Hereditary Diffuse Leukoencephalopathy with Spheroids Characterized by Spastic Hemiplegia Preceding Mental Impairment

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Abstract

Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is a young-adult-onset autosomal dominant white matter disease characterized by progressive cognitive dysfunction. We herein report the case of a 20-year-old woman who developed spastic hemiplegia. Brain magnetic resonance imaging revealed increased bilateral T2 signal intensity and bright diffusion-weighted imaging signals with a low apparent diffusion coefficient within the frontoparietal white matter. The lesion gradually expanded for over one year. The patient was initially diagnosed with multiple sclerosis (MS); however, she did not respond to immunosuppressive therapy. DNA sequencing showed a heterozygous c.2381T>C mutation in colony-stimulating factor 1 receptor. HDLS with a pure motor phenotype is sometimes difficult to differentiate from MS.

Key words: hereditary diffuse leukoencephalopathy with spheroids, CSF1R mutation, multiple sclerosis, diffusion-weighted image, apparent diffusion coefficient

Introduction

Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is a young-adult-onset autosomal dominant white matter disease characterized by progressive cognitive dysfunction, behavioral changes, motor impairment and seizures (1). The diagnosis is usually made following a brain biopsy or autopsy based on the presence of neurodystrophy and large areas of neuroaxonal swelling known as spheroids (2). After several mutations in colony-stimulating factor 1 receptor (CSF1R) were recently shown to underlie HDLS (3), various clinical courses and imaging features of the disease were revealed through genetic diagnosis. We herein report a case of HDLS with progressive spastic hemiplegia that was initially diagnosed as multiple sclerosis (MS).

Case Report

A 20-year-old left-handed Japanese woman was admitted to our neurological department due to progressive right spastic hemiplegia that had started five months before admission. The patient’s development was normal and her previous medical history was unremarkable, including neither head trauma nor seizures. She had no history of drug abuse, including alcohol. She had been a good volleyball player while a student, and after graduating from high school, she enrolled in nursing school. Her mother had a 10-year history of cognitive decline that had progressed until she became functionally mute with a diagnosis of frontotemporal dementia at 40 years of age. Her maternal grandmother died in her 40s, and she had a younger brother who exhibited no mental or physical problems.

Upon admission, the patient was alert and oriented, with a
full Mini-Mental State Examination score. The general findings were unremarkable. A neurological examination showed slight spasticity, motor weakness, sensory loss, exaggerated deep tendon reflexes and an extensor plantar response in the right extremities. She had no visual or urinary problems. Routine laboratory findings were unremarkable. Tests with negative or normal results were as follows: anti-nuclear antibodies, HIV, soluble interleukin-2 receptor, angiotensin-converting enzyme, anti-aquaporin 4 antibodies, very long chain fatty acids, arylsulfatase A and a cerebrospinal fluid (CSF) analysis, including myelin basic protein, oligoclonal bands and the IgG index. The activity of galactocerebrosidase was slightly low, although not significantly. An aerobic exercise test showed a slight increase in the levels of lactate and pyruvate. A nerve conduction study, electroencephalogram and visual evoked potential were normal.

Brain magnetic resonance imaging (MRI) revealed bilateral, but left dominant, increased T2 and fluid-attenuated inversion recovery (FLAIR) signal intensity within the frontoparietal white matter, corticospinal tract and splenium of the corpus callosum (Fig. 1A, B). The arcuate fasciculus was spared. Bright diffusion-weighted image (DWI) signals and a low apparent diffusion coefficient (ADC) were recognized in the areas of T2/FLAIR signal abnormalities, except for the brainstem (Fig. 1C, D). No post-gadolinium enhancement was noted. 18F-fluorodeoxy glucose positron emission tomography (PET) showed no abnormal uptake in these areas. MRI of the spine was normal. N-isopropyl-123I-p-iodoamphetamine single photon emission computed tomography imaging revealed substantial left dominant decreases in flow in the frontoparietal white matter. Magnetic resonance angiography was completely normal.

The patient’s clinical course and radiological features suggested MS, except for the absence of CSF abnormalities. She was tentatively diagnosed with MS on the first admission and treated with intravenous and oral corticosteroids and plasmapheresis without benefit.

At the one-year follow-up visit, the patient was wheelchair-bound and demonstrated worsened right spastic hemiplegia as well as a slight cognitive decline, emotional incontinence, dysarthria and spasticity on the left side. Brain MRI disclosed enlarged bilateral white matter lesions with increased T2/FLAIR signal intensity, bright DWI and low ADC (Fig. 1E-H).

After providing genetic counseling for the patient and her father, we obtained their informed consent and extracted genomic DNA from peripheral blood leukocytes obtained from the patient and her parents using an ABI 3130 Genetic Analyzer (Applied Biosystems, Foster City, USA), and exons 12-22 of CSF1R were amplified with polymerase chain reaction (PCR). A direct sequence analysis of the PCR-amplified DNA revealed a heterozygous c.2381T>C muta-

Figure 1. Neuroimaging findings. Brain MR images at the first admission are shown in the upper row (A-D). (A) (B) FLAIR images show increased intensity in the corpus callosum, pyramidal tract, and frontoparietal white matter. (C) Bright DWI and (D) low ADC were observed in the areas of FLAIR signal abnormalities (arrowheads). The bottom row (E-H) shows MR images obtained 1 year later in which signal abnormalities were more extensive. FLAIR: fluid-attenuated inversion recovery, DWI: diffusion-weighted image, ADC: apparent diffusion coefficient.
tion in exon 18 in the patient and her mother (Fig. 2). This mutation has previously been reported in patients with HDLS (3).

