Detection of Pyramidal Tract Lesions in Amyotrophic Lateral Sclerosis with Magnetization-Transfer Measurements

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PURPOSE: To determine the presence of small lesions in the pyramidal tract in patients with amyotrophic lateral sclerosis (ALS) by using magnetization-transfer (MT) measurements and MR imaging. **METHODS:** MT ratios (MTRs) were measured in the posterior limb of the internal capsule in nine patients with ALS and in nine healthy volunteers. **RESULTS:** The mean value of MTRs (%) in patients with ALS was 15.76 ± 1.48, while that of the control subjects was 19.83 ± 1.54. The difference was statistically significant. **CONCLUSIONS:** MT measurements are useful for detecting abnormalities associated with degeneration of the pyramidal tract in patients with ALS.

Index terms: Magnetic resonance, magnetization transfer; Sclerosis, amyotrophic lateral

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Establishing the diagnosis of amyotrophic lateral sclerosis (ALS) at an early stage of the disease is occasionally difficult, since certain clinical features such as pyramidal tract involvement may be absent. In some cases of ALS, symmetric, high-signal areas on T2-weighted magnetic resonance (MR) images have been reported in the posterior limbs of the internal capsules in addition to high signal from the corona radiata and the pons (1). These MR abnormalities have been interpreted as reflecting pyramidal tract degeneration in advanced ALS. Because such changes are rarely seen in early ALS (1, 2), imaging methods sensitive to the detection of pyramidal tract degeneration may enable earlier diagnosis.

Magnetization-transfer ratios (MTRs) can be used to detect abnormalities beyond the resolution of conventional MR images. Abnormalities identified through the use of MTRs have been reported in inflammatory diseases of the central nervous system (3), in metastatic brain lesions (4), and in multiple sclerosis (5). The purpose of this study was to determine whether MT measurements could be used to detect abnormalities of the pyramidal tracts in patients with ALS.

Subjects and Methods

MTRs were measured in nine patients with ALS (eight men and one woman; 46 to 66 years old; mean age, 52 years) and in nine age-matched control subjects (Table 1). The diagnosis of ALS was made on the basis of clinical and electromyographic findings, as defined by the El Escorial criteria for the diagnosis of ALS (6). The duration of illness from the time of onset ranged from 6 months to nearly 3 years. The average interval between symptom onset and MR examination was 14.5 months. All the patients included in this study had classic ALS; those with primary lateral sclerosis or progressive spinal muscular atrophy were excluded. Control subjects (six men and three women) were healthy volunteers who were medically stable and free of neurologic diseases.

All MR studies were performed on a 1.5-T system with a quadrature head coil. The head of each patient was secured between sponge wedges, which prevented motion during and between the acquisition of images. The imaging protocol consisted of standard spin-echo sagittal T1-weighted localizing sequences (600/17/1 [repetition time/echo time/excitations]; section thickness, 5 mm) and axial fast spin-echo T2-weighted sequences (2500/90/1; echo train length, 8; section thickness, 6 mm) of the whole brain. Other imaging parameters included a 22-cm field of view, and a 256 × 192 matrix.

Noncontrast MR imaging was performed in the axial plane by using an MT-prepared three-dimensional radio-

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TABLE 1: Clinical features, MR imaging findings, and magnetization transfer ratios (MTRs) in nine patients with amyotrophic lateral sclerosis (ALS) and in nine control subjects

	Age, y/Sex	Disease Duration, y	ALS Score	MR of Posterior Limb of Internal Capsule		
				T1-Weighted Images	T2-Weighted Images	MTR, %
Patients						
1	47/M	2.75	48	−	+	17.73
2	50/M	0.5	161	+	+	16.75
3	64/M	1.5	50	−	−	14.75
4	63/M	0.5	76	−	+	16.35
5	64/M	1.75	68	−	−	13.51
6	55/M	1.5	43	−	−	14.91
7	69/M	0.75	125	−	−	15.31
8	66/M	0.75	46	−	−	17.61
9	55/F	1.25	120	−	−	15.31
Control Subjects						
1	66/F			−	−	19.53
2	54/F			−	−	18.44
3	53/M			−	−	17.39
4	60/F			−	−	19.46
5	50/M			−	−	19.46
6	48/F			−	−	22.56
7	67/M			−	−	19.46
8	44/M			−	−	21.06
9	49/M			−	−	21.15

