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Alteration of White Matter MR Signal Intensity in Frontotemporal Dementia

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PURPOSE: To determine the diagnostic potential of MR imaging to show white matter involvement in frontotemporal dementia. **METHODS:** We evaluated MR signal intensity in cerebral white matter by visually inspecting and by quantitatively measuring signal intensity on MR images in 22 patients with frontotemporal dementia. The findings were compared with those in 22 age- and sex-matched patients who had had Alzheimer disease for the same length of time and with 16 age- and sex-matched healthy control subjects. **RESULTS:** Patients with frontotemporal dementia had a significant increase in white matter signal intensity in the frontal and/or temporal lobes on T2- and proton density–weighted images. Visual inspection of regular proton density–weighted images and measurements made on the T2- and proton density–weighted images were sensitive to changes in white matter signal. **CONCLUSION:** Increased MR signal intensity in the frontotemporal white matter on T2- and proton density–weighted MR images is a useful diagnostic sign of frontotemporal dementia and distinguishes this condition from Alzheimer disease.

Index terms: Dementia; Degenerative disease; Brain, magnetic resonance

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Frontotemporal dementia is a clinical entity of non-Alzheimer degenerative dementia in which behavioral disorders arise from frontotemporal cerebral atrophy (1). According to the Lund/Manchester groups (1), two types of histologic change (ie, Pick type and frontal lobe degeneration with or without motor neuron disease) underlie the atrophy and share an identical anatomic distribution in the frontal and temporal lobes. The common abnormalities are neuronal loss, spongiform changes, and an astrocytic gliosis in the outer cortical layers and white matter. The last is more severe in Pick type than in frontal lobe degeneration, and the presence of intraneuronal inclusion (Pick) bodies and inflated neurons in cortical layers (Pick cell) and intense gliosis distinguish Pick type from frontal lobe degeneration (2). Classification of frontotemporal dementia with intense white matter gliosis but without inclusion bodies and inflated neurons is still controversial (3). This system distinguishes the clinical syndrome of frontotemporal dementia from other disorders that may also affect frontotemporal structures, including Alzheimer disease, and avoids the vexing clinical and pathologic arguments about Pick disease by considering the Pick type of change as a histologic variant of frontotemporal atrophy manifesting clinically as frontotemporal dementia, and therefore is of clinical value.

Frontotemporal dementia is a significant constituent of degenerative dementias; in particular, of those of presenile onset (4, 5). This disorder was present in 9% of 400 patients with pathologically documented organic dementia in the Lund longitudinal study (4). Knopman et al (5) reported that, in their series of 460 dementia

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patients referred to a regional brain bank, Pick disease was present in 6.8% of patients under age 70 years at death and in 3.0% of all the patients. Frontotemporal dementia is frequently misdiagnosed as Alzheimer disease (6); however, clinical distinction between these two conditions is essential not only for disease-specific treatment of patients but for research purposes, such as clinical trials. Although the Lund/Manchester groups proposed descriptive clinical and pathologic criteria for frontotemporal dementia (1), definitive clinical tests for diagnosis of this disorder are lacking.

Although the spatial resolution of current magnetic resonance (MR) imaging systems is not high enough to detect pathologic changes in the thin cortical layer, MR imaging can show cerebral white matter gliosis in frontotemporal dementia that may cause MR signal changes, thereby distinguishing frontotemporal dementia from Alzheimer disease when white matter involvement is minimal (7). The purpose of the present study was to evaluate the potential of MR imaging to show white matter involvement in frontotemporal dementia and to assess the value of white matter MR signal intensity changes in the diagnosis of dementia.

Subjects and Methods

All patients who were admitted to our hospital from July 1993 through December 1995 for cognitive disorders were examined comprehensively both by neurologists and psychiatrists and were given electroencephalographic and neuropsychological examinations, including the Mini-Mental State Examination (8) Alzheimer Disease Assessment Scale (9), Wechsler Adult Intelligence Scale-Revised (8), and Western Aphasia Battery (8). MR images of the brain and MR angiograms of the neck and head, as well as cerebral glucose metabolism or cerebral blood flow images obtained by positron emission tomography (PET) with fludeoxyglucose F 18 or the $C^{15}O_2$ steady-state method or single-photon emission computed tomography (SPECT) with ^{123}I-iodoamphetamine were used to differentiate patients with nondegenerative cognitive disorders, such as cerebrovascular diseases and intracranial mass lesions.

Frontotemporal Dementia Group

Unlike with Alzheimer disease, criteria for frontotemporal dementia have not been established yet. Nevertheless, recent studies have focused on the clinical (6, 10), neuropsychological (11, 12), and neuroimaging features of this disorder (1, 13). We used stringent criteria to establish a diagnosis of frontotemporal dementia, including both clinical and neuroimaging measurements so as to maximize the specificity of the clinical diagnosis. The inclusion criteria were as follows: International Classification of Diseases (ICD)-10 diagnostic criteria for dementia (14); the core diagnostic (behavioral, affective, speech, spatial orientation/praxis, physical, investigational) features of the Lund/Manchester clinical criteria for frontotemporal dementia (1); a score of 5 or more on the Gustafson-Nilsson Pick scale and of 5 or less on the Gustafson-Nilsson Alzheimer scale, which is a 16-item test that scores the frequency of intellectual deficits, motor signs, behavioral disorders, and the temporal progression of deficits (a score of less than 5 on the Alzheimer scale and of more than 5 on the Pick scale have a high sensitivity and specificity for the diagnosis of autopsy-proved Pick disease) (10); frontal lobe dysfunction on the Frontal Dysfunction Battery (Luria's fist-edge-palm test, Red-Green test, 2–1 tapping test, Stroop's color-word test, and Color-form sorting test) (8); and frontal, temporal, or frontotemporal hypoperfusion/metabolism and relative sparing of parietal and occipital lobes on SPECT or PET scans (15–17). Exclusion was based on the diagnostic exclusion features of the Lund/Manchester clinical criteria for frontotemporal dementia (1) and on the presence of an advanced stage of frontotemporal dementia with severe deficits or behavioral disorders that would make assessment difficult.

