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ORIGINAL RESEARCH

Symmetric Temporal Abnormalities on MR Imaging in Amyotrophic Lateral Sclerosis with Dementia

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BACKGROUND AND PURPOSE: Our aim was to clarify imaging findings of amyotrophic lateral sclerosis with dementia (ALSD).

MATERIALS AND METHODS: T2-weighted MR images (T2WI) of 3 patients with ALSD (2 men, 1 woman; 58–71 years of age) and 21 patients with ALS without dementia (12 men, 9 women; 46–74 years of age) were examined for frontotemporal lobar atrophy and signal-intensity alterations in the white matter of the anterior temporal lobes, corticospinal tracts (CST), and precentral gyri and in precentral cortices. The brain of one of the patients with ALSD was examined at autopsy.

RESULTS: All patients with ALSD showed bilateral frontotemporal atrophy mostly with temporal lobe dominance. In the ALSD group, T2WI demonstrated hyperintensity in the subcortical white matter on the medial side of the anterior temporal lobes, whereas in the group without dementia, none showed this imaging finding. MR images demonstrated no abnormal signal-intensity changes in CST in the internal capsule or the brain stem in the ALSD group. In the group without dementia, 6 patients (28.6%) showed this imaging finding. In neuropathologic examinations of the brain of 1 patient with ALSD, myelin-stained sections of the brain demonstrated loss of myelin in the subcortical white matter on the medial side of the anterior temporal white matter.

CONCLUSIONS: A symmetric pattern of frontotemporal atrophy and anteromedial subcortical hyperintensities in the temporal lobes on T2WI could be characteristic of ALSD.

Recent evidence suggests that amyotrophic lateral sclerosis (ALS) is not an isolated motor neuron disorder but a multisystem disorder with varying presentations and with widespread extramotor neuropathologic involvement.[1] Some patients with otherwise typical ALS also develop dementia, often a prominent feature of frontotemporal lobe dysfunction.[2] Neuropathologic examinations of patients with ALS and dementia (ALSD) revealed that the medial cortex of the anterior temporal lobe was constantly and most remarkably involved.[3,4]

In patients with classic ALS, widespread sensorimotor and frontal cortical atrophy has been described.[5] Although imaging studies have suggested the involvement of brain structures beyond the motor neuron systems in patients with ALSD, studies in which there were specific imaging findings of ALSD are very few.[5] The purpose of our study is to clarify imaging findings of ALSD.

Materials and Methods

Patients

We reviewed 24 consecutive patients with ALS who had undergone MR imaging studies between October 2005 and September 2006 (Table). All met the World Federation of Neurology criteria for ALS.[6] The patients were subdivided into 2 groups: namely, the ALSD group and the classic ALS group. The ALSD group comprised 3 patients (2 men, 1 woman; age range, 58–71 years; mean age, 64.7 ± 6.5 years; disease duration before MR imaging, 3.0 ± 2.6 years) whose revised Hasegawa Dementia Scales (HDS-R) were 17/30, 14/30, and 9/30, respectively; the classic ALS group comprised 21 patients (12 men, 9 women; age range, 46–74 years; mean age, 63.0 ± 8.3 years; disease duration, 3.2 ± 2.3 years) without dementia symptoms. There was no statistical difference between the 2 groups concerning age and disease duration. Our institutional review board did not require us to seek approval for a retrospective study using routinely obtained clinical data. Patients' informed consent was also not required.

Imaging Acquisition

MR imaging was performed with a 1.5T MR imaging scanner (Signa Excite III HD, Version 12.0; GE Yokogawa Medical Systems, Tokyo, Japan). The following sequences were obtained in each patient: 1) transverse T2 and proton attenuation conventional spin-echo (SE) (TR/TE/acquisitions, 2300/30–100/1; FOV, 22 × 16.5 cm; section thickness, 6.0 mm; section gap, 1 mm; matrix, 256 × 192); and 2) coronal T2-weighted (T2WI) fast spin-echo (FSE) (TR/TE/acquisitions, 4000/30/2; FOV, 22 × 17.6 cm; section thickness, 3.0 mm; section gap, 0.7 mm; matrix, 256 × 256).

