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□ ORIGINAL ARTICLE □

Corpus Callosum Atrophy in Patients with Hereditary Diffuse Leukoencephalopathy with Neuroaxonal Spheroids: An MRI-based Study

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Abstract

Objective Hereditary diffuse leukoencephalopathy with neuroaxonal spheroids (HDLS) is an adult-onset white matter disease that presents clinically with cognitive, mental and motor dysfunction. Several autopsy reports have indicated that the corpus callosum (CC), the largest bundle of white matter, is severely affected in patients with HDLS. The aim of this study was to evaluate corpus callosum atrophy (CCA) quantitatively in HDLS patients.

Methods We assessed CCA in six genetically-proven HDLS patients (HDLS group), in comparison with that observed in 20 patients with vascular dementia (VaD group) and 24 age-matched patients without organic central nervous system (CNS) disease (non-CNS group). Using midsagittal MR images, five measurements of the CC were obtained: the width of the rostrum (aa'), body (bb') and splenium (cc'), the anterior to posterior length (ab) and the maximum height (cd). Next, the corpus callosum index (CCI) was calculated as (aa' + bb' + cc')/ab.

Results All HDLS patients had white matter lesions in the CC and frontoparietal lobes on the initial MRI scans. Compared with that observed in the VaD and age-matched non-CNS groups, the CCI was significantly decreased in the HDLS group (with VaD group, $p<0.01$; with non-CNS group, $p<0.01$).

Conclusion This study showed significant atrophy of the CC in all HDLS patients on the initial MRI scans obtained 6-36 months after onset. We propose that the early appearance of CCA, frequently accompanied by high-intensity in the genu and/or splenium, on T2 images is an important diagnostic clue to HDLS.

Key words: hereditary diffuse leukoencephalopathy with neuroaxonal spheroids (HDLS), colony stimulating factor 1 receptor (CSF1R), white matter lesions (WMLs), corpus callosum atrophy (CCA), corpus callosum index (CCI)

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Introduction

Hereditary diffuse leukoencephalopathy with neuroaxonal spheroids (HDLS) is an adult-onset white matter disease caused by mutations in colony stimulating factor 1 receptor [*CSF1R* (1)]. HDLS is characterized clinically by cognitive, psychiatric and motor dysfunction that is frequently accom-

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Table 1. Clinical Characteristics of Six HDLS Patients

Patient	1	2	3	4	5	6
Sex	F	M	M	M	M	F
Age at disease onset (years)	51	41	53	40	55	27
Age at death (years)	alive	41	56	alive	62	alive
Family history	+	-	+	+	+	-
Neuropsychiatric symptoms						
Cognitive decline	+	+	+	+	+	+
Depression/Anxiety	-	+	+	+	+	?
Behavioral change	+	+	+	+	+	+
Frontal releasing signs	+	+	+	+	+	+
Pyramidal tract signs	+	-	+	-	+	+
Parkinsonism	+	+	+	+	+	?
Apraxia	-	+	+	+	?	+
Epilepsy	+	-	+	-	-	+
CSF1R mutation	R782H	K793T*	R777W	R777W	S759F	I794T*

*: genetically-determined sporadic case carrying a *de novo* mutation, ?: unknown or equivocal because of difficulty to evaluate symptoms

panied by epilepsy (2). The age of onset is quite variable, ranging from 8 to 78 years, and the mean duration of the illness has been reported to be 10 years (2) or 5.8 years (3). Due to its wide variety of neuropsychiatric symptoms and age of onset, HDLS mimics many neurological diseases, including vascular dementia (VaD), cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), frontotemporal dementia (FTD), multiple sclerosis (MS) and multisystem atrophy [MSA (4-7)].

MRI has significant value in evaluating the distribution and degree of white matter lesions (WMLs) and is indispensable for diagnosing HDLS. Recently, Sundal et al. reported the characteristics of 20 MRI scans of 15 patients with pathologically- and genetically-proven HDLS (3). They revealed that WMLs are predominantly frontal in patients with HDLS and that WMLs extending beyond the frontal lobes indicate rapid disease progression.

They also proposed a brain MRI scoring system for evaluating HDLS that appears to be very useful for tracking the natural history of HDLS and predicting the prognosis; however, this system places more emphasis on signal changes in the white matter (total WML score 42) than on atrophy (total atrophy score 13) (3).