The frontotemporal dementia group consisted of 22 patients. Mean age was 65.3 ± 7.9 (SD) years for the 13 women and nine men, and the mean duration of illness was 3.7 ± 2.1 years. Results of neuropsychological examination are shown in Table 1, and neurologic, neurobehavioral, and neuroimaging features are summarized in Table 2. The mean score of the Gustafson-Nilsson Pick scale was 7.2 ± 1.2 (range, 6 to 9) and that of the Alzheimer scale was 3.6 ± 1.0 (range, 1 to 5). Sixteen patients had more than three of five distinctive clinical features suggested by Mendez et al (6) (presenile onset, an initial personality change, hyperorality, disinhibition, and roaming behavior) to be highly sensitive and specific for the diagnosis of autopsy-proved Pick disease. One patient's score was associated with the amyotrophic form of motor neuron disease.

Alzheimer Group

Twenty-two patients with probable Alzheimer disease were randomly sampled from the same cohort of patients who were admitted to our hospital for examination and matched for sex, age, and duration of dementia. Inclusion criteria were probable Alzheimer disease according to the criteria of the National Institute of Neurological Disease and Stroke/Alzheimer's Disease and Related Disorders Association (18); mild to moderate severity of dementia; and hypoperfusion in the parietal, medial temporal, or both lobes on PET scans (19, 20). Exclusion criteria were complications of other neurologic disease. All patients in this group were examined in the same manner as de-

TABLE 1: Results of neuropsychological tests

	Frontotemporal Dementia Group		Alzheimer Disease Group	
	Range	Mean ± SD	Range	Mean ± SD
Mini-Mental State Examination	2–28	17.3 ± 7.5	11–24	18.3 ± 4.2
Alzheimer Disease Assessment Scale	13–57	33.8 ± 14.4	9–47	24.6 ± 10.2
Full-Scale IQ*	50–91	65.0 ± 11.1	56–109	72.7 ± 13.1
Verbal IQ*	51–98	65.0 ± 10.3	58–108	75.3 ± 11.7
Performance IQ*	54–117	69.7 ± 15.2	50–108	73.1 ± 15.6
Western Aphasia Battery	9–90	67.3 ± 18.8	61–94	80.5 ± 8.6

* Wechsler Adult Intelligence Scale–Revised.

TABLE 2: Clinical and neuropsychological features of patients with frontotemporal dementia

Signs and Symptoms	No. of Positive Findings
Neurobehavioral findings	
Early loss of insight	21
Initial personality change	20
Early signs of disinhibition	19
Distractibility	19
Reduction of spontaneity of speech	16
Echolalia and perseveration	15
Presenile onset	14
Early loss of social awareness	13
Roaming behavior	12
Irritability, dysphoria	9
Amimia	9
Hyperorality/Krüber-Bucy syndrome	5
Neurologic findings	
Early primitive reflexes	7
Extrapyramidal signs	3
Motor neuron disease	1
Frontal lobe dysfunction	
Response inhibition	13
Motor sequence	10
Problem solving	8
PET/SPECT findings	
Frontal hypoperfusion/metabolism	7
Temporal hypoperfusion/metabolism	3
Frontotemporal hypoperfusion/metabolism	12

scribed for the frontotemporal dementia group. The mean age was 65.2 ± 8.1 years for the 13 women and nine men, and the mean duration of illness was 2.6 ± 2.1 years. Results of the neuropsychological examination are given in Table 1.

Control Group

Sixteen age- and sex-matched control subjects were selected randomly from healthy persons who had an MR examination at our institution as part of a medical checkup. Inclusion criteria were normal findings at physical and neurologic examination; no history of psychiatric disorders; and no risk factors for cerebrovascular disease (hypertension, heart disease, and diabetes mellitus). Subjects were excluded if infarcts or mass lesions were detected on their MR studies. The mean age was 63.5 ± 9.5 years for the nine women and seven men.

MR Acquisition

MR imaging was performed on a 1.5-T superconducting magnet (Signa Advantage, General Electric Medical Systems, Milwaukee, Wis). Axial double-echo fast spin-echo T2-weighted images (3000/105/4 [repetition time/effective echo time/excitations]), double-echo fast spin-echo proton density–weighted images (3000/35/4), and spin-echo T1-weighted images (550/15/4) were obtained for 14 locations parallel to the anteroposterior commissure plane with a section thickness of 5 mm and an intersection gap of 2.5 mm, covering the area from the base of the cerebellum to the vertex. In all acquisitions, the field of view was 200 × 200 mm and the matrix size was 256 × 256. In addition, sagittal and coronal T1-weighted images with a section thickness of 5 mm and an intersection gap of 2.5 mm were acquired for evaluation of lobar atrophy.

Visual Inspection

All images, obtained with a laser film imager (Ektascan 1120, Kodak, Rochester, NY) with regular window level and width set at 10% below and above the brain structure intensity, were reviewed to look for circumscribed frontotemporal lobar atrophy and signal intensity alterations in the white matter by two neuroradiologists blinded to clinical data. Judgment was entrusted to a third neuroradiologist when disagreement between the two reviewers occurred. Circumscribed frontotemporal atrophy, delineated as a knife-blade configuration, was defined as thin convolutions in a part or throughout the whole of one or two lobes with clear contrast between this area and adjacent intact lobes or gyri (21). Signal intensity change in the frontal and temporal white matter was evaluated by visual inspection on T1-, T2-, and proton density–weighted images and compared with intensity of the gray matter and of the parietooccipital white matter. Signal intensity was considered normal if no signal increase or decrease was seen, and it was judged abnormal if signal intensity was higher (on T2- and proton density–weighted images) or lower (on T1-weighted images) than that of the parietotemporal