MR Imaging Analysis

All MR images were reviewed for frontotemporal lobar atrophy and signal-intensity alterations in the white matter of the anterior temporal lobes, corticospinal tracts (CSTs), and precentral gyri and in precentral cortices by 2 neuroradiologists blinded to the clinical data. In cases of interobserver disagreement, final decisions were reached by a consensus. The degree of atrophy was assessed by visual analysis of the size of the subarachnoidal spaces, ranked by 3 points (3, severe; 2, moderate; 1, mild or absent). When the width of the subarachnoidal spaces was larger than the thickness of the adjacent gyri, we ranked the degree of atrophy as 3. When the width of the subarachnoidal spaces

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Clinical and MR imaging findings in patients with ALS

Patient No.	Age (y)	Sex	Duration Before MRI (y)	Dementia (HDS-R)	Bulbar Symptoms	Upper Motor Neuron Symptoms	Lower Motor Neuron Symptoms, Upper Extremities	Lower Motor Neuron Symptoms, Lower Extremities	Atrophy Frontotemporal Lobes*	HI Anterior Temporal White Matter	HI Bilateral Precentral White Matter	HI Bilateral Corticospinal Tracts	HI Bilateral Precentral Cortices	Small Infarction or Unidentified Bright Objects
1	58	M	1	+, 17/30	+	−	+	+	2, T, bilateral	+, bilateral	−	−	+	−
2	65	M	6	+, 14/30	+	−	+	+	3, T, bilateral	+, bilateral	+	−	−	+
3	71	F	2	+, 9/30	+	−	+	+	2, Fr, bilateral	+, bilateral	−	−	−	+
Subtotal	64.7 ± 6.5		3.0 ± 2.6	100%					2.33	100%	33.3%	0%	33.3%	66.7%
4	46	M	1	−	+	+	+	+	1	−	−	−	−	−
5	50	F	6	−	+	+	+	+	1	−	−	−	+	−
6	54	F	6	−	−	+	+	+	1	−	−	−	−	−
7	55	F	2	−	+	+	+	+	2, Fr, bilateral	−	+	+	+	−
8	57	M	1	−	+	+	+	+	1	−	−	−	−	+
9	57	M	3	−	+	−	−	−	1	−	−	−	−	+
10	58	F	1	−	+	+	+	+	1	−	+	+	+	+
11	60	F	1	−	+	+	+	−	1	−	−	+	+	−
12	62	F	0	−	+	+	+	−	1	−	+	+	+	+
13	62	F	2	−	+	+	+	+	2, Fr, bilateral	−	−	+	+	+
14	62	M	4	−	+	+	+	+	2, T, bilateral	−	−	−	+	+
15	62	M	6	−	+	+	+	−	1	−	−	−	−	+
16	65	M	7	−	+	+	+	−	2, T, bilateral	−	−	−	−	−
17	67	M	2	−	−	+	−	+	1	−	+	−	+	−
18	69	M	8	−	+	+	+	+	1	−	−	−	+	+
19	70	F	2	−	+	+	+	+	1	−	+	−	+	+
20	71	M	5	−	+	+	+	+	2, T, bilateral	−	+	−	+	+
21	74	F	1	−	+	+	+	+	1	−	+	−	−	+
22	74	M	2	−	−	−	+	+	2, Fr, bilateral	−	−	−	−	+
23	74	M	4	−	+	+	+	+	1	−	+	+	+	+
24	74	M	4	−	+	−	+	+	1	−	+	−	+	+
Subtotal	63.0 ± 8.3		3.2 ± 2.3	0%					1.33	0%	42.9%	28.6%	61.9%	66.7%
Total	63.2 ± 8.0		3.2 ± 2.3	12.5%					1.46	12.5%	41.7%	37.5%	58.3%	66.7%

Note:—HI indicates hyperintensity; Fr, frontal dominance; T, temporal dominance; +, present; −, absent.
* 3 indicates severe; 2, moderate; 1, mild or absent.

was equal to the thickness of the adjacent gyri, the degree of atrophy was ranked as 2. When we could hardly determine whether the atrophy was present, the degree of atrophy was ranked as 1.

