INTERNAL MEDICINE

□ CASE REPORT □

Early Involvement of the Corpus Callosum in a Patient with Hereditary Diffuse Leukoencephalopathy with Spheroids Carrying the *de novo* K793T Mutation of *CSF1R*

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Abstract

We herein report the case of a 41-year-old Japanese man with hereditary diffuse leukoencephalopathy with spheroids (HDLS) who carried the *de novo* K793T mutation in the colony-stimulating factor 1 receptor gene (*CSF1R*). He showed a gradual decline of his cognitive and mental functions over the following six months. On brain MRI, a thin corpus callosum with T2- and FLAIR-high signal intensity in the splenium was conspicuous, whereas cerebral deep and periventricular white matter lesions were mild. We propose that a diagnosis of HDLS should be considered in patients with presenile dementia presenting with corpus callosum lesions on MRI, even in cases with a lack of any apparent family history.

Key words: HDLS, *CSF1R*, *de novo* mutation, corpus callosum

(Intern Med 52: 503-506, 2013)
(DOI: 10.2169/internalmedicine.52.8879)

Introduction

Hereditary diffuse leukoencephalopathy with spheroids (HDLS) is an autosomal-dominant white matter disease caused by mutations in the colony-stimulating factor 1 receptor gene (*CSF1R*) (1). It is characterized clinically by adult-onset behavioral, cognitive and motor dysfunction and pathologically by a widespread loss of axons and myelin sheaths and the appearance of axonal spheroids and pigmented macrophages (2-4). Several sporadic patients who fulfill the clinical and pathological criteria for HDLS have been reported (5-8). However, it remains unknown whether these sporadic cases reflect phenotypic copies, reduced disease penetrance or are caused by *de novo* mutations in the genes responsible for the HDLS phenotype (4).

We herein describe the case of an HDLS patient who carried a novel *de novo* K793T mutation in *CSF1R*. This is the second family, next to the Norwegian family described by Rademakers et al. (1), in which both parents have been shown to not carry the causative *CSF1R* mutation. The cases of these families clearly suggest that a subset of sporadic cases of HDLS are caused by *de novo CSF1R* mutations. Furthermore, we propose that involvement of the corpus callosum on MRI may be an early diagnostic clue indicating a diagnosis of HDLS.

Case Report

A 41-year-old Japanese man had been well until 40 years of age when he began to show a decline in his cognitive function. He was first noticed to have difficulty performing occupational tasks and handling a cell phone in October 2011. In January 2012, he twice developed confusion and unresponsiveness while during drinking alcohol. His wife encouraged him to visit the hospital in February 2012, where he was suspected of having presenile dementia. Thereafter, he became unable to use a personal computer or drive a car and had to quit working. His wife noted that his speech and gait had become awkward. His previous medical history was unremarkable. There was no particular family history of psychiatric or neurological diseases. His parents

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Received for publication August 28, 2012; Accepted for publication November 14, 2012
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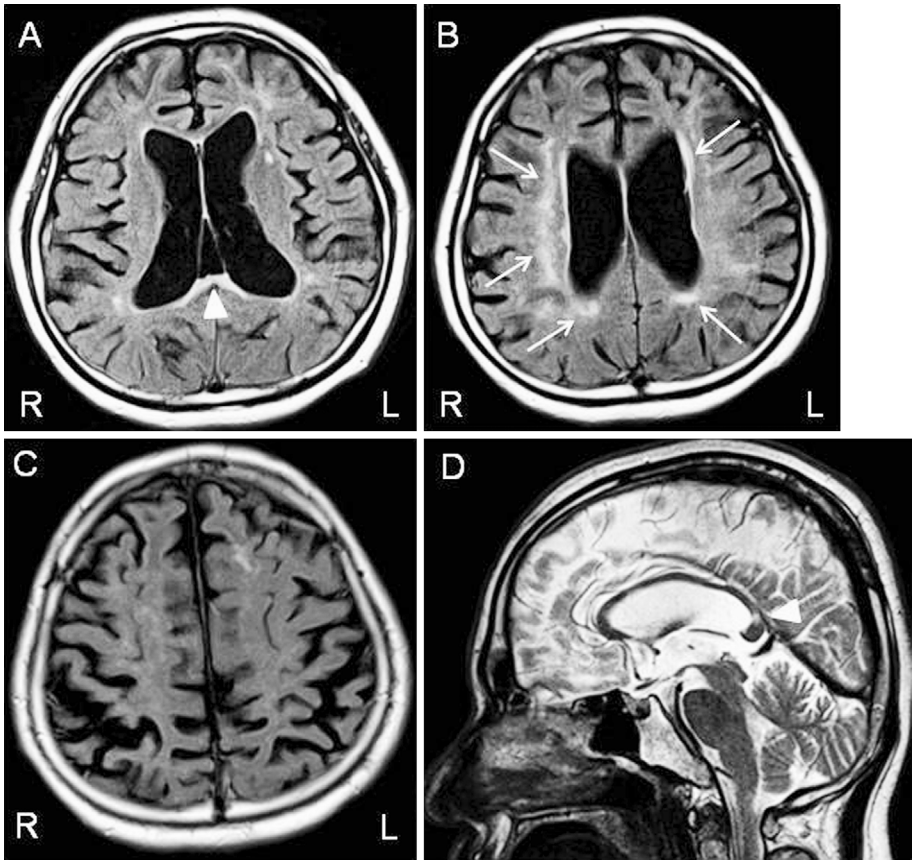