Note.—− indicates normal; +, abnormal.

frequency spoiled gradient-recalled acquisition in the steady state echo sequence (T1-weighted images reflect the effect of MT far better than T2-weighted images do). The pulse sequence that was designed to minimize T2 effects (50/5; flip angle, 30°; section thickness, 5 mm; matrix, 256 × 128), resulted in a relatively T1-weighted image. MT contrast was achieved with application of 18-millisecond half-cycle, sinc-shaped saturation pulses at a frequency of 1 kHz below water resonance before each excitation. The interval between the end of the saturation pulses and the beginning of each excitation was approximately 1 millisecond. Corresponding reference images at identical 5-mm intervals were obtained without the saturation pulses so that imaging parameters were otherwise identical to those of the saturated images.

MTRs are defined as the percentage of signal loss between unsaturated and saturated images. They were calculated by using the equation $[(Mo - Ms)/Mo] \times 100$, where Mo is the measured signal intensity on the reference image and Ms is the measured signal intensity on the MT image. Signal intensity on the calculated image represented the amount of MT between the free and bound water pool.

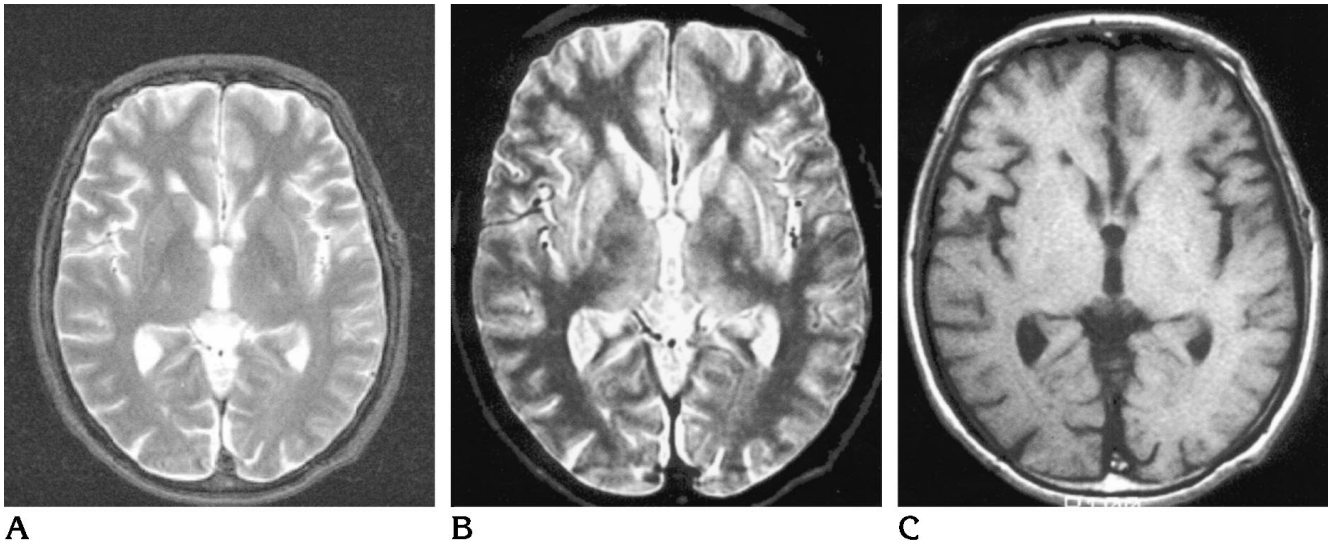
The MTRs of a 3-mm-diameter circular region of interest (ROI) were measured in four areas of the cerebral white matter (the frontal, temporal, parietal, and occipital lobes); in two areas of the internal capsule (the genu and the posterior third quarter of the posterior limb); in the genu of the corpus callosum and seven areas of the cerebral and subcortical gray matter in the left hemisphere (frontal, temporal, parietal, and occipital cortex, caudate nucleus, putamen, and thalamus); and in a single area of the ventricular cerebrospinal fluid on the calculated images. The patients showed no laterality of symptoms at neurologic examination.