Signal-intensity changes in the anterior temporal white matter and precentral white matter were evaluated by visual inspection on transverse SE T2WI and coronal FSE T2WI and were compared with the intensity of the gray and white matter in other lobes. Signal intensity was considered normal if no signal-intensity increase or decrease was seen, and it was judged abnormal if signal intensity was higher than that of the white matter in other lobes and close to that of gray matter. Periventricular hyperintense lesions and other ischemic lesions were not counted in the intensity assessment. Signal-intensity change in the corticospinal tract was evaluated on transverse proton-density–weighted MR images. Signal intensity was considered abnormal if that of the posterior limb of the internal capsule at the level of the basal ganglia was higher than that of other white matter. Signal-intensity change in the precentral gyrus was evaluated on transverse SE T2WI images. Signal intensity was considered decreased if the signal intensity of the precentral cortices at the high convexity levels was lower than that of other cortices.

Pathologic Analysis

The brain of 1 patient with ALSD (patient 2) was pathologically analyzed. Formalin-fixed paraffin-embedded tissue sections from the brain were prepared with hematoxylin-eosin (H&E), Klüver-Barrera, Holzer, methenamine-Bodian, and Gallyas-Braak silver impregnation stains. We also compared imaging and pathologic findings.

Results

MR Imaging Findings

All 3 patients with ALSD showed symmetric frontotemporal atrophy (Table and Figs 1 and 2). In particular, in 2 of 3 patients, temporal lobe dominance was present. Compared with this, only 6 of 21 patients with ALS without dementia showed frontotemporal atrophy.

In all 3 patients with ALSD, T2WI demonstrated symmetric hyperintensity in the subcortical white matter on the medial side of the anterior temporal lobes (Figs 1 and 2), whereas none of the 21 patients without dementia showed this finding. Two of the 3 patients (66.7%) with ALSD also showed symmetric hyperintensity in the subcortical white matter of the frontal base and insula (Fig 2*B*). One of the 3 patients (33.3%) with ALSD showed hyperintensity in the bilateral precentral white matter on T2WI, in comparison with 9 of the 21 patients (42.9%) in the classic ALS group.

MR images demonstrated no abnormal signal-intensity changes in CST in the internal capsule or the brain stem in any of the 3 patients with ALSD. In the group without dementia, 6 patients (28.6%) showed this imaging finding. Low-signal-intensity changes were observed in the motor cortices on T2WI of 1 of the 3 patients (33.3%) with ALSD, indicating degeneration of the motor cortices (Fig 1). This feature was present in 13 of the 21 patients (61.9%) with classic ALS. Although two thirds of the patients in each group had multiple small infarctions or unidentified bright objects on MR images, these lesions were located only in the basal ganglia or deep white matter of the cerebral hemispheres.

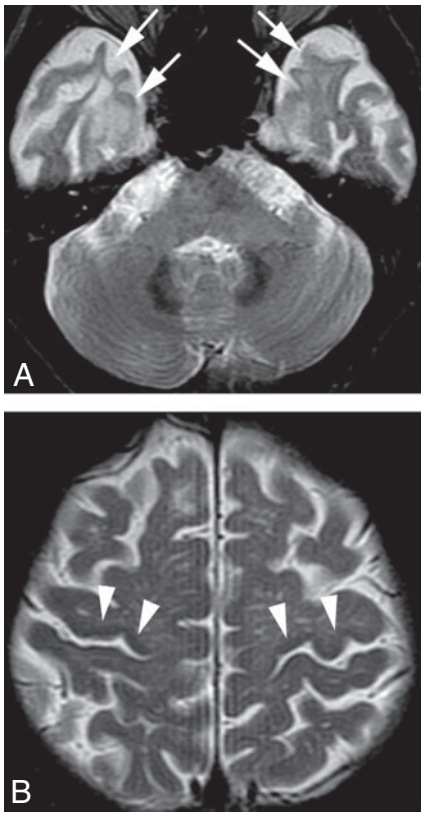

Fig 1. Patient 1, ALSD. *A,* Transverse SE T2WI shows symmetric temporal atrophy and symmetric hyperintensity (*arrows*) in the subcortical white matter on the medial side of the anterior temporal lobes. *B,* Transverse SE T2WI obtained at the level of high convex shows hypointensity along the precentral cortices (*arrowheads*).