Figure 1. Brain MRI images. Brain MRI images of the patient (at 41 years of age) are shown. Dilatation of the lateral ventricles and hyperintense foci are observed in the cerebral deep and periventricular white matter on FLAIR-weighted images (arrow, A-C). The corpus callosum is atrophic and shows high signal intensity in the splenium (arrowhead) on FLAIR-weighted (A) and T2-weighted images (D).

and two sisters were healthy.

On admission in April 2012, the patient was found to be normotensive and the general findings were not particular. He was cooperative, although he did not appear to have any awareness of being ill. A neurological examination showed a slow initiation of speech, dysarthria, slight left hemiplegia and an unstable gait. The patient's deep tendon reflexes were slightly exaggerated; however, his plantar responses were flexor. No rigidity or involuntary movements were observed. The Mini-Mental State Examination score was 23 points and the Frontal Assessment Battery (FAB) score was 10 points. These tests demonstrated poor attention, calculation and comprehension and a disturbance in verbal fluency; however, the patient's short-term memory was relatively well preserved.

The routine laboratory findings were unremarkable. Tests with negative or normal results were as follows: vitamin B1, vitamin B12, anti-nuclear antibody, syphilis, HIV, soluble interleukin 2 receptor and angiotensin converting enzyme. A cerebrospinal fluid examination showed a slight increase in the levels of total protein (51 mg/dL) and tau protein (290 pg/mL, normal value: 0-200 pg/mL). Brain MRI disclosed frontoparietal lobe atrophy and ventricular dilatation with high-intensity lesions in the cerebral deep white matter (Fig. 1). Hyperintense foci were more evident in the right hemisphere than in the left. The corpus callosum was atrophic and showed high signal intensity in the splenium (Fig. 1). No microbleeds were detected in the white matter or basal ganglia on T2*-weighted images (data not shown). There was no atrophy or signal changes in the cerebellum or brainstem. Cerebral angiography showed no findings of atherosclerosis. The findings of a nerve conduction study were normal.

The clinical and neuroradiological findings reminded us of the possibility of frontotemporal dementia, leukoencephalopathy or leukodystrophy of several genetic causes, vascular dementia (VaD) (including Binswanger disease), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), multiple sclerosis (MS) or progressive multifocal leukoencephalopathy (PML). Immediately before this patient was referred to us, we experienced another patient with leukoencephalopathy who exhibited presenile dementia and a thin corpus callosum on MRI, similar to our patient, and was diagnosed as having HDLS based on a brain biopsy and a *CSF1R* analysis (9). Therefore, we first searched for the *CSF1R* mutation after obtaining informed consent from the patient's wife and parents.

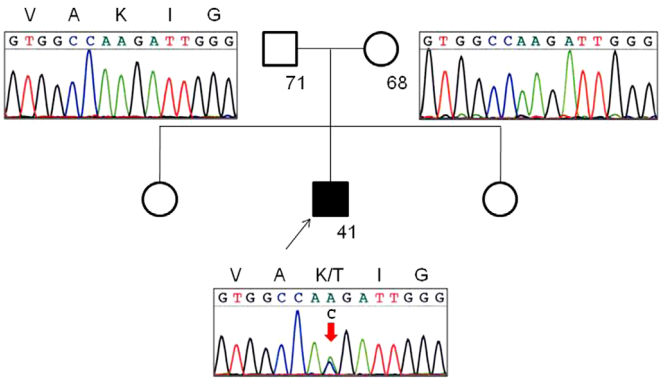

Figure 2. Molecular analysis of *CSF1R*. The sequencing results of exon 18 of *CSF1R* indicate a heterozygous c.2378A>C (p. Lys793Thr) substitution in the patient (indicated by the red arrow). The cDNA and protein numberings are relative to NM_005211.3 starting at the translation initiation codon and NP_005202.2, respectively. Neither parent has the mutation.