Since the discovery of *CSF1R* as the causative gene, it has become possible to make a definitive diagnosis of HDLS in the early stage of the disease (1). We recently experienced a 41-year-old HDLS patient with the K793T mutation in *CSF1R* (patient 2, Table 1) (8). He was independent in daily life [modified Rankin Scale (mRS) 2] at the first presentation. His initial MRI scans (obtained six months after onset) showed minor WMLs within the frontoparietal lobes, corresponding to a total WMLs score of only 9/42 points on the MRI grading scale (3), however, diffuse atrophy of CC was already evident (8). This distinctive finding prompted us to assess early CC involvement in HDLS patients in greater detail.

Corpus callosum atrophy (CCA) has been noted in the postmortem examinations of advanced HDLS patients with diffuse widespread WMLs and severe brain atrophy (9-14).

Sundal et al. reported that CC involvement is frequently observed in HDLS patients on initial MRI scans, with the disease duration ranging from 0.5 to 5.0 years (3); however, in that study, CCA was roughly evaluated according to either its 'presence' or 'absence.' Therefore, in this study, we assessed MRI scans quantitatively to evaluate CCA in HDLS patients, especially in the early stage of disease without the presence of widespread WMLs on MRI.

Materials and Methods

Subjects

We examined 10 brain MRI scans of six HDLS patients (four men and two women; age at MRI scan: 29-57 years; mean age±standard deviation, 47.3±9.3 years) (Table 2). Mutations in *CSF1R* were identified in all patients. Three patients (patients 1, 3 and 4) had a family history consistent with autosomal inheritance (15), and two patients (patients 2 and 6) were confirmed to carry a *de novo CSF1R* mutation. One patient (patient 5) with a *CSF1R* mutation also had an affected brother; however, detailed information on their parents was not available. The detailed clinical information of the six HDLS patients is summarized in Table 1.

When enrolling patients with VaD, we adopted the guidelines of the National Institute for Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences [NINDS-AIREN (16)]. We reviewed the medical records at our institution from April 2007 through March 2011. A diagnosis of VaD was made in patients fulfilling both the probable VaD criteria in the NINDS-AIREN and the following additional requirements: 1) an age under 80 years, 2) no family history of neurological or psychiatric diseases, 3) midsagittal MR images available for measurement. We ultimately identified 20 consecutive patients with VaD (11 men and nine women; age at MRI scan: 42-79 years, mean 68.5±7.9 years). The degree of clinical disability at the time of the MRI scan was assessed in the HDLS and VaD groups using the mRS defined by Sulter et al. (17).

The age-matched control group without organic central

Table 2. Summary of the MRI Findings

HDLS (n = 6) Patient	Age at onset (years)	Age at MRI (years)	Disease duraation until the MRI scan (months)	mRS#	HDLS MRI severity score*			Corpus callosum atrophy								Evans index
					Total WML score (corpus callosum)	Total atrophy score (corpus callosum)	Total score	ab (L)	aa'	bb'	cc' (B: body)	cd (H: height)	CCI	B/H	B/L	
1 (1)	51	52	19	2	12 (5)	4 (1)	16	61.0	5.39	5.71	2.53	28.14	0.224	0.090	0.042	0.293
1 (2)		57	72	5	23 (6)	10 (1)	33	64.7	2.62	3.85	2.02	34.90	0.131	0.057	0.031	0.371
2 (1)	41	41	6	2	5 (1)	4 (1)	9	72.9	5.10	6.37	2.95	30.56	0.198	0.097	0.040	0.330
2 (2)		41	11	3	9 (3)	4 (1)	13	73.9	3.72	4.40	2.73	31.33	0.147	0.087	0.037	0.344
3 (1)	53	56	36	3	12 (5)	5 (1)	17	69.0	6.07	6.05	4.18	30.27	0.236	0.138	0.061	0.290
3 (2)		57	48	5	16 (6)	9 (1)	25	NA	NA	NA	NA	NA	NA	NA	NA	0.320
4 (1)	40	41	14	2	15 (6)	9 (1)	24	78.3	8.91	6.08	2.32	34.30	0.221	0.068	0.030	0.360
4 (2)		42	28	3	16 (6)	9 (1)	25	79.1	9.64	4.45	3.13	36.15	0.218	0.087	0.040	0.371
5	55	57	33	4	21 (6)	8 (1)	32	NA	NA	NA	NA	NA	NA	NA	NA	NA
6	27	29	8	4	17 (4)	4 (1)	22	60.7	6.73	9.37	2.33	19.83	0.304	0.119	0.038	0.286
average	44.500	47.300	27.500	3.300			21.600	69.954	6.023	5.785	2.775	30.685	0.210	0.093	0.040	0.331
SD	9.691	9.285	19.679	1.100			7.432	6.818	2.237	1.612	0.628	4.815	0.050	0.024	0.009	0.034
VaD (n = 20)																
average		68.500		2.750				72.620	8.160	7.992	4.689	28.479	0.289	0.169	0.065	0.272
SD		7.940		0.887				5.484	1.566	1.540	0.750	4.151	0.050	0.039	0.011	0.026
non-CNS (n = 24)																
average		49.917						71.141	10.157	10.609	5.635	27.221	0.371	0.208	0.079	0.246
SD		13.789						4.253	2.076	1.808	1.054	2.789	0.056	0.039	0.014	0.022