ROIs of the cerebral white matter were selected at areas of maximum distance from both the gray matter and the ventricle to avoid partial volume averaging; they were located anterolaterally to the anterior horn of the lateral ventricle in the frontal lobe, lateral to the temporal horn, posterior to the trigone in the occipital lobe, and in the centrum semiovale in the parietal lobe above the level of the lateral ventricle. The ROIs of the internal capsule were located in the posterior third quarter of the posterior limb medial to the posterior aspect of the putamen, where the large myelinated fibers of the pyramidal tract are located and where degeneration of the tract occurs in ALS (7, 8).

Imaging evaluations, ROI measurements, and calculations were performed by a neurologist and a radiologist. At the time of MR imaging, each patient provided a complete medical history and underwent a neurologic examination, including scoring on Appel's ALS rating scale (9). The MTRs for the ALS patients and the control subjects were statistically compared by means of the Mann-Whitney U test. The MTRs were given as mean ± standard deviation.

Results

Figures 1A and B show focal high-intensity areas in the posterior third quarter of the posterior limb of the internal capsule, Figure 1C



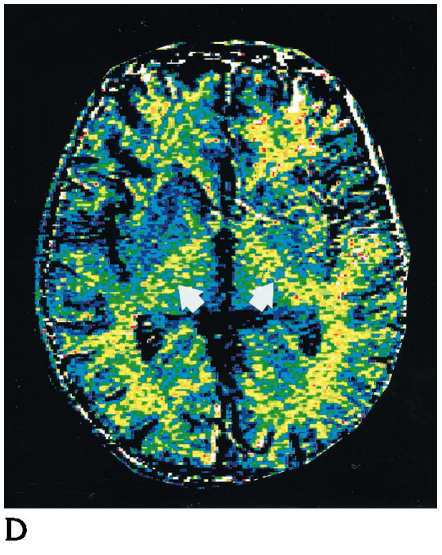
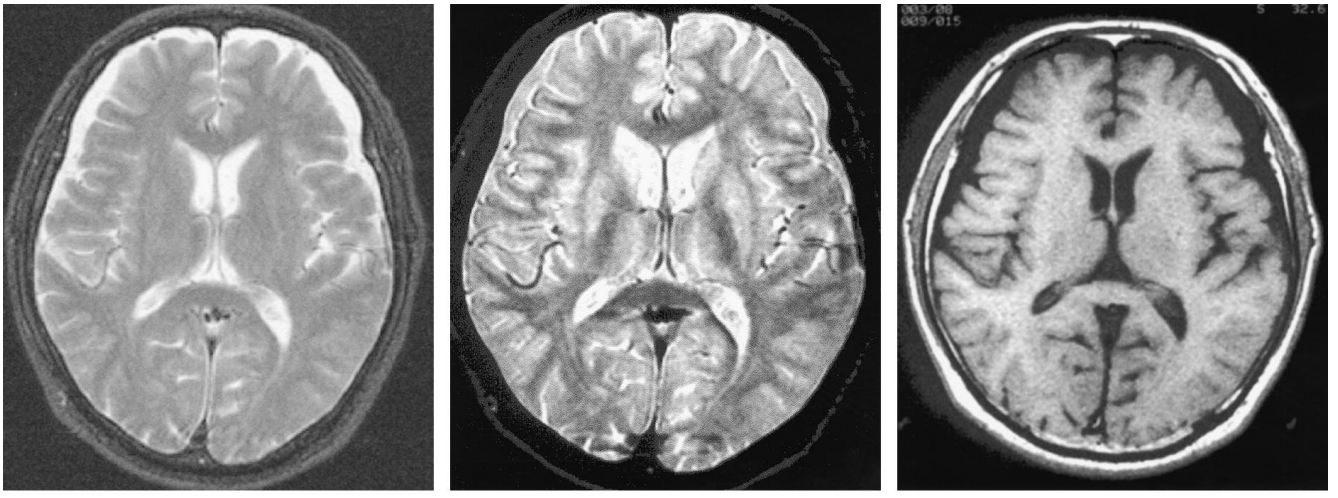