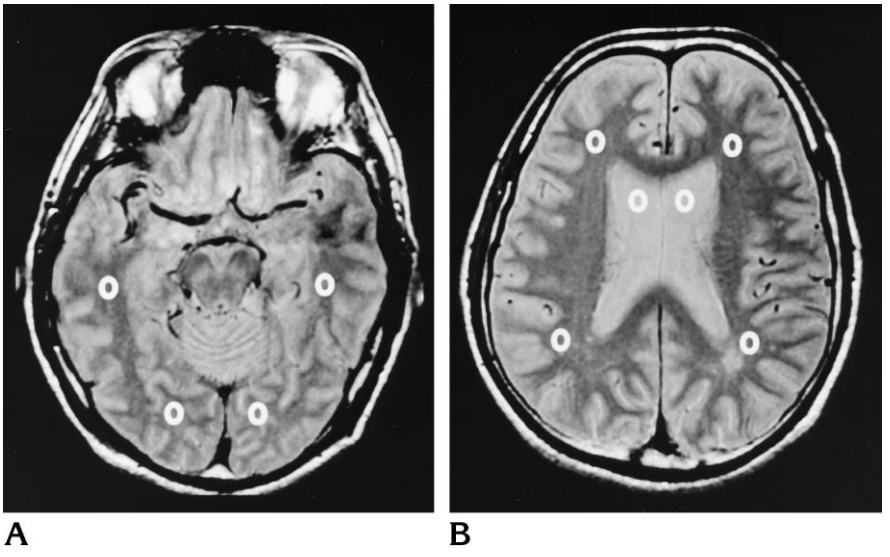

Fig 1. *A* and *B*, Axial proton density–weighted images (3000/21/2) in a control subject show ROI placement (*circles*) for intensity measurements in the frontal, temporal, parietal, and occipital subcortical white matter, and in the lateral ventricles. Note the distinct cortical gray matter–white matter junction, indicating normal white matter signal intensity.

white matter and close to that of the gray matter (on T1-, T2-, and proton density–weighted images). Periventricular hyperintense lesions and other ischemic lesions—which were distinguishable by shape, distribution, and signal intensity—were not counted in the intensity assessment. Topographic distribution of altered intensity was also recorded.

Measurement of White Matter Signal Changes

The MR data sets of all images were directly transmitted to a personal computer (Power Macintosh 8100/80, Apple, Cupertino, Calif) from the MR unit and analyzed by means of the public-domain National Institutes of Health (NIH) Image version 1.56 program (written by Wayne Rasband at NIH and available from the Internet by anonymous ftp from zippy.nimh.nih.gov or on floppy disk from NTIS, 5285 Port Royal Rd, Springfield, VA 22161, part number PB93–504868) with residential macro programs developed in our institution. To fit a limitation of the software (eight-bit pixel value), 12 bits of MR pixel data were converted to eight bits at the scale factor of 0.5 by the minimum (pixel value of 1) and maximum (pixel value of 507) levels.

All measurements were carried out by a neuroradiologist blinded to the clinical data. On a display monitor, a mean value of pixels in a region of interest (ROI) was measured to obtain a signal value of the white matter for the frontal, parietal, temporal, and occipital lobes (Fig 1). Elliptical ROIs of approximately 30 mm^2 (40 pixels, 1 pixel = 0.74 mm^2) were placed 2 mm or more apart from the boundary between the cortex and the white matter so as to exclude the U-fiber. We used a section at a level +22.5 mm of the anterior-posterior commissure (AC-PC) plane for measurement of the frontal and parietal lobes (the middle frontal gyrus and supramarginal gyrus), and a section at a level −15mm of the AC-PC plane for measurement of the temporal and occipital lobes (the middle temporal gyrus and lingual gyrus) in the middle frontal gyrus for the frontal lobe and the supramarginal gyrus, for the parietal lobe at the level of 22.5 mm dorsal to the axiocervical–posterior cervical (AC-PC) plane, and in the middle temporal gyrus for the temporal lobe and the lingual gyrus, and for the occipital lobe at a level −15 mm of the AC-PC plane. Signal intensity was measured on T1-, T2-, and proton density–weighted images. The gray matter–white matter boundary was best seen in healthy subjects on proton density–weighted images. However, when the boundary was obscure, ROIs were determined on the most appropriate image (T1-, T2-, or proton density–weighted) and then propagated to others. To measure the signal intensity of cerebrospinal fluid (CSF), additional ROIs of the same size were placed in the anterior horns of both lateral ventricles. A coefficient of variation (CV = standard deviation/mean) of pixel values in an ROI of less than 5% for T1- and proton density–weighted images or of less than

TABLE 3: Visually identified signal intensity changes and circumscribed lobar atrophy

		Type of MR Imaging		
	Atrophy	Proton Density–Weighted	T2-Weighted	T1-Weighted
Frontal lobe				
Frontotemporal dementia group (n = 22)	9	15	2	0
Alzheimer group (n = 22)	0	1	0	0
Control group (n = 16)	0	0	0	0
Temporal lobe				
Frontotemporal dementia group (n = 22)	10	14	4	0
Alzheimer group (n = 22)	0	4	0	0
Control group (n = 16)	0	0	0	0