NA: not analyzed, #: modified Rankin Scale (17), *: proposed by Sundal et al. (3)

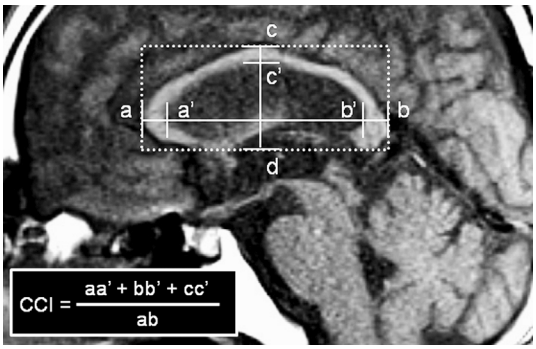

Figure 1. Determination of the corpus callosum index (CCI) using a midsagittal slice on a T1-weighted MR image (HDLS patient 2 in Table 1, 41-year-old man).

nervous system diseases (non-CNS group) included 24 patients (15 men and nine women; age at MRI scan: 29-73 years, mean 49.9±13.8 years). Their diagnoses were as follows: myasthenia gravis (n=6), psychosomatic disorder (n=5), benign paroxysmal positional vertigo (n=3), Guillain-Barré syndrome or Fisher syndrome (n=3), spinal canal stenosis (n=2), spinal cord tumor (n=2; able to exclude multiple sclerosis), brachial plexus neuropathy or neuralgic amyotrophy (n=2) and facioscapulohumeral muscular atrophy (FSH) (n=1). Brain MRI was conducted to rule out intracranial lesions in these patients. None of the patients had WMLs on MRI, except for a small amount of lacunar infarctions.

MRI assessments

The brain MRI scans of the VaD group and non-CNS group were performed in our hospital with a 1.5 Tesla Magnetom Avanto scanner (Siemens AG, Erlangen, Germany). T1-weighted images were obtained using a spin-echo technique (TE=12-26 ms, TR=250-500 ms, slice thickness=3-4 mm). The scans of the HDLS patients were performed in four different hospitals, patients 1-4 being examined using the same scanner as at our hospital (1.5 Tesla Magnetom Avanto, using the same acquisition protocol as the other groups). All of the MRI scans were measured independently once each by one of the authors (YK) and two additional examiners (YT and KT) who were blind to the clinical information, including the diagnoses and ages of the patients. All measurements were obtained using a computerized measurement tool on screen on a picture archiving and communication system (PACS) workstation. We measured the corpus callosum using midsagittal T1-weighted images according to previous reports (18-20). Five measurements of the CC were obtained (Fig. 1): the width of the rostrum (aa'), body (cc', abbreviated as B) and splenium (bb'), the anterior to posterior length (ab, abbreviated as L) and the maximum height (cd, abbreviated as H). The corpus callosum index (CCI), which has been reported to be a marker for brain atrophy in MS patients (18, 19), was calculated as (aa'+bb'+cc')/ab. The ratios B/L and B/H were also calculated. The Evans index (the maximum distance between the two anterior horns/the maximum transverse inner diameter of the skull at the same level) was measured using axial T1-weighted images. A comparison between the three investigators' evaluations of each indicator of the CCA and the Evans index was made with the intraclass correlation coefficiency (*ICC*) and internal consistency using Cronbach's alpha coefficient. In addition, we assessed the severity of WMLs and brain atrophy according to the MRI grading system proposed by Sundal et al. (3).

Statistical analysis

The statistical analysis was carried out using the nonparametric Mann-Whitney U-test to compare the indicators of CCA (aa', bb', cc' (B), ab (L), cd (H), BL, BH and CCI) and the Evans index between the HDLS group and each control group. We considered p values of <0.05 or less to be statistically significant.