Neuropathologic Findings

Moderate frontal and anterior temporal atrophies were observed in the brain. Myelin-stained sections of the brain demonstrated loss of myelin in the subcortical white matter on the medial side of the anterior temporal white matter (Fig 2*D*). The frontotemporal cortex showed mild-to-moderate neuronal loss and gliosis of layers II and III with spongiosis (Fig 2*E*), which was severe on the medial side of the anterior temporal tip. Diffuse severe fibrous gliosis was observed in the subcortical white matter of the frontotemporal white matter.

Degenerative changes were found in both the lower motor neuron and upper motor neuron systems, consistent with classic ALS. Bunina bodies were observed in the spinal motor neurons (Fig 2*F*). Ubiquitin-positive cytoplasmic inclusions were found among granular cells of the dentate gyrus of the hippocampus (Fig 2*G*). The final neuropathologic diagnosis of the brain was ALSD.

Discussion

Our results revealed that the T2WI of patients with ALSD showed bilateral symmetric frontotemporal atrophy and symmetrically increased signal-intensity changes in the subcortical white matter on the medial side of the anterior temporal lobes, which were thought to be characteristic of ALSD.

In ALSD, the onset of dementia may precede, follow, or coincide with motor symptoms.[7] In addition to CST degeneration, neuropathologic examinations of patients with ALSD

