Measure of Magnetization Transfer in Multiple Sclerosis Demyelinating Plaques, White Matter Ischemic Lesions, and Edema

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PURPOSE: To define the percentage of magnetization transfer of multiple sclerosis (MS) plaques, ischemic white matter lesions, and vasogenic edema to determine whether this measurement can help differentiate these entities. **METHODS:** Findings were compared in 25 patients with proved MS, 20 patients with white matter ischemic lesions, and 72 patients with white matter edema (caused by tumors, infections, or acute/subacute infarctions) in the periventricular system, centrum semiovale, and subcortical white matter. Magnetization transfer was performed using an on-resonance binomial pulse. The percentage of magnetization transfer of the normal white matter was also calculated. **RESULTS:** Magnetization transfer was significantly higher in white matter ischemic lesions (range, 31% to 38%; mean, 34% ± 0.6%) than in demyelinating plaques of MS (range, 19% to 28%; mean, 22.5% ± 1%) and in edema (range, 29% to 37%; mean, 30.2% ± 0.4%). No statistical difference in percentage of magnetization transfer was found among lesions in the periventricular system (34% ± 0.6%), centrum semiovale (35% ± 0.5%), or subcortical white matter (33% ± 0.6%), or in vasogenic edema associated with tumors, infections, or infarction. **CONCLUSION:** Differences in magnetization transfer suggest less change of demyelination in white matter ischemic lesions than in MS plaques and are significantly different in this respect from similar MS plaques. Magnetization transfer of edema was less than that of normal white matter or fell between ischemic abnormalities and MS plaques. Percentages of magnetization transfer below the mid-20% range is highly suggestive of demyelination. Vasogenic edema, our surrogate for increased water content of white matter, caused a decrease in the percentage of magnetization transfer.

Index terms: Brain, edema; Brain, ischemia; Magnetic resonance, magnetization transfer; Sclerosis, multiple

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Neuropathologic lesions involving the white matter that result from such demyelinating diseases such as multiple sclerosis (MS), ischemia, leukodystrophies, and perivascular edema are depicted by magnetic resonance (MR) imaging as high-signal-intensity lesions on proton density–weighted and T2-weighted images and usually as low/intermediate signal lesions on T1-weighted images. While demyelination accounts for the white matter lesions seen in MS, the pathogenesis of periventricular white matter lesions among otherwise healthy elderly persons requires further clarification (1, 2).

White matter hyperintensity seen on MR images is not specific for infarction but can be seen in any state of tissues in which the water content is increased, including simple gliosis (3). Clinical and pathologic studies comparing these white matter hyperintense lesions suggest various causes, including gliosis and/or an ischemic process, but no definite consensus has been reached among investigators (4–20). The purpose of this study was to characterize these white matter lesions commonly observed in the elderly and to compare them with MS plaques and acute white matter vasogenic edema by using magnetization transfer MR imaging. Acute vasogenic edema was used to determine the

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effect of free hydrogen protons on the percentage of magnetization transfer of white matter, assuming that this represented increased water content without demyelination. In a recently published study, Wong et al (21) attempted to analyze these white matter lesions with the use of magnetization transfer.

Subjects and Methods

This study was performed prospectively over a 4-month period (March through June 1992). The study population consisted of 25 patients (16 women and 9 men, 21 to 65 years old) with definite MS diagnosed clinically, with supporting laboratory data; 20 patients (11 men and 9 women, 26 to 76 years old) with nonspecific white matter lesions in the periventricular system, centrum semiovale, and subcortical white matter; and 72 patients (38 men and 34 women, 25 to 81 years old) with white matter (vasculogenic) edema associated with tumors of the central nervous system (n = 40), infarctions (n = 17), and infections (n = 15). The nonspecific white matter lesions reflected ischemic changes associated with aging (7). Although we recognize that autopsy studies of such lesions show a heterogeneous group of abnormalities, we refer to them collectively as *ischemic white matter lesions* in this article.