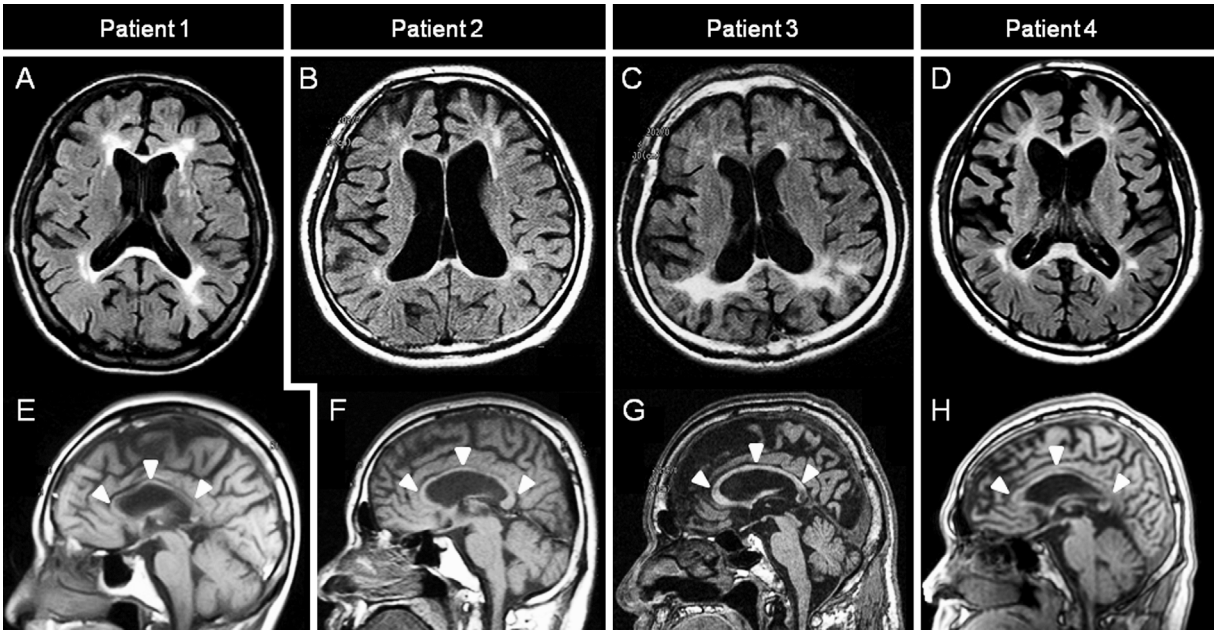

Figure 2. **Representative MRI findings of four HDLS patients. A-D: Axial FLAIR images showing patchy or confluent periventricular-dominant white matter lesions and hyperintensity signals in the CC, especially in the splenium. E-H: Midsagittal T1-weighted images showing severe diffuse CC atrophy (arrowheads). (A and E: Patient 1 at age 52 (approximately 19 months after onset); B and F: Patient 2 at age 41 (approximately 11 months after onset); C and G: Patient 3 at age 56 (approximately three years after onset); D and H: Patient 4 at age 42 (approximately 14 months after onset), each patient number corresponding to that in Tables 1 and 2).**

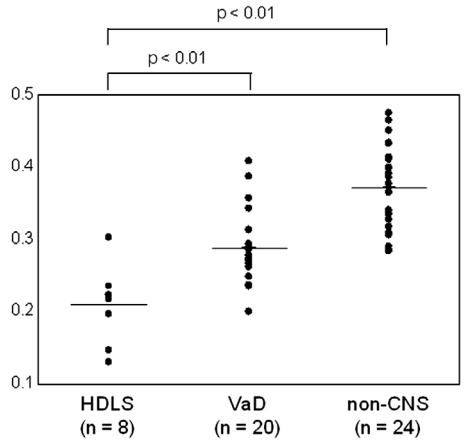

Figure 3. **Distribution of the corpus callosum index (CCI) in the patients with HDLS, vascular dementia (VaD) and control individuals without organic central nervous system diseases (non-CNS). The CCI was significantly decreased in the HDLS group (0.210±0.050) compared with that observed in the VaD group (0.289±0.050) ($p<0.01$) and age-matched non-CNS group (0.371±0.056) ($p<0.01$). The horizontal bar indicates the mean of each group.**

Results

All patients with HDLS had WMLs in the CC and fronto-parietal lobes (Fig. 2; Table 2). The WMLs extended to the temporal lobes in three patients. The total MRI severity scale for HDLS (3) ranged from 9 to 33 (Table 2). As the disease progressed, volume loss of the cerebral white matter became evident. None of the patients had high-intensity signals in the temporal tips or external capsules. Four patients (seven scans) were screened for cerebral microbleeds using T2*-weighted images; however, no such bleeding was detected, whereas 11 of the 12 patients (91.7%) examined in the VaD group had cerebral microbleeds.

