

Discussion

MRI is useful in the diagnosis of MLC due to the characteristic subcortical cysts and extended cerebral white matter involvement in the disorder. These features act as neuroradiological hallmarks in this disease. The present case exhibited typical subcortical cysts in the bilateral temporal tips and frontal lobes, leading to the diagnosis of MLC. The cerebral peduncle and the posterior limb of the internal capsules were affected in the present case, although it has previously been reported that central white matter structures such as the corpus callosum, internal capsule, and brain...
stem have a tendency to be preserved compared to the other supratentorial regions (1).

Approximately 80% of MLC patients exhibit mutations in the *MLC1* gene, although the remaining patients have not been found to exhibit any mutations in the gene, even with extended mutation analysis (5-7). These observations indicate genetic heterogeneity in this disease. Various mutations in the *MLC1* gene, including missense mutations, frame-shifts, and splice site mutations, have been reported worldwide (2). In the present patient, an S93L mutation was detected in a homozygous state. This mutation appears to be particularly common in Japanese patients with MLC (2-4, 8) but it has also been reported in Finland, Turkey, and Italy (2, 9).

The cardinal symptoms of MLC are macrocephaly, motor and mental deterioration, and seizures that are easily controlled with anticonvulsant drugs. Approximately 40% of MLC patients experience a characteristic episode of acute motor disability with gradual improvement, which is known to occur even after falling without direct head injury, as ob-

Figure 2. Subcortical cysts in the temporal and frontal lobes. T2-weighted (A and C) and FLAIR (B, D, and E) images. D and E are serial images (6 mm thickness). Arrowheads in B, D, and E indicate subcortical cysts.

Figure 3. Multi-voxel proton MR spectroscopic imaging of the deep white matter lesion of the right posterior lobe (TR=2,000 ms, TE=288 ms). NAA: N-acetylaspartate, Cho: choline, Cr: creatine.
served in the present case (7). Furthermore, extrapyramidal movement disorders such as dystonia, athetosis, and tics have been reported in the advanced stage (5, 10-12). The present patient also suffered from choreoathetosis. In this context, the low intensity of the bilateral putamina on T2-weighted images in our patient is of interest; however, the exact mechanism of abnormal involuntary movements in this disease remains unclear. Although there is no correlation between the severity of the phenotype and genotype of the MLC1 gene (13), the common clinical course of motor symptoms proceeds as follows: approximately half of the patients lose the ability to walk by the first decade of life (7), and the majority of affected patients become wheelchair-dependent in their teens (13). The present patient showed a milder clinical course compared with previously reported cases, as she could walk independently until at least her mid thirties. Little information regarding the average life span in MLC is available, because this disease was defined only recently (1). Some reported patients have died in their teens or twenties, but several adult cases of MLC have been reported (3, 4, 8, 14, 15). The patient described in the present case was over 50 years old at the time of diagnosis. To the best of our knowledge, this case is the oldest patient with genetically confirmed MLC in Japan. Saijo et al (4) reported a 41-year-old patient with MLC who was already wheelchair-dependent at the age of 11, indicating the possibility that appropriate care leads to a better prognosis, as proposed by previous researchers (3, 4). Although MLC is a rare neurological disorder, undiagnosed cases may exist. Increased information about adult cases will be helpful for clarifying the natural history and long-term prognosis of this disease.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We are grateful to Mrs. T. Seino and Mrs. N. Sakamoto for their technical assistance.

References