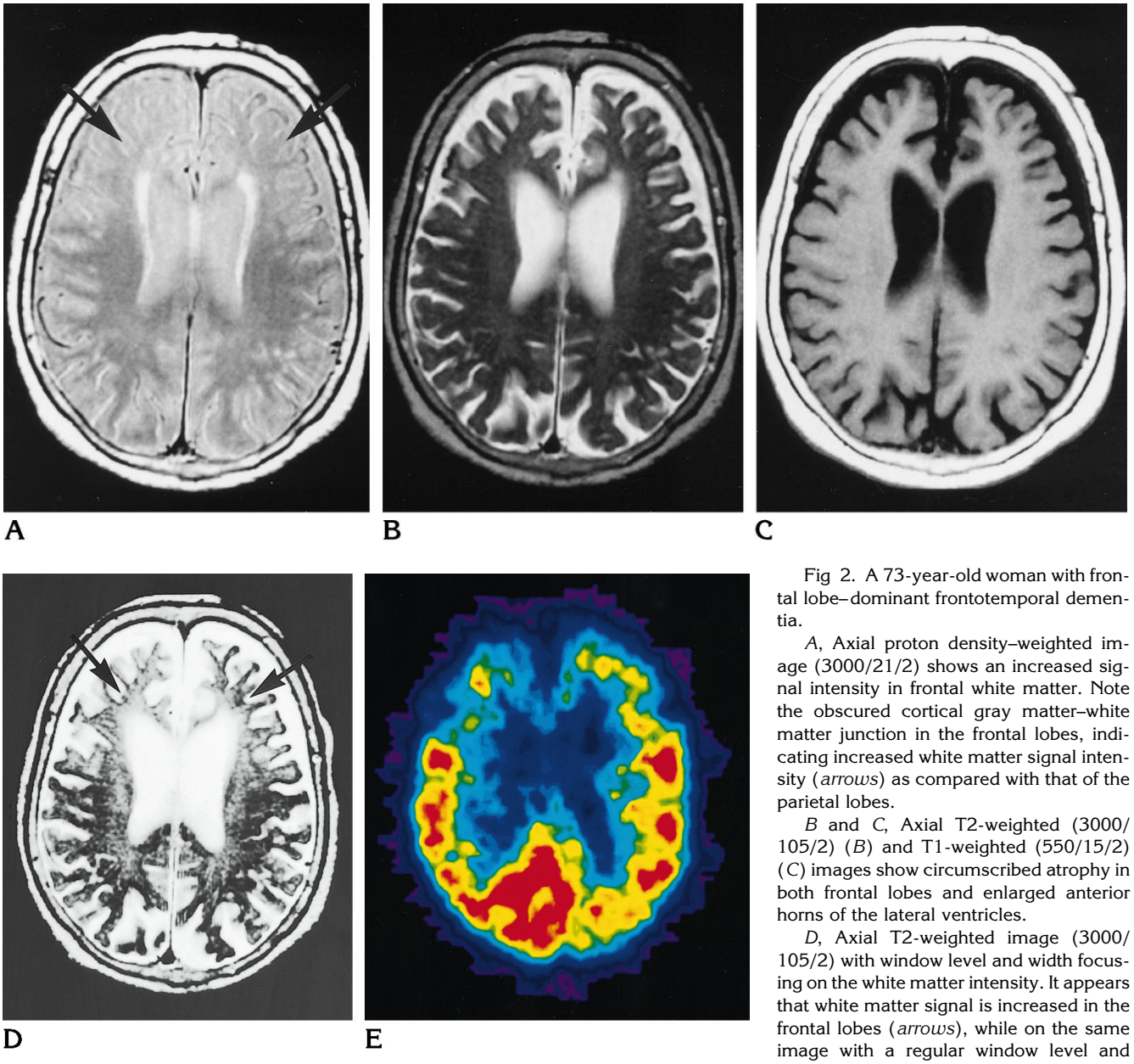

Fig 2. A 73-year-old woman with frontal lobe–dominant frontotemporal dementia.

A, Axial proton density–weighted image (3000/21/2) shows an increased signal intensity in frontal white matter. Note the obscured cortical gray matter–white matter junction in the frontal lobes, indicating increased white matter signal intensity (*arrows*) as compared with that of the parietal lobes.

B and *C*, Axial T2-weighted (3000/105/2) (*B*) and T1-weighted (550/15/2) (*C*) images show circumscribed atrophy in both frontal lobes and enlarged anterior horns of the lateral ventricles.

D, Axial T2-weighted image (3000/105/2) with window level and width focusing on the white matter intensity. It appears that white matter signal is increased in the frontal lobes (*arrows*), while on the same image with a regular window level and width (*B*) the white matter intensity appears normal.

E, Axial PET blood flow image obtained with $C^{15}O_2$ shows hypoperfusion in the frontal lobes.

10% for T2-weighted images was used as an operational criterion for appropriateness of ROI placement (in control subjects and patients, CVs ranged from 1% to 4% for T1- and proton density–weighted images, and from 4% to 10% for T2-weighted images). If a CV exceeded the criterion, suggesting that the ROI should include something nonhomogeneous, the ROI was repositioned.

White matter or CSF intensity was expressed as an average of right- and left-sided values. To normalize MR signal differences among subjects, caused by diversity of the hardware, especially magnet homogeneity, the white matter–CSF ratio was determined. In measurements on proton density–weighted images of 10 healthy subjects, CV was 10.3% for white matter signal value and 1.7% for the corresponding intensity ratio, indicating that the latter is more reliable and more suitable for intersubject comparison than the actual value. Repeated intensity measurements by two reviewers in 10 healthy subjects showed a high interrater reliability (frontal region on proton density–weighted images: Pearson $r = .988$, $P < .001$).

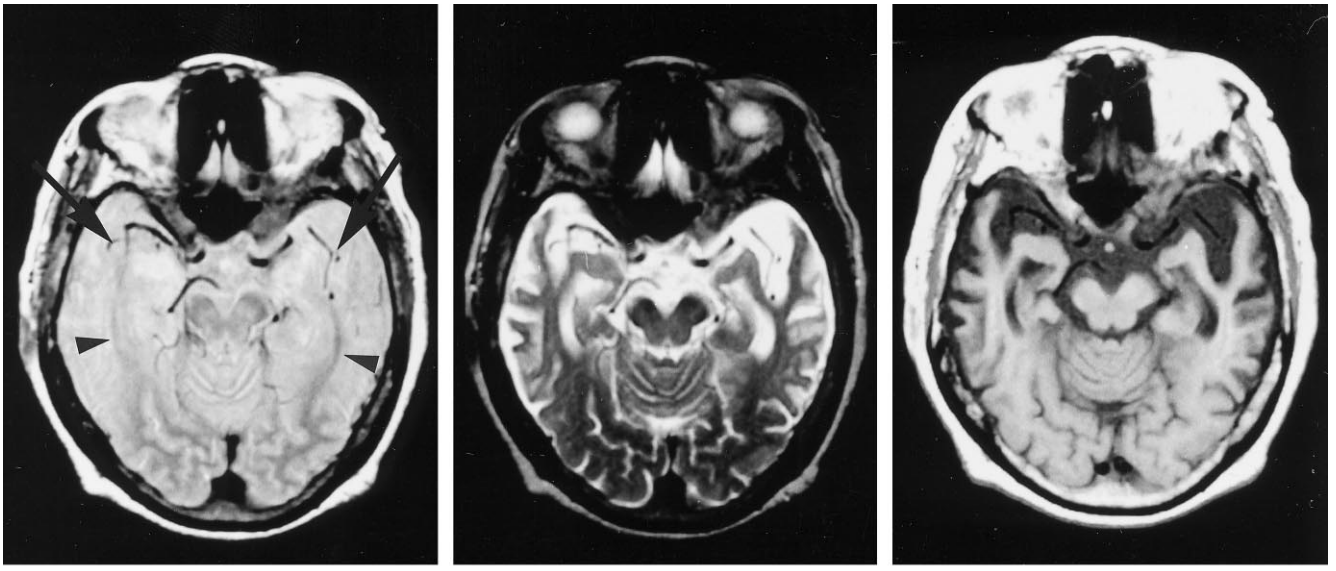

Fig 3. A 67-year-old woman with temporal lobe–dominant frontotemporal dementia.