Hyperintense signals and atrophy in the CC were detected on all 10 MRI scans in the six patients (Fig. 2; Table 2). The CCI was significantly decreased in the HDLS group (0.210±0.050) compared with that observed in the VaD group (0.289±0.050) ($p<0.01$) and age-matched non-CNS group (0.371±0.056) ($p<0.01$) (Fig. 3; Table 2). The B/H index (cc'/cd in Fig. 1) was also significantly reduced in the HDLS group (0.093±0.024) compared to that observed in the VaD group (0.169±0.039) ($p<0.01$) and non-CNS group (0.208±0.039) ($p<0.01$). Similarly, the B/L index (cc'/ab in Fig. 1) was significantly reduced in the HDLS group (0.040±0.009) compared to that observed in the VaD group (0.065±0.011) ($p<0.01$) and age-matched non-CNS group (0.079±0.014) ($p<0.01$). The Evans index, an indicator of lateral ventricle dilatation, was significantly larger in the HDLS group (0.331±0.034) than in the VaD group (0.272±0.026) ($p<0.01$) or non-CNS group (0.246±0.022) ($p<0.01$). The inter-rater reliability and internal consistency of the total measurements were almost good (*ICC*=0.755-0.951; Cronbach's alpha=0.907-0.986) (Table 3).

Table 3. Inter-rater Reliability and Internal Consistency of the Indicators of Corpus Callosum Atrophy and the Evans Index

	HDLS group (n = 8)		VaD group (n = 20)		Non-CNS control group (n=24)		Total (n = 52)	
Items	*ICC*	Cronbach's alpha	*ICC*	Cronbach's alpha	*ICC*	Cronbach's alpha	*ICC*	Cronbach's alpha
ab (L: length)	0.992	0.999	0.949	0.987	0.920	0.976	0.951	0.986
aa'	0.899	0.962	0.575	0.840	0.615	0.823	0.755	0.907
bb'	0.820	0.940	0.627	0.840	0.585	0.840	0.792	0.927
cc' (B: body)	0.656	0.883	0.577	0.801	0.736	0.895	0.832	0.940
cd (H: Height)	0.855	0.943	0.892	0.977	0.815	0.953	0.867	0.963
B/H	0.688	0.916	0.724	0.895	0.692	0.889	0.933	0.979
B/L	0.615	0.864	0.598	0.815	0.737	0.895	0.842	0.950
CCI	0.840	0.946	0.738	0.904	0.565	0.876	0.830	0.938
Evans index	0.913	0.970	0.844	0.950	0.853	0.960	0.859	0.952

ICC: Intraclass correlation coefficiency

Discussion

The occurrence of CCA with WMLs has been reported in some demential disorders, such as VaD, including Binswanger's disease, and CADASIL, MS and leukodystrophies, including HDLS. This was a quantitative study conducted to understand CC involvement in HDLS itself, and the aim was not primarily to compare the disease with the occurrence of CCA in VaD for diagnostic purposes to distinguish it from HDLS. We selected a VaD group as a control simply because VaD is the most common and representative disease involving CCA with WMLs.

Due to their clinical and neuroradiological similarities, it is sometimes difficult to differentiate between HDLS and other diseases involving CCA with WMLs, especially in the early stage of the disease. The lack of a family history does not preclude the possibility of HDLS, as several sporadic patients who fulfill the clinical and neuropathological criteria for HDLS have been reported (4, 5, 8, 21). Furthermore, the occurrence of HDLS due to a *de novo CSF1R* mutation has hitherto been confirmed in two families in which the parents of the patient had no mutations of interest (1, 8), and one such family was newly added in this study (patient 6). The most reliable method of discriminating HDLS is currently genetic testing for *CSF1R*. Because genetic testing for *CSF1R* is not presently commercially available, identifying laboratory or neuroradiological hallmarks of HDLS is of value in order to select candidates for further processing to genetic testing.

Recently, Sundal et al. reported that 14 of 15 patients exhibited CC involvement (the disease duration at the initial MRI study ranged from 0.5 to 5.0 years). The CC involvement included atrophy (eight patients), T2 and FLAIR high signal intensity (11 patients) and both atrophy and signal changes in the CC (five patients) (3). These data appear to indicate that hyperintense signals and atrophy in the CC are not correlated with each other. This may be partly because CCA was evaluated using a score of 0 (absence of atrophy) or 1 (presence of atrophy). Therefore, we evaluated CCA quantitatively in this study.