Fig 1. Case 2: 50-year-old man with ALS of 6 months' duration and an ALS score of 161. T2-weighted fast spin-echo image (2500/90/1) (*A*) and proton density–weighted image (2500/18/1) (*B*) show high-intensity areas in the posterior limb of the internal capsule. T1-weighted image (600/17/1) (*C*) shows slightly low-intensity areas in the corresponding areas. The MT image (*D*) shows reduced intensities (ie, low MT ratios) in the corresponding areas (*arrows*).

shows focal slightly low-intensity areas in the corresponding areas, and Figure 1D shows focal low-intensity in the corresponding areas on an MT image in a patient with ALS (case 2). Figures 2A through C show no abnormality on a T2-weighted image obtained with fast spin-echo, a proton density–weighted image, and a T1-weighted image, respectively; while Figure 2D shows a low-intensity area on an MT image. The mean MTRs and standard deviations in the patients with ALS and in the control subjects are given in Table 2. The MTRs (%) of the pyramidal tract area in the posterior limb of the internal capsule were 15.76 ± 1.48 in the ALS patients and 19.83 ± 1.54 in the control subjects; the mean MTRs decreased significantly in the ALS patients ($P < .0007$). There was no significant difference in other areas. The MTRs (%) of the ventricular cerebrospinal fluid were 0.00 both in ALS patients and in control subjects.

Focal high-signal areas were observed along the course of the pyramidal tract in the posterior limb of the internal capsule in three (33%) of the nine patients with ALS (cases 1, 2, and 4) on T2-weighted images obtained with fast spin-echo, whereas the hypointense area was observed on conventional T1-weighted images in one patient (case 2). T2-weighted images showed abnormalities in one patient with severe disease and in two patients with mild disease. No abnormalities were observed in the other six patients. On the other hand, all the MTRs of the pyramidal tract area in the posterior limb of the internal capsule were decreased below the normal value measured in the ALS patients. There was no significant relationship among the mean



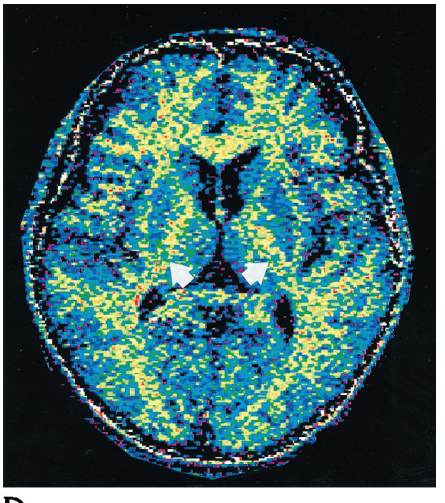


Fig 2. Case 3: 64-year-old man with ALS of 18 months' duration and an ALS score of 50. No areas of abnormal intensity are seen in the posterior limb of the internal capsule on the T2-weighted fast spin-echo image (2500/90/1) (*A*), the proton density–weighted image (2500/18/1) (*B*), or the T1-weighted image (600/17/1) (*C*), whereas reduced intensities (ie, low MT ratios) are seen in the corresponding areas (*arrows*) on the MT image (*D*).