All the studies were performed on a 1.5-T MR imaging unit using a head coil, an 18-cm to 24-cm field of view, and a 256 × 256 matrix. The brain MR protocol included sagittal T1-weighted images (800/20/1 [repetition time/echo time/excitations]) with 5-mm-thick sections and 2.5-mm intersection space; axial T2-weighted images (200/30.80/2) with 4-mm-thick sections and 1.0-mm intersection space; and axial precontrast and postcontrast T1-weighted images (800/20/1) with and without magnetization transfer, with 5-mm-thick sections and a 1.0-mm intersection space. All patients signed a written consent form allowing the additional magnetization transfer sequence. For magnetization transfer images, only the saturation pulse was added; the other parameters were identical (4).

Magnetization transfer was performed with an on-resonance zero-degree binomial (1-2-1) pulse to saturate the restricted hydrogen (H_r) pool (22, 23). This pulse has a broad passband with no significant saturation of free hydrogen pool (H_f), and is reasonably insensitive to the main magnetic field (B_O) inhomogeneities (22).

The percentage of magnetization transfer of the brain was calculated on the difference image using the formula percentage of magnetization transfer = Mo−Ms/Mo (where Mo indicates signal intensity on the baseline or non–magnetization transfer image and Ms indicates signal intensity on the magnetization transfer–saturated image). Higher signal on this image means a greater change of magnetization transfer. The percentage of magnetization transfer was calculated by drawing regular regions of interest (measuring 0.5 mm^2 and 25 mm^2) on the calculated difference image for three to four randomly selected lesions in each of the white matter categories. The centrum semiovale, subcortical, and periventricular regions of interest were chosen, and three measurements per patient were defined by reference to a T2-weighted image of the same brain section on which the areas of abnormal white matter signal could be delineated clearly. The focal white matter ischemic changes seen in the healthy adult population were classified into three categories on the basis of their location: periventricular system, centrum semiovale, and subcortical white matter. Measurements of the Virchow-Robin spaces were avoided owing to their characteristic locations and their signal intensity behavior, which is similar to that of cerebrospinal fluid. The MS lesions were recognized as those with a high signal abnormality on proton density–weighted and T2-weighted sequences. The size and location of the MS lesions were comparable to that of the white matter ischemic lesions (ie, periventricular system, centrum semiovale, and subcortical white matter). Finally, acute white matter edema (perivascular) was also included to determine the effect of free hydrogen protons on the percentage of magnetization transfer of edematous white matter, assuming that this white matter was not demyelinated. The mean, standard deviation, and standard error of the mean were calculated for each category of lesions and for each of the above-designated groups. Background noise was measured as the signal intensity of air (in a region not contaminated by the phase-encode artifact) and divided by the square root of π (24). Adjacent normal white matter was measured in all patients. Tests for statistical significance (two-tailed *t* test) were applied.

TABLE 1: Percentage of magnetization transfer among different white matter lesions

Lesion Type	Mean ± SEM, %	Range, %
Ischemic white matter	34.2 ± 0.3	31–38
Multiple scloerisis plaques	22.5 ± 1.0	19–28
Perivascular edema	30.2 ± 0.4	29–37
Normal white matter	38.4 ± 0.2	36–40

Results

The results are as depicted in Table 1. The mean percentage of magnetization transfer of the normal white matter in all the three groups studied was 38.4% ± 0.2% (mean ± SEM) and the range was 36% to 40%. This value is consistent with our previous measurements as well as with the measurements of other investigators (25) obtained by using techniques comparable to ours. There was no statistical difference ($P >$ .001) in the mean percentage of magnetization