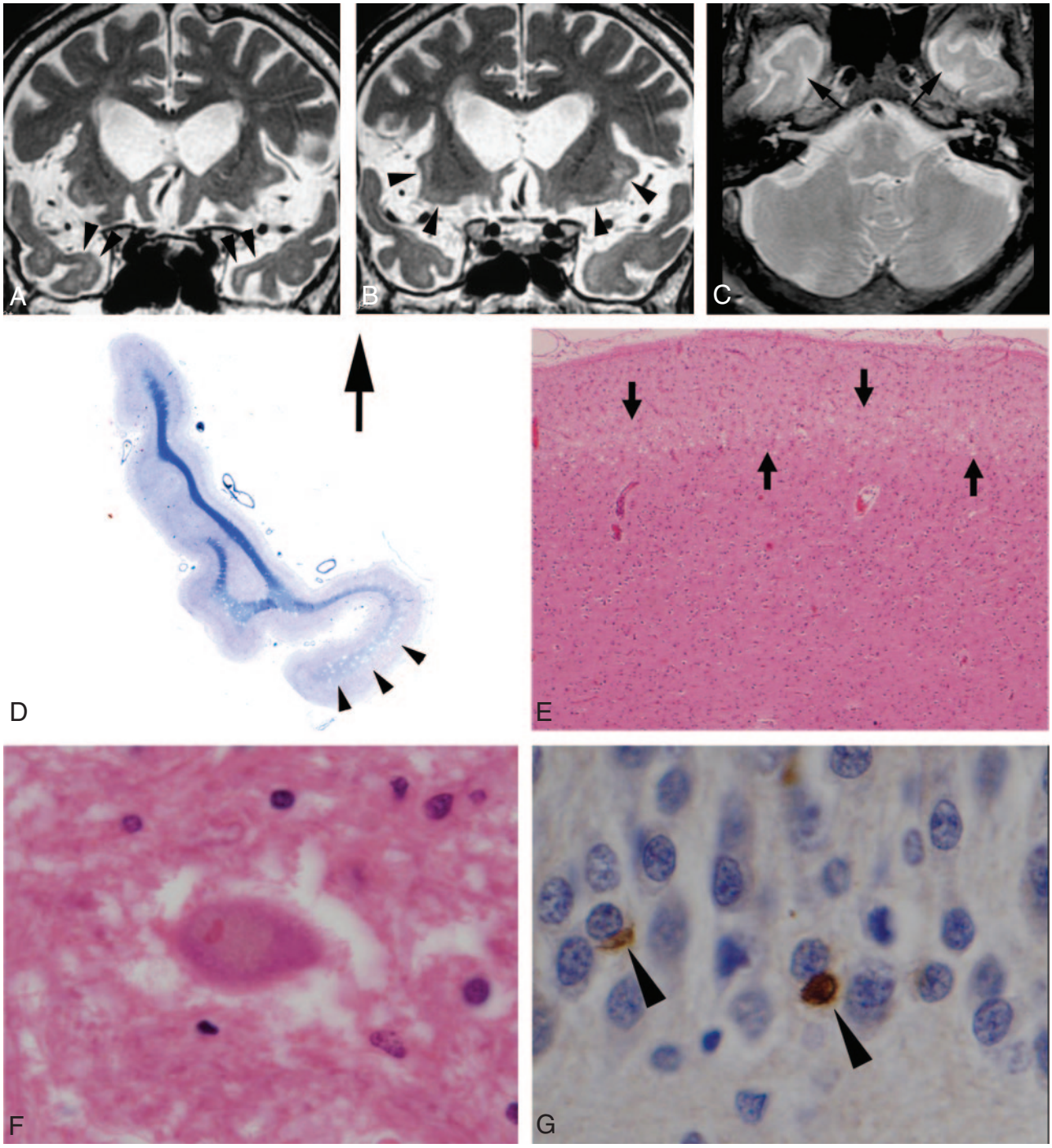

Fig 2. Patient 2, ALSD. *A*, Coronal FSE T2WI obtained at the level of the temporal tip shows symmetric temporal atrophy and symmetric hyperintensity (*arrowheads*) in the anteromedial temporal white matter. *B*, Coronal FSE T2WI obtained at the level of the temporal tip also shows symmetric hyperintensity (*arrowheads*) in the subcortical white matter of the frontal base and insula. *C*, Transverse SE T2WI shows symmetric hyperintensity (*arrows*) in the subcortical white matter of the anterior temporal lobes. *D*, Photograph of postmortem coronal specimen (myelin-stained section) obtained at the level of the temporal tip shows loss of myelinated fibers in the right anteromedial temporal lobe (*arrowheads*). *Arrow* indicates the top of the image. *E*, Microphotograph of the cortex in the temporal pole shows that the superficial layers II and III exhibit spongiosis (*arrows*) (H&E, original magnification ×40). *F*, In the microphotograph, Bunina bodies are observed in the spinal motor neurons (H&E, original magnification ×600). *G*, In the microphotograph of the dentate gyrus, ubiquitin-positive cytoplasmic inclusions are present in the granular cells (*arrowheads*) (immunostaining with anti-ubiquitin, original magnification ×400).

usually demonstrate ubiquitin-immunoreactive dystrophic neurites and neuronal cytoplasmic inclusions in layer II of the neocortex and the dentate granule cells of the hippocampus.[3,4] Similar cortical pathology is found in patients with frontotemporal dementia (FTD) without motor symptoms, which has been called FTD-MND (motor neuron disease) type. The relationship among classic ALS, ALSD, and FTD-MND type is uncertain. Some believe, however, that they are clinically and neuropathologically overlapping disorders that fall into a category of neurodegenerative disease with ubiquitin-positive inclusions.[3,4,8] Patients with ALSD demonstrate a shorter survival time than patients with classic ALS, perhaps due to the lack of compliance or interest in participating in invasive therapies such as enteric nutrition or in noninvasive positive-pres-

sure ventilation.[9] It is, therefore, important to differentiate ALSD from classic ALS.

Matsusue et al[10] reported 3 patients with pathologically confirmed ALSD. MR images of the patients showed frontotemporal atrophy. Moreover, T2WI of one revealed increased signal-intensity changes in the subcortical white matter in the anterior temporal lobes.[10] T2WI of 3 postmortem brains demonstrated hyperintensities in the subcortical white matter in the medial sides of the anterior temporal lobes. Although signal-intensity changes were demonstrated in only 1 patient who underwent FSE T2WI, the hyperintensities were consistent with our findings. Neuropathologic examinations in their study revealed spongiosis, neuronal loss, and gliosis in the cerebral cortices. In the white matter, particularly in the subcortical white matter, loss of myelin, gliosis, and rarefaction were observed. These findings were consistent with previous studies and ours.[3,4]