MTRs, the ALS scores, and the duration of illness; nor was there a correlation between low MTRs and signal intensity on T1- or T2-weighted images.

Discussion

There are no biological markers that establish the diagnosis of ALS, and because of the wide variety of clinical features that accompany this disease, definite diagnosis may be difficult. Many motor neuron disease syndromes resemble ALS (6), but these may be ruled out by clinical, electrophysiological, laboratory, and neurologic examinations. These include spondylitic myelopathy (especially cervical spondylitic amyotrophy without sensory disturbance), dysimmune motor system degeneration, motor neuropathies and neuropathies associated with monoclonal gammopathies of unknown origin, Waldenström macroglobulinemia, and osteosclerotic myeloma, vascular diseases, Hodgkin and non-Hodgkin lymphoma, infections (human immunodeficiency virus 1, human T-cell lymphotropic virus 1, encephalitis lethargica, varicella-zoster, brucellosis, cat-scratch disease, Creutzfeldt-Jakob disease, syphilis, and delayed postpoliomyelitis), nonmalignant endocrine abnormalities, acquired enzyme defects (detoxification and enzymes), exogenous toxins (lead, mercury, arsenic, thallium, cadmium, manganese, aluminum, organic pesticides, and lupin seeds), and physical injury (electric shock and radiation therapy). Early and correct diagnosis of ALS is important, because recent therapeutic trials have disclosed that riluzole, a glutamate release inhibitor and insulinlike growth factor, can slow the course of the disease (10,

TABLE 2: Mean magnetization transfer ratios (±SD) in each of 14 lesions in patients with amyotrophic lateral sclerosis (ALS) and in control subjects

	Patients with ALS	Control Subjects
White matter		
Frontal	22.70 ± 1.75*	22.59 ± 0.86
Temporal	20.81 ± 2.04*	22.24 ± 1.63
Parietal	21.84 ± 2.04*	21.02 ± 2.49
Occipital	22.20 ± 2.22*	21.45 ± 1.94
Genu of corpus callosum	22.51 ± 1.94*	22.43 ± 1.52
Genu of the internal capsule	22.11 ± 1.66*	22.06 ± 1.92
Posterior limb of the internal capsule	15.76 ± 1.48†	19.83 ± 1.54
Gray matter		
Frontal	16.30 ± 0.87*	16.06 ± 1.37
Temporal	15.43 ± 1.86*	15.44 ± 1.21
Parietal	15.66 ± 1.20*	15.82 ± 1.83
Occipital	16.28 ± 1.25*	15.94 ± 1.24
Caudate nucleus	15.18 ± 0.87*	14.66 ± 2.30
Putamen	14.92 ± 1.07*	14.64 ± 1.77
Thalamus	16.01 ± 1.05*	16.56 ± 1.55

* Not significant.
† $P < .0007$.

11), and some of the motor neuron disease syndromes are treatable.

Postmortem examinations show degeneration of the entire upper motor neuron system from the cerebral motor cortex through the corticospinal tract of the internal capsule, brain stem, and spinal cord in approximately 47% of patients with ALS (12). There is, however, limited information about the imaging findings in ALS. Goodin et al (1) reported the characteristic abnormal signal intensity of the corticospinal tract from the motor cortex through the corona radiata, the posterior limb of the internal capsule, the cerebral peduncle, and the pons on MR images of the brain. Nonspecific white matter changes in ALS patients were also demonstrated (13). The presence of low signal intensity in the motor cortex on T2-weighted images was recently described (14–16). Only a single study reported the MR findings of ALS patients in relation to the grade of clinical severity (17).