A, Axial proton density–weighted image (3000/21/2) shows increased signal intensity in the bilateral temporal white matter (*arrows*). Low signal bands represent the white matter of normal signal intensity (*arrowheads*). The area of increased white matter signal intensity extends beyond the atrophic region.

B and *C*, Axial T2-weighted (3000/105/2) (*B*) and T1-weighted (550/15/2) (*C*) images show a distinct circumscribed atrophy in both temporal lobes.

Statistical Analysis

Statistical analysis was carried out using Fisher's exact probability test for nominal data, two-way analysis of variance, and Scheffe's post hoc analysis. A statistically significant level was set at $P < .05$ (two-sided). In addition, to delineate the value of the MR sign of white matter involvement, the analysis was done on a normal/abnormal basis, where the cut-off value for normal signal intensity range was set at the mean $\pm$ 2 $\times$ SD of the control group. The κ statistics were calculated to assess the interrater reliability. Data were analyzed with Systat for Macintosh, version 5.2.1 (Systat, Inc, Evanston, Ill).

Results

Visual Inspection

Agreement between the two reviewers was adequate for rating both atrophy and intensity (κ = .925 for atrophy assessment, κ = .775 on proton density–weighted images and κ = 1 on T2-weighted images for intensity assessment). Table 3 summarizes the results of visual inspection for circumscribed lobar atrophy and signal intensity. Circumscribed lobar atrophy was present only in the patients with frontotemporal dementia (four in the frontal lobe, five in the temporal lobe, and five in both lobes; Figs 2 and 3). Proton density–weighted imaging was far more sensitive for detecting signal intensity changes than T2- and T1-weighted imaging. On proton density–weighted images, white matter signal intensity in either the frontal or temporal lobe or both was judged abnormally increased in 20 patients in the frontotemporal dementia group (six in the frontal lobe, five in the temporal lobe, and nine in both lobes; Figs 2 and 3), whereas abnormal intensity was apparent only in five patients (one in the frontal lobe, three in the temporal lobe, and one in both lobes) on T2-weighted images and in none on T1-weighted images. On proton density–weighted images, the area of increased signal intensity extended from subcortical to deep white matter and was amorphous in shape and exceeded that of cortical atrophy in 14 patients. Five patients in the Alzheimer group had mildly increased signal intensity on proton density–weighted images (one in the frontal lobe and four in the temporal lobe). No signal intensity change was apparent among patients in the Alzheimer group on T1- and T2-weighted images (Fig 4). Among the control group, neither lobar atrophy nor white matter intensity changes were detected on any images (Fig 5).

Frontotemporal white matter signal hyperintensity on proton density–weighted images distinguished patients with frontotemporal dementia from healthy control subjects with a

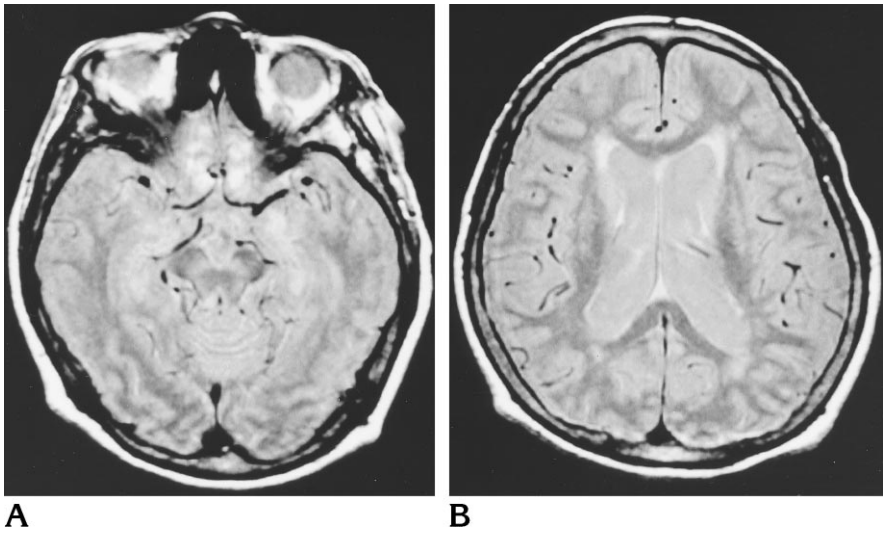

Fig 4. A 74-year-old woman with Alzheimer disease. Axial proton density-weighted images (3000/21/2) show a distinct cortical gray matter–white matter junction.

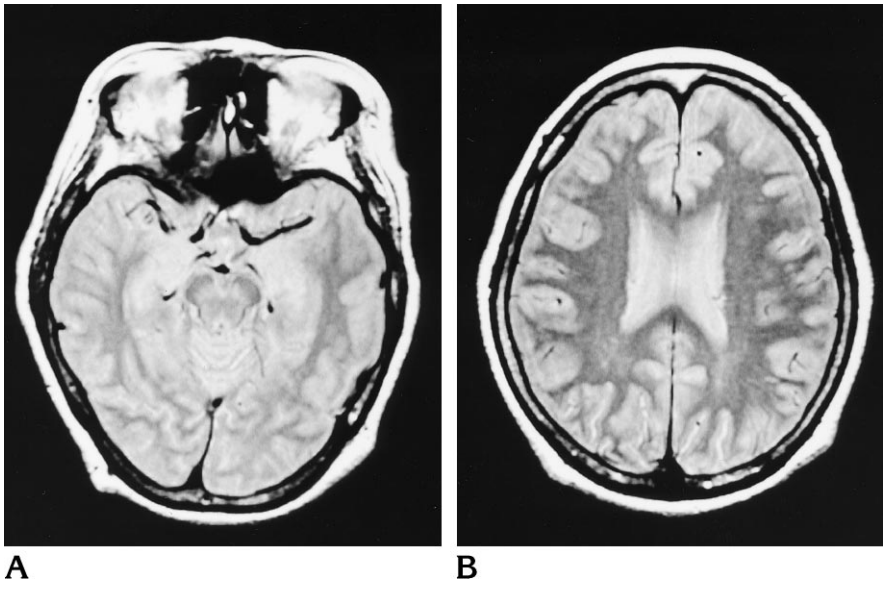

Fig 5. A 64-year-old woman from the control group. Axial proton density–weighted images (3000/21/2) show distinct cortical gray matter–white matter junction.

sensitivity of 91% and a specificity of 100%; Alzheimer patients were distinguished with a sensitivity of 91% and a specificity of 77%. On the other hand, circumscribed frontotemporal atrophy distinguished patients with frontotemporal dementia from healthy subjects with a sensitivity of 64% and a specificity of 100%; Alzheimer patients were distinguished with a sensitivity of 64% and a specificity of 96%.