Genomic DNA was extracted from peripheral blood samples obtained from the patient and his parents using the Gentra Puregene Blood Kit (QIAGEN). Exons 12-22 of *CSF1R*, the mutation 'hot spots' in HDLS patients, were PCR-amplified according to a previous report (1), purified and subjected to direct sequencing. We found the p.K793T (c.2378A>C) mutation in the patient, but not in his parents (Fig. 2). Similar to the *CSF1R* mutations reported previously (1, 9), this mutation is involved in a highly conserved amino acid in the intracytoplasmic tyrosine kinase domain of *CSF1R*. An in silico analysis using PolyPhen-2 indicated that the change was probably damaging. This mutation was not detected in 80 Japanese control individuals.

Discussion

Previously, a definitive diagnosis of HDLS was made based on postmortem, neuropathological examinations only. Owing to the availability of molecular analyses of *CSF1R*, however, our patient was diagnosed as having HDLS in the early stage when he was still self-supporting at home approximately six months after the onset of symptoms.

Brain MRI, which disclosed lateral ventricle enlargement with corpus callosum lesions, was an important tool in the diagnosis of our patient. Sundal et al. reported the MRI characteristics of 15 HDLS patients with *CSF1R* mutations (10). Of these 15 patients, 14 exhibited corpus callosum involvement (the disease duration at the initial MRI study ranged from 0.5 to 5.0 years). Corpus callosum involvement included atrophy (eight patients), T2- and FLAIR-high signal intensity (11 patients) and both atrophy and signal changes in the corpus callosum (five patients) (10). In our patient, MRI performed at a disease duration of approximately six months showed atrophy and signal changes in the corpus callosum. At this stage, the cerebral deep and periventricular white matter lesions were mild and not confluent. These findings suggest that early involvement of the corpus callosum can be a diagnostic clue of HDLS.

A number of neurological diseases involving presenile dementia should be differentiated from HDLS. One of the key points for making the differential diagnosis is the regional distribution of white matter lesions. For example, white matter lesions in X-linked adrenoleukodystrophy are observed predominantly in the parietooccipital lobes (11), whereas those in HDLS are frontal dominant (10). White matter lesions in the temporal tip and external capsules are pathognomonic in CADASIL (12); however, they were not observed in seven HDLS patients, including the present patient (Kinoshita et al. unpublished observation). However, the MRI findings of HDLS closely resemble those of primary progressive MS or VaD, as they commonly show relatively symmetrical white matter lesions with corpus callosum atrophy (8, 13-15). We are now carrying out a detailed examination of the MRI characteristics of HDLS patients in comparison with those of VaD patients (Kinoshita et al. manuscript in preparation).

The patient was sporadic with both parents being healthy until their late sixties or early seventies. The mode of inheritance of HDLS is autosomal-dominant; however, several sporadic patients who met the clinical and neuropathological criteria for HDLS have been reported (5-8). Such patients might be reported under a diagnosis of pigmentary orthochromatic leukodystrophy (POLD), which shows quite similar clinical and neuropathological features to HDLS (4). Based on their clinical and neuropathological similarities, HDLS and POLD have been proposed to belong to a single disease entity (2, 4, 16-18). Therefore, the molecular basis of HDLS and POLD has increasingly attracted much attention since the discovery of *CSF1R* as a causative gene for HDLS.

Our case suggests that the incidence of HDLS may be much higher than previously estimated because sporadic HDLS cases might be overlooked unless postmortem examinations are undertaken. We propose that more careful attention should be paid to HDLS as a possible cause of presenile dementia, regardless of a patient's family history. Now, a premortem diagnosis of HDLS can be established using a molecular analysis of *CSF1R*. Making an early diagnosis is of great importance in furthering the understanding of sequential changes in clinical and neuroradiological findings among patients with HDLS.

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

Acknowledgement

We thank Ms. Eri Ishikawa and Kayo Suzuki (Research Center for Human and Environmental Sciences, Shinshu University) for their technical assistance in the molecular analysis of *CSF1R*.

This work was supported by Grants-in-Aid from the Research Committee for Hereditary Cerebral Small Vessel Disease and Associated Disorders, the Ministry of Health, Labour and Welfare of Japan.

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