As to data regarding the measurement of CC in healthy Japanese subjects, Takeda et al. reported CC measurements in 205 Japanese individuals without CNS disorders (94 men, mean age: 57.3±20.8 years; range: 6-90 years; and 111 women, 61.2±17.6 years; range: 9-86 years). These values are similar to those of our study, including the widths of the rostrum (aa'): mean ± SD 9.91±1.82 (our non-CNS group, 10.16±2.08), body (bb'): 5.58±1.08 (5.64±1.05), splenium (cc'): 9.94±1.56 (10.61±1.81) and anterior to posterior length (ab): 69.7±4.24 (71.14±4.24), although there was a difference in the range of ages between the two studies. In another study, the CC measurements of 15 Japanese healthy men (mean age: 56.2±6.9) were reported as follows: aa': 10.6±1.4, bb': 5.3±1.1, cc': 10.4±1.4 and ab: 72.7±8.5 (22). These data were also very close to those of our measurements, as well as the ranges of ages, in the non-CNS group. In addition, the CCI was 0.362 when calculated using the mean data for the trial (our non-CNS group: 0.371±0.056). These results support the reliability of the CCI data for our non-CNS group, in spite of the limitation in the number of cases.

In our study, all of the patients had abnormal hyperintensive signals in the CC on their initial MRI scans (disease duration ranging from six to 36 months). Furthermore, the CCI was significantly decreased when compared with that observed in the VaD and age-matched non-CNS groups. In this study, the mean age at MRI in the VaD group (68.5 years) was much higher than that noted in the HDLS group (47.3 years). Takeda et al. showed that the widths of the rostrum (aa'), body (cc', B) and splenium (bb') of the CC decrease with age in normal Japanese individuals (20). Conversely, the maximum height (cd, H) and anterior to posterior length (ab, L) gradually increase with age. These data indicate that the CCI, B/H and B/L decrease with age. Taking the difference in the mean age between the HDLS and VaD groups into consideration, we can say that the decreases in the CCI, B/H and B/L in the HDLS group were conspicuous compared with those observed in the VaD group.

In addition, the CCI observed in the HDLS patients was much less than that at diagnosis in the MS patients (0.345±

0.04; mean age 42±11 years, n=169) reported by Yaldizli et al. (19). Therefore, we think that CCA should be monitored more carefully in HDLS patients.

The LADIS study indicated that CCA is associated with cognitive decline that coexists independently with white matter hyperintensity and stroke (23, 24). In particular, overall CCA is correlated with the slowing of processing or mental speed (23, 24). In patients with HDLS, frontal lobe signs and symptoms are frequently observed in the early stage of the disease. This is consistent with the observation of Sundal et al. that WMLs are predominantly frontal (3), as supported by the findings of this study. Additionally, it is possible that the early involvement of the CC contributes to the psychomotor dysfunction observed in HDLS patients.

CCA is observed in elderly persons, as well as in patients with cerebrovascular and neurodegenerative diseases (25-31). Several underlying mechanisms for CCA have been postulated (25-30). In Alzheimer's disease patients, CCA primarily reflects the loss of the corresponding cortical neurons (Wallerian degeneration hypothesis) (26, 28, 29) and/or age-related myelin breakdown (retrogenesis hypothesis) (28, 29, 32). Conversely, in patients with cerebrovascular diseases, CCA is closely related to cerebral WMLs (26, 27, 31), assuming that ischemic damage causes focal edema and inflammation with subsequent axonal disruption (26). The mechanism underlying the development of CCA in patients with HDLS is likely to be different from that observed in those with Alzheimer's disease or cerebrovascular disease because CCA develops in the earlier stage of the disease and progresses more rapidly in HDLS.

HDLS is neuropathologically characterized by the extensive loss of myelin sheaths, axonal destruction and the presence of numerous axonal spheroids, pigmented macrophages and astrogliosis (2, 9-14). These changes were clearly observed in the centrum semiovale of the cerebral white matter in one of our patients (patient 2) (8). That patient died of sepsis caused by severe intestinal infection at age 41 in the early stage of the disease (mRS3). Macroscopically, the CC was diffusely thin (data not shown). Histologically, the localized portion of the splenium of the CC that exhibited T2 and FLAIR high signals on MRI demonstrated a severe loss of myelin and axons with axonal spheroids, as seen in the centrum semiovale. This is a primary pathological process of axonal disruption in HDLS. On the other hand, the basic structure was relatively preserved in the other parts of the CC, where the number of axons was decreased; however, the findings of tissue destruction, including localized myelin loss, disarrangement of axons and the presence of spheroids and activated macrophages, were quite mild. This likely reflects a secondary change due to axonal damage in the proximal parts of the commissural fibers. CC involvement in HDLS patients is therefore considered to be caused by these combined pathological processes. Additionally, ischemic changes, including small infarcts and microvascular fibrohyalinosis, were almost absent in the entire CC; therefore, the pathologic mechanism appears to be basically different between HDLS and cerebrovascular disease.