The posterior third quarter of the posterior limb of the internal capsule and the lateral third quarter of the cerebral peduncle contain large myelinated fibers of the pyramidal tract, and, in ALS, demyelination associated with degeneration occurs histopathologically in this area (7, 8). The high signal on T2-weighted MR images in these areas has been regarded as reflecting the pathologic conditions in pyramidal tract degeneration. In some cases, abnormal signals were also seen in the paraventricular white matter and in the posterior limbs of the internal capsule (1, 14, 17). However, the sensitivity of MR imaging to pyramidal tract degeneration in ALS is limited. Udaka et al (18) reported abnormalities in four (19%) of 21 ALS patients on T2-weighted images, whereas Cheung et al (17), in a series of 17 patients with ALS, reported abnormalities in six patients (35%) on T2-weighted images and in eight patients (47%) on proton density–weighted images. The high signal areas on T2-weighted images of the posterior limb of the internal capsule are not always pathologic, since they are occasionally seen in healthy subjects (19). On the basis of these findings, Guermazi (20) pointed out that high signal areas in the corticospinal tract on T2-weighted images must be analyzed with caution, and that T1- and proton density–weighted images are more important for differentiating real degeneration from normal areas. Nonetheless, MTRs may be superior to conventional MR images in detecting pyramidal tract degeneration of ALS at an early stage.

MT measurements can reflect the structural variations within a tissue (21, 22). A model for this mechanism incorporates at least two distinct pools of water protons within biological tissues: bound immobile protons associated with macromolecules, such as myelin, and free mobile protons associated with free water. Although the exact physical mechanism of MT has not been completely delineated, cross-relaxation and chemical exchange between the spins in the two pools of water protons are regarded as the basis of MT contrast (22, 23). Pulsed MT imaging is achieved by the application of an off-resonance radio frequency before the pulse sequence to preferentially saturate immobile protons of macromolecules, which then transfer magnetization to mobile protons in free water (22). This results in suppression of tissue signal intensity from immobile protons.

The change in net magnetization of bulk water depends not only on the power of the saturation pulses but also on the macromolecular matrix (the pool of bound protons). The amount transferred can be quantitated by calculation of the MTR. Lexa et al (24), in a comparison of the MT measurements with histopathologic wallerian degeneration of the visual pathways in cats,

found a corresponding decrease in the MTR, which reflected demyelination at the late stages of this degenerative process.

Dousset et al (25) reported that the MTRs were mildly reduced in focal edematous lesions without demyelination in the white matter of guinea pigs with experimental allergic encephalomyelitis but that they were significantly decreased in focal white matter lesions in patients with multiple sclerosis (MS). On the basis of these observations, they hypothesized that demyelination produced the decrease in MTRs, and that lesions varied in transfer ratio in proportion to the extent of myelin loss. Tomiak et al (26) and Gass et al (27) also reported reduction of mean MTRs in focal white matter MS plaques; the range of MTR values seemed to reflect the structural changes in the tissue resulting from demyelination and axonal loss.

Proton density, T2 and T1 relaxation times, and apparent diffusion constant have been used as tissue parameters in MR imaging. Henkelman et al (28) reported that anisotropy was observed in T2 and T1 values on ordinary MR images but not on those with MT contrast. In quantitative studies using such MR parameters as T2 and T1 relaxation times in the tissue with anisotropic anatomic structures, such as the pyramidal tract, the signal intensity and T2 and T1 relaxation times may be influenced by anisotropy. On the other hand, MTRs are barely influenced by anisotropy and are one of the parameters that reflects the interactions between water and macromolecules of the tissue. MTRs are thus useful for the quantitative study of tissues with an anisotropic anatomic structure, such as the pyramidal tract.

Our study showed a significant decrease of MTR in the posterior limb of the internal capsule of ALS patients. We speculate that this decrease reflects degeneration of the pyramidal tract. MTRs may be more useful and more sensitive than MR images in detecting subtle and early degeneration of the pyramidal tract in patients with ALS, as MT values may provide objective and semiquantitative information related to the severity of pyramidal tract degeneration.

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