Intensity Measurement

Both on T2- and proton density–weighted images, the white matter–CSF intensity ratio in the frontal lobes was greater in the frontotemporal dementia group than in the control group (by 10.5% for proton density–weighted images, $P <$ .001, and by 20.9% for T2-weighted images, $P <$ .001) and was also greater in the frontotemporal dementia group than in the Alzheimer group (by 8.3% for proton density–weighted images, $P <$ .001, and by 14.2% for T2-weighted images, $P <$ .001). In the temporal lobes, the white matter–CSF intensity ratio was greater in the frontotemporal dementia group than in the control group (by 7.1% for proton density–weighted images, $P <$ .001, and by 18.7% for T2-weighted images, $P <$ .001). In the frontotemporal dementia group, the white matter–CSF intensity ratios of the frontal lobes on proton density–weighted images were greater than those of the parietal lobes (by 6.8% for proton density–weighted images, $P <$ .001) and the occipital lobes (by 12.3% for proton density–

TABLE 4: White matter–cerebrospinal fluid intensity ratio, mean ± SD

Lobe	Group		
	Frontotemporal Dementia	Alzheimer Disease	Control
Frontal			
Proton density–weighted images	0.871 ± 0.062*†	0.804 ± 0.026	0.788 ± 0.027
T2-weighted images	0.346 ± 0.043*†	0.303 ± 0.021	0.286 ± 0.017
T1-weighted images	2.487 ± 0.156	2.478 ± 0.132	2.469 ± 0.093
Temporal			
Proton density–weighted images	0.816 ± 0.046*	0.787 ± 0.024	0.762 ± 0.030
T2-weighted images	0.325 ± 0.036*	0.301 ± 0.026	0.274 ± 0.022
T1-weighted images	2.324 ± 0.126	2.362 ± 0.122	2.309 ± 0.080
Parietal			
Proton density–weighted images	0.815 ± 0.038	0.786 ± 0.029	0.777 ± 0.025
T2-weighted images	0.322 ± 0.025	0.300 ± 0.02	0.292 ± 0.019
T1-weighted images	2.444 ± 0.129	2.430 ± 0.122	2.431 ± 0.092
Occipital			
Proton density–weighted images	0.776 ± 0.041	0.773 ± 0.036	0.755 ± 0.025
T2-weighted images	0.306 ± 0.021	0.302 ± 0.023	0.286 ± 0.017
T1-weighted images	2.235 ± 0.137	2.269 ± 0.142	2.279 ± 0.081

* $P < .01$, difference between the patients with frontotemporal dementia and control subjects.

† $P < .01$, difference between the patients with frontotemporal dementia and those with Alzheimer disease.

weighted images, $P < .001$, and by 12.9% for T2-weighted images, $P < .001$). Also, the white matter–CSF intensity ratio of the frontal lobes was greater than that of the temporal lobes (by 6.7%, $P < .001$) on proton density–weighted images. There was no significant difference of the white matter–CSF intensity ratio for any region between the Alzheimer and control groups. On T1-weighted images, the white matter–CSF intensity ratio did not differ significantly either within regions or among groups (Table 4).

Signal intensity in the frontotemporal dementia group was abnormally elevated in 14 patients on proton density–weighted images (10 in the frontal lobe, two in the temporal lobe, and two in both lobes) and in 13 patients on T2-weighted images (seven in the frontal lobe, three in the temporal lobe, and three in both lobes). In the Alzheimer group, signal intensity was not abnormal in any patient on proton density–weighted images but it was abnormal in three patients on T2-weighted images (one in the frontal lobe, one in the temporal lobes, and one in both lobes). The differences between the patients with frontotemporal dementia and those with Alzheimer disease were significant ($P = .005$ for proton density–weighted images and $P = .01$ for T2-weighted images). In the frontotemporal dementia group, frontal and temporal signal intensity was within the normal range in six patients on both T2- and proton density–weighted images (Fig 6).

In a few patients in the frontotemporal dementia group, the white matter–CSF intensity ratio exceeded the cut-off value in the parietal lobes or occipital lobes (three patients in the parietal lobe, one patient in the occipital lobe, and one patient in both lobes on proton density–weighted images; and in two patients in the parietal lobe, one patient in the occipital lobe, and one patient in both lobes on T2-weighted images). Frontotemporal white matter signal hyperintensity on proton density–weighted images, when the cut-off value was set at mean plus 2 SD of the control group, distinguished frontotemporal dementia patients from control subjects with a sensitivity of 73% and a specificity of 100% and from Alzheimer patients with a sensitivity of 73% and a specificity of 91%. Similarly, signal hyperintensity on T2-weighted images distinguished frontotemporal dementia patients from control subjects with a sensitivity of 86% and a specificity of 94% and from Alzheimer patients with a sensitivity of 86% and a specificity of 73%.