Coronal myelin-stained sections in our study demonstrated the loss of myelin on the medial side of the anterior temporal lobe. We thought that these signal-intensity changes reflected the progression of neuronal degeneration, especially the demyelination secondary to axonal loss or changes and gliosis in the anterior temporal lobes. Although patients with ALS with cognitive impairment had statistically greater white matter atrophy than those who were cognitively unaffected,[11] objective measurement of signal-intensity changes in the white matter is superior to visual evaluation of lobar atrophy. To the best of our knowledge, no signal-intensity changes in the anterior temporal lobes on MR images of patients with ALSD have been described in the English literature. In our study, MR images of 6 patients with ALS without dementia showed frontotemporal atrophy without signal-intensity changes in the anterior temporal lobes. This finding might indicate that ALS is not an isolated motor neuron disorder but a multisystem disorder; however, it was not unique to ALSD.

The medial temporal lobe is important for memory. Bilateral temporal lesions produce a severe anterograde learning disorder (ie, an inability to store new memories, often with retained ability to recall old ones). Moreover, discrete cortical regions exist in the anterior temporal lobes, in which object knowledge (such as that related to color, animals, tools, or action) is organized as a distributed system.[12] Anteromedial temporal lesions in ALSD could interfere with these functions; therefore, hyperintensity in the medial part of the anterior temporal lobes was thought to be characteristic of ALSD.

For patients with ALS, we used SE T2WI because iron deposits in the motor cortex were usually more easily detected by SE T2WI than by FSE T2WI.[13] Coronal T2WI were obtained by using the FSE sequence. In contrast to the susceptibility phenomenon, hyperintensity due to spongiosis and gliosis in the anteromedial temporal lobes was equally detected on transverse and coronal T2WI in our study.

In classic FTD such as Pick disease, asymmetry of the brain morphology is common and the dominant side (usually the left) tends to exhibit more atrophy.[14] In our patients with ALSD, however, symmetric atrophy of the frontotemporal lobes was observed, and this feature is though to be a useful clue for the differential diagnosis of ALSD from FTD or corticobasal degeneration. Some studies showed that most of the frontal regions were significantly more atrophied in the ALSD group than in the classic ALS group.[15] The discrepancy within the published morphometric studies in ALS and ALSD so far may be related to differences in patient cohorts and several methodologic factors of the data analysis process.

Other uncommon entities, including herpes encephalitis, paraneoplastic limbic encephalopathy, complex partial status epilepticus associated with hippocampal sclerosis, lupus erythematosus, neurosyphilis, myotonic dystrophy, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, gliomatosis cerebri, and congenital metabolic disorders, have similar imaging manifestations and should also be considered in the differential diagnosis of anterior temporal lesions. However, symmetric bilateral frontotemporal atrophy with symmetric hyperintensity on the medial side of the anterior temporal lobe was very rare in the previously described disorders.

In cases of classic ALS, T2WI may show hyperintensity in the CST of the brain and spinal cord, which reflects the degeneration of the CST.[16] Additionally, lesions in the motor cortex in ALS are often seen as hypointense on SE T2WI.[17,18] Hyperintensity in the CST was not present in any of our 3 patients with ALSD; however, SE T2WI of 1 patient (patient 1) showed hypointensity in the motor cortices. ALSD is thought to be a motor neuron disease mainly of the lower motor neuron system.[4,19] Therefore, degeneration of the CST and motor cortex is often relatively mild, leading to fewer represented imaging findings in these regions. In our study, signal-intensity changes on T2WI in the precentral white matter were seen more frequently than in the posterior limb of the internal capsule. The signal-intensity changes in the precentral white matter may include nonspecific senile changes.

The major limitation of our study was that the diagnoses of 2 of the 3 patients had not been proved by neuropathologic studies, and it was possible that the clinical diagnosis of ALSD might have been in error. Future studies are needed to more fully evaluate the various clinical-radiologic-pathologic correlations, and they will determine whether similar changes are present in patients without dementia who progress to ALSD.

In conclusion, T2WI of patients with ALSD showed bilateral symmetric frontotemporal atrophy with temporal dominance and symmetric increased signal-intensity changes in the subcortical white matter on the medial side of the anterior temporal lobes, which were thought to be characteristic of ALSD.

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