The present study is associated with several limitations. First, the number of HDLS patients was very small. The incidence of HDLS in the Japanese population remains unknown because genetic testing for *CSF1R* has only recently been introduced into clinical practice, and genetically-proven cases are very small in number at present. Second, the patients in the VaD group in this study were rather heterogeneous because this was a retrospective study. The mRS of the VaD group (2.75±0.89) was not significantly different from that of the HDLS group (3.30±1.10); however, the cognitive function levels varied from subnormal to severe dementia in the VaD group. As judged according to the mRS, cognitive, mental and motor dysfunction was variable in both the HDLS and VaD groups; therefore, it was not possible to make MRI comparisons between these two groups after adjusting for the clinical status. Third, there was overlap in the values of the CCI between the HDLS and VaD patients; therefore, we were unable to present any diagnostic cutoff values for distinguishing HDLS from VaD.

In conclusion, despite the several limitations described above, our quantitative neuroimaging study clearly showed the presence of CCA on the initial MRI scans (6-36 months after disease onset) in HDLS patients. Our findings suggest that the presence of CCA on MRI frequently accompanied by high intensity in the genu and/or splenium on T2 and FLAIR images is a useful finding indicative of HDLS.

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

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References

1. Rademakers R, Baker M, Nicholson AM, et al. Mutations in the colony stimulating factor 1 receptor (*CSF1R*) gene cause hereditary diffuse leukoencephalopathy with spheroids. Nat Genet **44**: 200-205, 2012.
2. Wider C, Van Gerpen JA, DeArmond S, Shuster EA, Dickson DW, Wszolek ZK. Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD). A single entity? Neurology **72**: 1953-1959, 2009.
3. Sundal C, Van Gerpen JA, Nicholson AM, et al. MRI characteristics and scoring in HDLS due to *CSF1R* gene mutations. Neurology **79**: 566-574, 2012.
4. Moro-de-Casillas ML, Cohen ML, Riley DE. Leucoencephalopathy with neuroaxonal spheroids (LENAS) presenting as the cerebellar subtype of multiple system atrophy. J Neurol Neurosurg Psychiatry **75**: 1070-1072, 2004.
5. Keegan BM, Giannini C, Parisi JE, Lucchinetti CF, Boeve BF, Josephs KA. Sporadic adult-onset leukoencephalopathy with neuroaxonal spheroids mimicking cerebral MS. Neurology **70**: 1128-1133, 2008.
6. Wong JC, Chow TW, Hazrati L-N. Adult-onset leukoencephalopa-

thy with axonal spheroids and pigmented glia can present as frontotemporal dementia syndrome. Dement Geriatr Cogn Disord **32**: 150-158, 2011.

7. Sundal C, Lash J, Aasly J, et al. Hereditary diffuse leukoencephalopathy with axonal spheroids (HDLS): A misdiagnosed disease entity. J Neurol Sci **314**: 130-137, 2012.

8. Kondo Y, Kinoshita M, Fukushima K, Yoshida K, Ikeda S. Early involvement of the corpus callosum in a patient with hereditary diffuse leukoencephalopathy with spheroids carrying the *de novo* K793T mutation of *CSF1R*. Intern Med **52**: 503-506, 2013.

9. van der Knaap MS, Naidu S, Kleinschmidt-Demasters BK, Kamphorst W, Weinstein HC. Autosomal dominant diffuse leukoencephalopathy with neuroaxonal spheroids. Neurology **54**: 463-468, 2000.

10. Terada H, Ishizu H, Yokota O, et al. An autopsy case of hereditary diffuse leukoencephalopathy with spheroids, clinically suspected of Alzheimer's disease. Acta Neuropathol **108**: 538-545, 2004.

11. Marotti JD, Tobias S, Fratkin JD, Powers JM, Rohdes CH. Adult onset leukodystrophy with neuroaxonal spheroids and pigmented glia: report of a family, historical perspective, and review of the literature. Acta Neuropathol **107**: 481-488, 2004.

12. Itoh K, Shiga K, Shimizu K, Muranishi M, Nakagawa M, Fushiki S. Autosomal dominant leukodystrophy with axonal spheroids and pigmented glia: clinical and neuropathological characteristics. Acta Neuropathol **111**: 39-45, 2006.