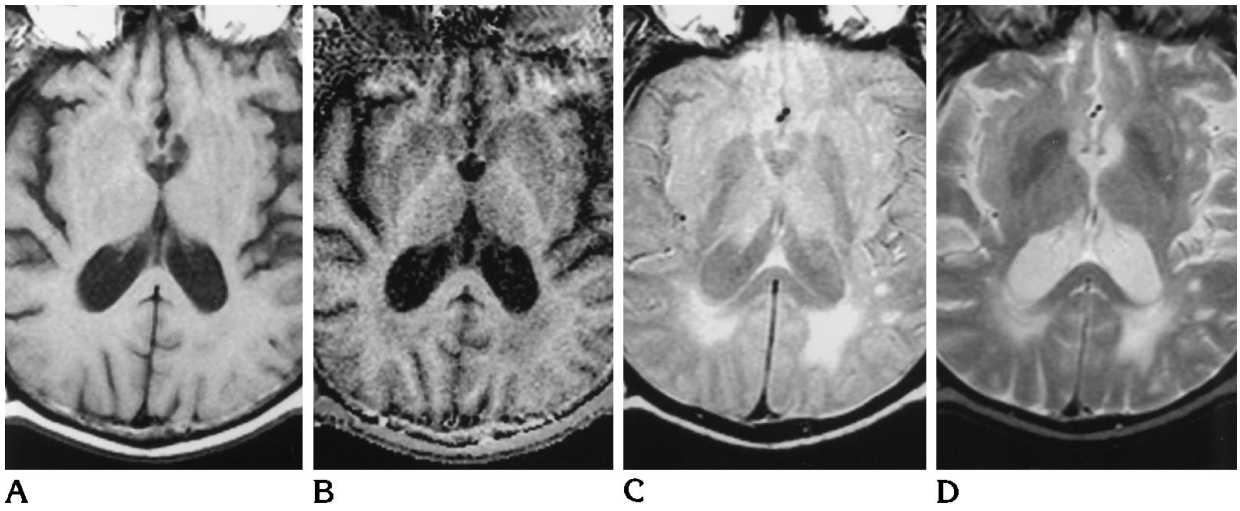

Fig 1. A 67-year-old asymptomatic patient with nonspecific white matter high-signal abnormalities.

A, Axial T1-weighted image at the level of the atrium shows subtle low signal intensity in the periventricular white matter of the occipital lobe.

B, The difference image shows minimally decreased signal.

Proton density–weighted (*C*) and T2-weighted (*D*) images at the same level show the corresponding high signal in the extensive lesions of the periventricular system, deep white matter, and subcortical white matter. All lesions show only a slight decrease in percentage of magnetization transfer.

transfer of the normal white matter among the three groups. The percentage of magnetization transfer in the demyelinating plaques of MS was the lowest (mean, 22.5% ± 1.0%; range, 19% to 28%). Vasogenic white matter edema had a low percentage of magnetization transfer (mean, 30.2% ± 0.4%; range, 29% to 37%), which was lower than that seen in nonspecific ischemic white matter lesions ($P < .05$) but above that of the MS lesions ($P < .01$) (Table 1 and Fig 1). The mean percentage of magnetization transfer in the white matter ischemic lesions was 34.2% ± 0.3% (range, 31% to 38%) and was the closest to that of the normal white matter. No statistical difference in the percentage of magnetization transfer in these lesions was found on the basis of their location (subcortical, centrum semiovale, or periventricular) in the white matter (Table 2).

TABLE 2: Percentage of magnetization transfer in white matter ischemic lesions by location

Location	Mean ± SEM, %
Periventricular system	33.9 ± 0.6
Centrum semiovale	35.3 ± 0.5
Subcortical white matter	32.8 ± 0.6

Discussion

Foci of high signal in the cerebral white matter are common incidental findings on MR images of the brain of control subjects or patients with a variety of diseases (1). These foci of hyperintensity are also referred to variously as leukoaraiosis, periventricular hyperintensities, white matter hyperintensities, and unidentified bright objects (10). The number of foci has been reported to coincide with age and several risk factors. Gerard and Weisberg (26) reported that these foci occur on MR images in the geriatric population with a frequency of 7.8% in asymptomatic patients with no cardiovascular risk factors; 31% in asymptomatic patients with hypertension, diabetes mellitus, or heart disease; and 78.5% in patients with cardiovascular risk factors and a history of a completed stroke, reversible ischemic neurologic deficit, or transient ischemic attack (25). The prevalence of foci of hyperintensity in patients with hypertension, migraine, and dementia and in asymptomatic control subjects has also been studied (14).

These nonspecific white matter lesions, usually appearing on T2-weighted MR images as small, focal (sometimes confluent) areas of increased signal intensity, are often found scattered throughout the deep cerebral white matter (especially in the frontal and parietooccipital