Discussion

We found that patients with frontotemporal dementia had significant signal changes of the white matter in the frontal and temporal regions

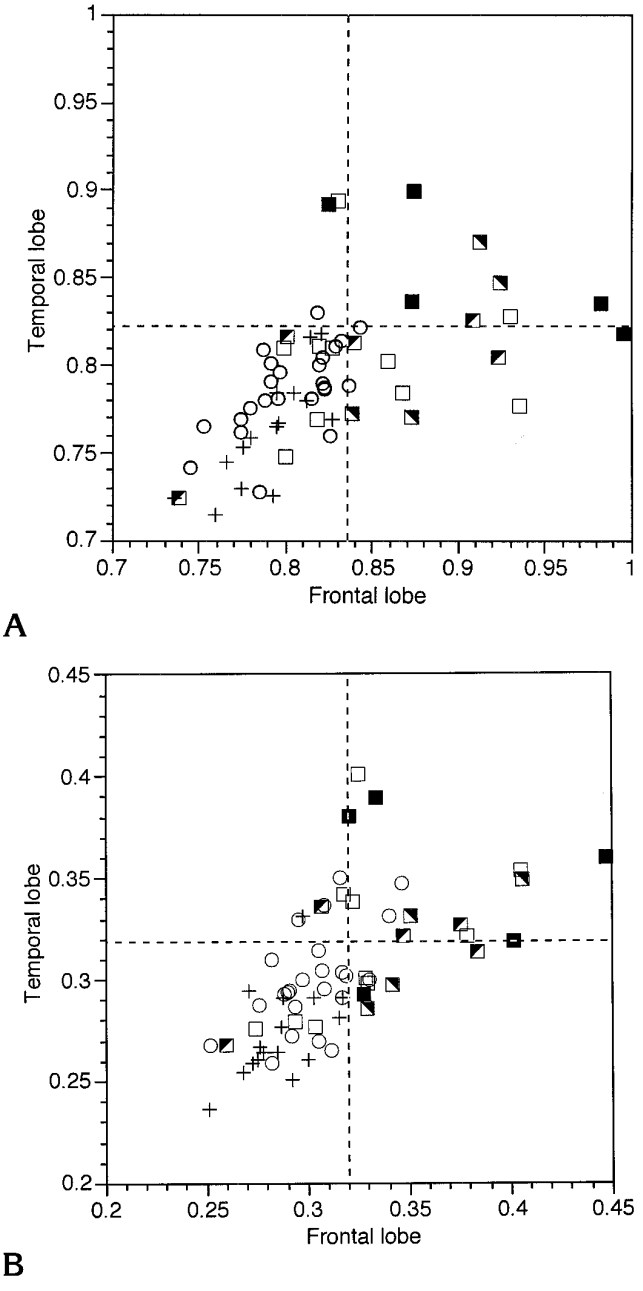

Fig 6. Plots of frontal and temporal signal intensity on proton density–weighted (*A*) and T2-weighted (*B*) images. *Broken lines* indicate the upper normal limits (mean + 2 × SD of the control subjects). *Open circles* indicate control subjects; *plus signs*, Alzheimer patients. For frontotemporal dementia (*squares*), MR evidence of circumscribed lobar atrophy is expressed as frontal atrophy (*square shaded on right*) temporal atrophy (*square shaded on left*), frontotemporal atrophy (*solid square*), and no lobar atrophy (*open square*).

on T2- and proton density–weighted MR images. The white matter signal changes in the frontal lobes in patients with frontotemporal dementia were greater than the signal changes in control subjects and in patients with Alzheimer disease, and the signal changes in the temporal lobes were greater than those in control subjects. Measurements of signal intensity on T2- and proton density–weighted images and visual inspection of proton density–weighted images but not of T2-weighted images were sensitive for the detection of signal changes of the white matter (Fig 7). A change in signal intensity was a more sensitive sign of frontotemporal dementia than was MR evidence of circumscribed lobar atrophy.

Myelin lipid, organized tightly in a compact structure, lowers the signal intensity of white matter on T2- and proton density–weighted images (22), and breakdown of myelin increases signal intensity on T2- and proton density–weighted images (23). Studies of hippocampal sclerosis have indicated that astrocytic gliosis raises the signal intensity on T2- and proton density–weighted images (24). Therefore, white matter astrocytic gliosis and mild demyelination predominantly affecting the frontal and temporal lobes in frontotemporal dementia (1) most likely contribute to alteration of signal intensity in the frontotemporal white matter. Unlike plaques of multiple sclerosis, in which demyelination accompanied by acute inflammation and edema may cause intense signal change on T2- and proton density–weighted images (25), less severe demyelination and lack of inflammation and edema in frontotemporal dementia probably account for this modest intensity change.

We noted six patients whose frontal and temporal signal intensity was within the normal range on both T2- and proton density–weighted images. In these patients, the abnormal findings might coincide with that of frontal lobe degeneration, in which white matter gliosis is reportedly less severe than in Pick type (1) (Fig 8). It is conceivable that signal intensity changes of the white matter differentiate Pick type from frontal lobe degeneration, as well as a circumscribed knife blade–shaped lobar atrophy (1). Furthermore, some disorders that may cause dementia, such as progressive subcortical gliosis (26) and corticobasal degeneration (27), affect the white matter by gliosis, in which the distribution of loci is distinctive from that in frontotemporal dementia. MR signal intensity

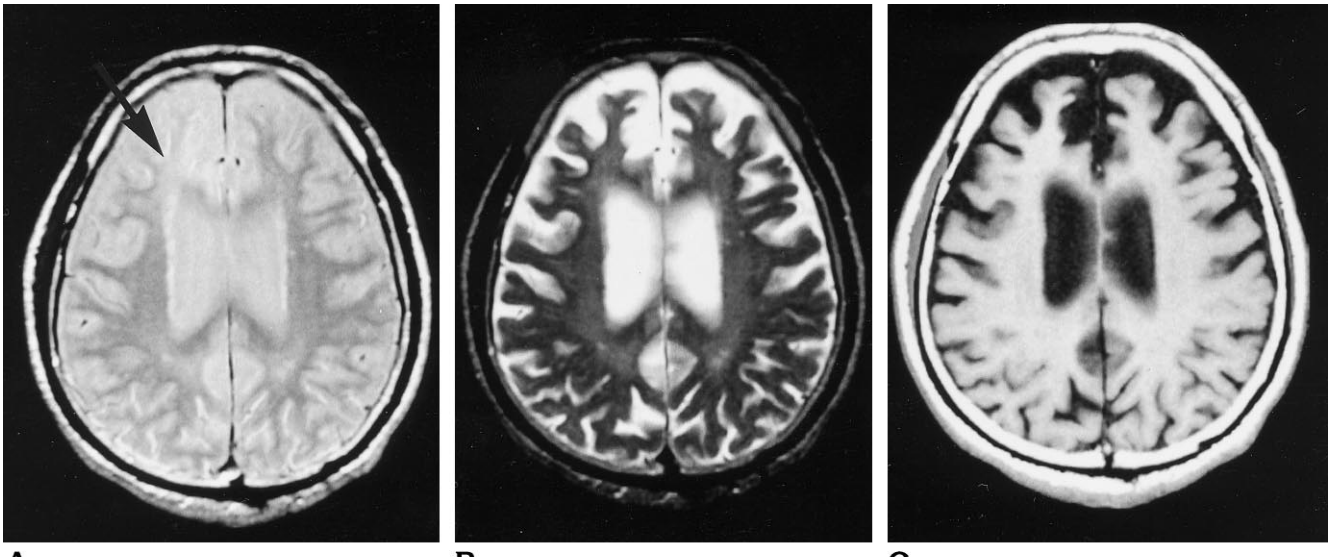

Fig 7. A 69-year-old man with frontal lobe–dominant frontotemporal dementia.