**Discussion**

We herein reported a case of HDLS in which a diagnosis of MS was initially considered due to the patient’s young age, subacute progressive spastic hemiplegia and white matter lesions.

The initial symptoms of HDLS typically include cognitive dysfunction and personality changes, accompanied by motor impairment, including weakness, spasticity, rigidity, tremors and seizures (1). HDLS patients are frequently misdiagnosed with Alzheimer’s disease, frontotemporal dementia, atypical parkinsonism and other leukoencephalopathy syndromes, such as adrenoleukodystrophy, metachromatic leukodystrophy, metachromatic leukodystrophy and Krabbe disease (1, 4, 5).

The primary symptoms in this case were subacute and progressive motor impairment without cognitive decline, which are common clinical features of MS in young women. In fact, the patient’s clinical course (one year of disease progression) and radiological findings (evidence of lesion dissemination in the space in the brain based on T2-weighted images in at least one area characteristic of MS, e.g., periventricular, juxtacortical or infratentorial) satisfied the McDonald criteria for primary progressive MS, except for the absence of CSF abnormalities (6). Moreover, the differential diagnosis of white matter lesions and callosal lesions, including neuromyelitis optica, progressive multifocal leukoencephalopathy (PML), Marchiafava disease and adrenoleukodystrophy, was unlikely taking into consideration the patient’s clinical history and laboratory data. In contrast to the patient, her mother primarily exhibited cognitive decline and was diagnosed with frontotemporal dementia, which is retrospectively consistent with the typical symptoms of HDLS. However, we initially did not regard the mother’s symptoms to be related to the patient’s disease due to the phenotypic differences.

Case reports regarding a pure motor type of HDLS have recently accumulated (7-9). Discriminating between HDLS and MS is often difficult, especially in such cases. As seen in the present patient and her family, the clinical phenotype of HDLS, including the initial symptoms and age of onset, vary considerably, even the pedigree. Inheritance in patients with HDLS may be concealed by such clinical heterogeneity. In fact, patients with HDLS are sometimes found to have sporadic disease (7, 10). The heritability of MS, on the other hand, has been established, such that the presence of genetic factors increases the risk of developing MS; the age-adjusted risk of recurrence in offspring is 2.07 (95%CI 1.41-2.73) (11). These facts suggest that the presence of neurological disorders in relatives does not provide sufficient evidence to discriminate between MS and HDLS. Appropriate comprehension of HDLS is required to make a correct and rapid diagnosis using genetic analyses, which should also be helpful for avoiding unnecessary treatment, including immunosuppressive therapy, for the pure motor type of HDLS, as observed in the present case.

Generally, the brain MRI findings of HDLS patients show white matter lesions that are hyperintense on T2-weighted and FLAIR images and hypointense on T1-weighted images unaccompanied by contrast uptake (12). Bifrontoparietal areas of T2/FLAIR hyperintensity are often asymmetric, especially in the early stage of the disease. The presence of lesions in deep, subcortical and periventricular areas is typical, with occasional involvement of the corticospinal tract and corpus callosum (12). Most of the MRI abnormalities observed in our case, including the presence of T2/FLAIR abnormalities in periventricular lesions, the corticospinal tract and the corpus callosum without contrast enhancement, are compatible with the well-documented radiological characteristics of this disease.

Previous authors have reported restricted diffusion in areas with corresponding dark ADC values in patients with HDLS (10, 13-16), while few cases of HDLS with restricted diffusion persisting over a long period, as observed in the present patient, have been documented. Mateen et al. reported one case of HDLS in which bright DWI with dark ADC values persisted for 19 weeks, and a brain biopsy revealed advanced axonal loss with spheroid formation, myelin loss and gliosis. The authors speculated that the restricted diffusion of extracellular water is associated with the presence of degraded myelin sheaths (14). Sundal et al. described the case of a patient who was followed with MRI for 16 months after disease onset, which revealed initially high signal intensity on DWI with restricted mean diffusivity. In that case, the high signal area on DWI and restricted diffusivity changed dynamically throughout the follow-up period. After the lesion reached the peripheral rim of the

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![Figure 2. DNA sequencing findings. A heterozygous c. 2381T>C mutation in exon 18 of CSF1R was identified in this patient (arrow). CSF1R: colony-stimulating factor 1 receptor](image-url)
white matter (a subcortical lesion), the signal on DWI decreased, while the mean diffusivity increased (14). The present patient continued to exhibit high DWI with a low ADC over one year. To the best of our knowledge, no previous reports have shown decreased ADC values in the same lesion sustained for a long period of time. Restricted diffusion appears to be caused by high viscosity of proteinaceous fluid and a high concentration of cells. Pathologically, axonal spheroids are filled with neurofilaments and organelles, which may cause diffusion restriction in HDLS patients (17).

Several diseases of the brain have been reported in patients with decreased ADC values, including acute cerebral infarction, multiple sclerosis, Creutzfeldt-Jakob disease, abscesses, metastasis and progressive multifocal leukoencephalopathy (18, 19). In the present case, the patient’s symptoms and laboratory results suggested neither ischemic stroke nor infectious disease. Moreover, the PET study showed no malignancies, including lymphoma. A normal mental status and electroencephalogram findings on the first admission did not positively indicate Creutzfeldt-Jakob disease. We did not assess the patient for the JC virus in association with progressive multifocal leukoencephalopathy because she had no immunological risk factors.

In conclusion, we herein described a case of adult-onset HDLS that initially mimicked MS both clinically and radiologically. Cases of HDLS showing a pure motor phenotype are sometimes difficult to clinically differentiate from MS.

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

Acknowledgement
This work was supported by a Grant-in-Aid (No. 22591595 to T.M.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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