13. Baba Y, Ghetti B, Baker MC, et al. Hereditary diffuse leukoencephalopathy with spheroids: clinical, pathologic and genetic studies of a new kindred. Acta Neuropathol **111**: 300-311, 2006.

14. Freeman SH, Hyman BT, Sims KB, Hedley-Whyte ET, Vossough A, Frosch MP. Adult onset leukodystrophy with neuroaxonal spheroids: clinical, neuroimaging and neuropathologic observations. Brain Pathol **19**: 39-47, 2009.

15. Kinoshita M, Yoshida K, Oyanagi K, Hashimoto T, Ikeda S. Hereditary diffuse leukoencephalopathy with axonal spheroids caused by R782H mutation in *CSF1R*: case report. J Neurol Sci **318**: 115-118, 2012.

16. Román GC, Tatemichi TK, Erkinjuntti T, et al. Vascular dementia: diagnostic criteria for research studies. Report of the NINDS-AIREN International Workshop. Neurology **43**: 250-260, 1993.

17. Sulter G, Steen C, De Keyser J. Use of the Barthel index and modified Rankin scale in acute stroke trial. Stroke **30**: 1538-1541, 1999.

18. Figueira FFA, dos Santos VS, Figueira GMA, da Silva ÂCM. Corpus callosum index: a practical method for lomg-term follow-up in multiple sclerosis. Arq Neuropsiquiatr **65**: 931-935, 2007.

19. Yaldizli O, Atefy R, Gass A, et al. Corpus callousm index and long-term disability in multiple sclerosis patients. J Neurol **257**: 1256-1264, 2010.

20. Takeda S, Hirashima Y, Ikeda H, Yamamoto H, Sugino M, Endo S. Determination of indices of the corpus callosum associated with normal aging in Japanese individuals. Neuroradiol **45**: 513-518, 2003.

21. Yamashita M, Yamamoto T. Neuroaxonal leukoencephalopathy with axonal spheroids. Eur Neurol **48**: 20-25, 2002.

22. Oishi M, Mochizuki Y, Shikata E. Corpus callosum atrophy and cerebral blood flow in chronic alcoholics. J Neurol Sci **162**: 51-55, 1999.

23. Jokinen H, Ryberg C, Kalska H, et al; LADIS group. Corpus callosum atrophy is associated with mental slowing and executive deficits in subjects with age-related white matter hyperintensities: the LADIS study. J Neurol Neurosurg Psychiatr **78**: 491-496, 2007.

24. Jokinen H, Frederiksen KS, Garde E, et al. Callosal tissue loss parallels subtle decline in psychomotor speed. a longitudinal quantitative MRI study. The LADIS Study. Neuropsychologia **50**: 1650-1655, 2012.

25. Meguro K, Constans JM, Courtheoux P, Theron J, Viader F, Yamadori A. Atrophy of the corpus callosum correlates with white matter lesions in patients with cerebral ischaemia. Neuroradiology **42**: 413-419, 2000.

26. Tomimoto H, Lin JX, Matsuo A, et al. Different mechanisms of corpus callosum atrophy in Alzheimer's disease and vascular dementia. J Neurol **251**: 398-406, 2004.

27. Ryberg C, Rostrup E, Sjöstrand K, et al; LADIS study group. White matter changes contribute to corpus callosum atrophy in the elderly: the LADIS study. AJNR Am J Neuroradiol **29**: 1498-1504, 2008.

28. Di Paola M, Di Iulio F, Cherubini A, et al. When, where, and how the corpus callosum changes in MCI and AD: a multimodel MRI study. Neurology **74**: 1136-1142, 2010.

29. Di Paola M, Luders E, Di Iulio F, et al. Callosal atrophy in mild cognitive impairment and Alzheimer's disease: different effects in different stages. Neuroimage **49**: 141-149, 2010.

30. Frederiksen KS, Garde E, Skimminge A, et al. Corpus callosum tissue loss and development of motor and global cognitive impairment: the LADIS study. Dement Geriatr Cogn Disord **32**: 279-286, 2011.

31. Lee DY, Fletcher E, Martinez O, et al. Vascular and degenerative processes differentially affect regional interhemispheric connections in normal aging, mild cognitive impairment, and Alzheimer disease. Stroke **41**: 1791-1797, 2010.

32. Bartzokis G. Age-related myelin breakdown: a development model of cognitive decline and Alzheimer's disease. Neurobiol Aging **25**: 5-18, 2004.