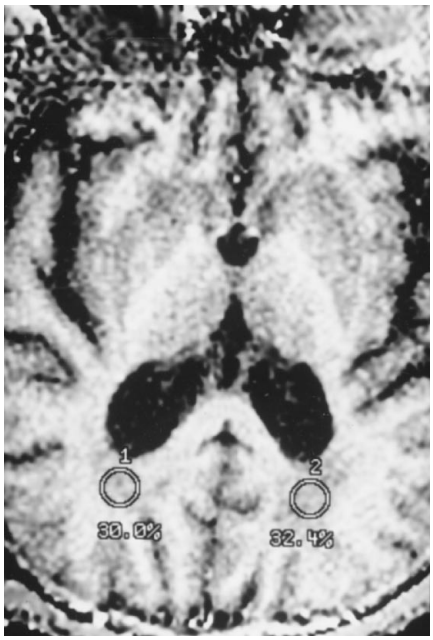

Fig 2. Magnetization transfer difference image (same as Fig 1B) with placement of regions of interest in areas of periventricular hyperintense white matter changes in both hemispheres.

areas) and capping the lateral ventricular margins (11, 12). If these deep white-matter foci are pathologic, it is possible that they represent edema and/or demyelination associated with ischemia (12).

MR imaging is especially sensitive when the insult being evaluated results in an increase in water content. The consequent increase in proton density and prolonged T2 relaxation time results in increased signal intensity on T2-weighted images. Not surprisingly, disease processes as varied as neoplasm, MS, infection, and infarction (all of which cause increased brain water) may yield a similar appearance on MR images. The clinical setting together with lesion morphology is helpful in formulating a relevant differential diagnosis. Magnetization transfer can now be added as a useful tool for evaluating such white matter disease and for refining the diagnosis.

The lowest percentage of magnetization transfer was for the demyelinating plaques of MS, both in terms of the mean and range. This result is related to the extent of demyelination (loss of myelin) and the loss of bound hydrogen protons. The mildly lowered percentage of magnetization transfer in the nonspecific white matter ischemic lesions (Figs 1 and 2) suggests no significant demyelination. These values suggest some increase in free water and/or decrease in bound water, and the range suggests the increase in free water is less than in vasogenic edema. The percentage of magnetization transfer in MS plaques was significantly lower than that in vasogenic edema, our surrogate for increased free water. The white matter edema showed approximately an 8% absolute decrease in the percentage of magnetization transfer as compared with 14% for MS plaques. Vasogenic edema was chosen to determine the effects of free water, since demyelination is not a normal feature. The presence of increased free water can therefore decrease the percentage of magnetization transfer but not to the levels seen in MS plaques. While edema can contribute to the decreased percentage of magnetization transfer in MS plaques, a value below the mid-20% range strongly suggests demyelination. Edema may be the cause of a decreased percentage of magnetization transfer in acute MS plaques without significant demyelination. Extrapolating these results to the observed values in MS lesions, part of the decrease in percentage of magnetization transfer may be attributed to increased free water (hydrogen protons) and part to demyelination and the loss of macromolecules. Similarly, the lowered percentage of magnetization transfer of white matter unidentified bright objects, irrespective of their location, is probably not due to demyelination and may be related to water content.

Wong et al (21) showed that the lower percentage of magnetization transfer in white matter periventricular hyperintense lesions is probably the result of increased water content. Their results are similar to ours; however, by including patients with MS and perivascular edema, we have clearly demonstrated the clinical usefulness of magnetization transfer in differentiating MS plaques from white matter hyperintense lesions caused by ischemia. The decreased percentage of magnetization transfer in edematous white matter illustrates the effect of excess free hydrogen protons on the percentage of magnetization transfer in white matter without any underlying demyelination.

A whole gamut of disease processes can cause abnormally increased T2 signal intensity in white matter, including infarction, gliosis, and nonspecific protein deposition (3, 27). A potential cause is ischemia without infarction (20). Such lesions can involve the deep white matter symmetrically and neuropathologically, and they are characterized by loss of myelin and

axon and oligodendroglial cells, with mild reactive gliosis, macrophage infiltration, and associated hyaline fibrosis of arterioles (20, 28). Since the deeper white matter is supplied by longer end-arteries penetrating the brain, these findings suggest vascular compromise as a cause of the white matter abnormalities.

In conclusion, white matter ischemic lesions encountered in the elderly show little demyelination as measured by percentage of magnetization transfer and are significantly different in this respect from chronic MS plaques. Vasogenic edema can decrease the percentage of magnetization transfer but not to a lower value than seen in demyelination. This measurement seems to set the lower limit on the percentage of magnetization transfer that can be attributed to increased water content alone; a value below this indicates macromolecular loss due to demyelination or necrosis.

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