A, Axial proton density–weighted image (3000/21/2) shows increased signal intensity in the right frontal white matter (*arrow*).

B, Axial T2-weighted image (3000/105/2) shows that the value of the signal intensity increases in the same region, although it is visually ambiguous.

C, Axial T1-weighted image (550/15/2) shows circumscribed atrophy in the right frontal lobe.

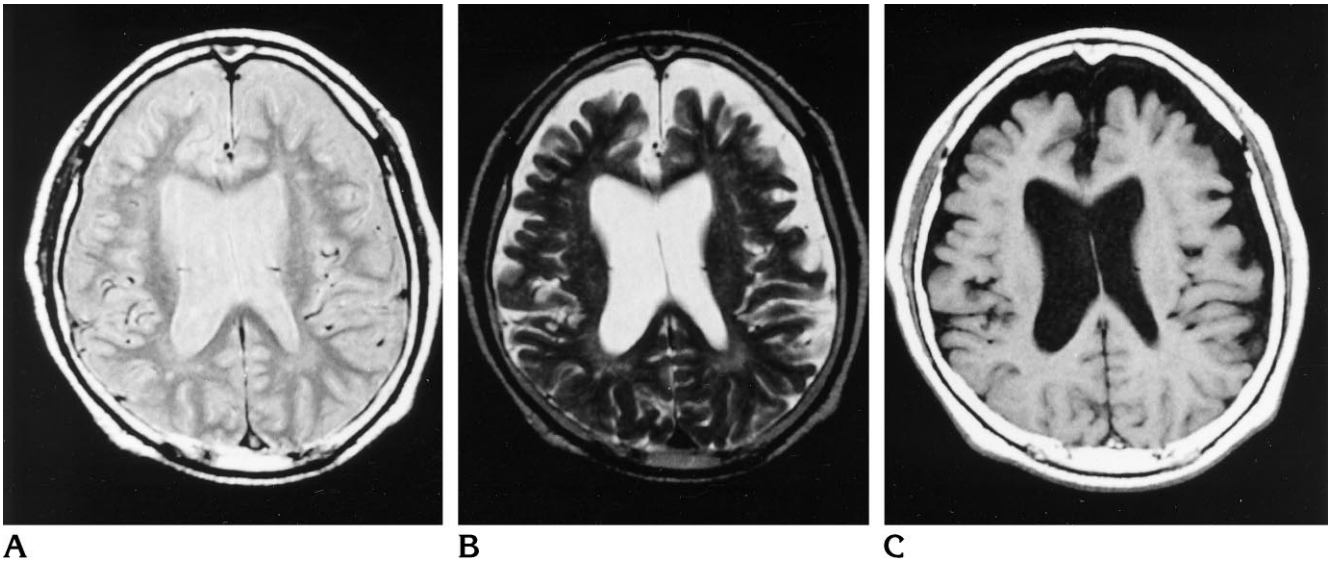

Fig 8. A 72-year-old man with frontotemporal dementia.

A, Axial proton density–weighted image (3000/21/2) shows that the white matter signal intensity appears to be unaffected.

B and *C*, Axial T2-weighted (3000/105/2) (*B*) and T1-weighted (550/15/2) (*C*) images show circumscribed atrophy in the bilateral frontal lobes.

changes of the white matter might offer a useful clue for clinical diagnosis of these disorders. Predominant involvement of the language-dominant frontal and temporal lobes by Pick disease leads to linguistic rather than behavioral symptoms, forming part of the clinical spectrum of progressive aphasia (28), although other disease processes also may produce this syndrome (29). In the present study, since we made much of the specificity of inclusion criteria of subjects, patients with this syndrome were not included, although evaluation of MR signal intensity in the frontotemporal white matter is likely to differentiate slowly progressive aphasia with Pick disease from other syndromes.

Visual inspection and signal intensity mea-

surements were equal for detecting signal intensity changes on proton density–weighted images. Visual inspection of T2-weighted images was not sufficient to detect the elevated white matter signal intensity well, since the window level and width of these images are not suitable for evaluation of white matter. If images were obtained with a window level and width aimed to observe the white matter, the white matter intensity change would be more perceivable, as was the case when evaluated on a cathode-ray tube display with an appropriate window level and width (Fig 2D). For quantitative intensity measurements, both T2- and proton density–weighted imaging are equally effective, while for visual inspection on images with a regular window level and width, proton density–weighted imaging is the technique of choice.

Signal intensity was elevated even in regions where lobar atrophy was not present. Therefore, this sign probably precedes the MR appearance of circumscribed lobar atrophy. Furthermore, quantitative and objective measurement of signal intensity changes in the white matter is superior to visual evaluation of lobar atrophy. In demented patients with visually normal signal intensity of white matter, measurement of specified white matter sites may help distinguish between Alzheimer disease and frontotemporal dementia for inclusion of patients in research protocols, or may be clinically useful when specific, effective treatments are developed.

In terms of signal acquisition technique, several possibilities exist for improving the modest sensitivity of frontotemporal signal changes in detecting frontotemporal dementia. Motion artifacts may obscure signal changes in the white matter. In the fast spin-echo method, no motion-compensating gradients are available for the first echo. Therefore, one possibility is the use of the standard spin-echo sequence with motion-compensating gradients, although the increased imaging time may result in more motion artifacts, which would discount any benefit. Another possibility is the use of the fluid-attenuated inversion recovery (FLAIR) sequence. As white matter lesions appear in contrast with nulled CSF signal, the FLAIR technique has reportedly been superior to T2-weighted spin-echo imaging for detecting white matter lesions such as demyelinating plaques (30–32). These possibilities should be tested in future studies.

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