Magnetization Transfer Effects in MR-Detected Multiple Sclerosis Lesions: Comparison with Gadolinium-Enhanced Spin-Echo Images and Nonenhanced T1-Weighted Images

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PURPOSE: To define the relationship between magnetization transfer and blood-brain-barrier breakdown in multiple sclerosis lesions using gadolinium enhancement as an index of the latter.

METHODS: Two hundred twenty lesions (high-signal abnormalities on T2-weighted images) in 35 multiple sclerosis patients were studied with gadolinium-enhanced spin-echo imaging and magnetization transfer. Lesions were divided into groups having nodular or uniform enhancement, ring enhancement, or no enhancement after gadolinium administration. For 133 lesions, T1-weighted images without contrast enhancement were also analyzed. These lesions were categorized as isointense or hypointense based on their appearance on the unenhanced T1-weighted images.

RESULTS: There was no difference between the magnetization transfer ratio (MTR) of lesions as a function of enhancement. MTR of hypointense lesions on unenhanced T1-weighted images was, however, lower than the MTR of isointense lesions. CONCLUSION: We speculate that diminished MTR may reflect diminished myelin content and that hypointensity on T1-weighted images corresponds to demyelination. Central regions of ring-enhancing lesions had a lower MTR than the periphery, suggesting that demyelination in multiple sclerosis lesions occurs centrifugally. In addition, the short-repetition-time pulse sequence seems useful in the evaluation of myelin loss in patients with multiple sclerosis.

Index terms: Sclerosis, multiple; Blood-brain barrier; Brain, magnetic resonance


The prevalence and morbidity of multiple sclerosis (MS) have led to strong interest in the evaluation and treatment of the disease. To assess the efficacy of treatment regimens, it is important to have a sensitive monitor of “disease activity.” Several authors have suggested that changes on magnetic resonance (MR) imaging may be a more sensitive indicator of disease burden and activity than clinical grading scales (1–4). Assessment of disease activity is difficult, however, because of complex plaque pathogenesis. Investigators have attempted to link clinical status to blood-brain-barrier breakdown and volumetric analysis of lesion burden (4). In addition to quantifying the number of plaques and the extent of active inflammation, as denoted by blood-brain-barrier breakdown with contrast enhancement, it would be valuable to determine the degree of demyelination. Unfortunately, standard spin-echo images have not been helpful in this regard, because hyperintensity on long-repetition-time images is related to increased water content and is nonspecific, occurring with inflammatory changes in the presence or absence of demyelination (5).

In addition to conventional spin-echo imaging, several techniques have been investigated in an attempt to define better the pathologic changes in MS plaques and provide a more quantitative assessment of the stage and extent of disease. Measurement of relaxation times and MR spectroscopy have attracted the most attention, but both are time-consuming and lim-
Materials and Methods

In the initial phase of our study, 87 white matter lesions in 18 patients, ages 18 to 65 years (mean age, 35.8 years), were studied with gadolinium-enhanced MR and magnetization transfer. All patients had clinical MS as defined by the Posner criteria (8). Images of the brain were obtained on a 1.5-T scanner using a quadrature head coil and included sagittal T1-weighted images, 3- to 5-mm axial T2-weighted fast-spin-echo images, magnetization transfer images (see below), and 3- to 5-mm contiguous axial postgadolinium T1-weighted images (600-750/26-27/1 [repetition time/echo time/excitations]). Gadolinium was given at a dose of 0.1 mmol/kg of body weight up to a maximum of 20 mL. In each case, all data were acquired in a single session. Because the initial goal of the study was to define the relationship between magnetization transfer and enhancement, cases for the first phase were randomly selected (by J.F.H.) from a cohort of MS study patients, with the criterion for selection being the presence of one or preferably multiple enhancing white matter lesions. Lesions were considered to enhance if they demonstrated significant hyperintensity to surrounding white matter on the postgadolinium T1-weighted images (a subtle ring of hyperintensity was not sufficient). Because we initially planned to correlate MTR to the presence of enhancement, we did not prospectively choose to obtain precontrast T1-weighted images in the first phase of our study.

In the second phase, we studied 133 white matter lesions in 17 consecutive patients, ages 20 to 48 (mean age, 35.6 years), with MS. After recognizing in the first phase that MTR corresponded more closely to the signal intensity (on T1-weighted images) of nonenhancing lesions than to the presence or degree of enhancement, we revised our primary objective for this group of patients to a comparison of lesion appearance and signal intensity on postgadolinium T1-weighted images to the MTR, regardless of enhancement. In addition to the pulse sequences described for the initial phase, images included 3-mm contiguous axial T1-weighted images, before (600/11/1) and after (600/27/1) administration of intravenous gadolinium.

Magnetization transfer images were obtained for each patient using the pulse sequence described by Schnall (Schnall et al, “Technique for Magnetization Transfer Imaging at 1.5 T Using Steady State Pulsed Saturation” (abstract 175), presented at the Society of Magnetic Resonance in Medicine meeting, San Francisco, Calif, 1991). Magnetization transfer data were collected before gadolinium administration in all cases. Five-millimeter contiguous axial images were acquired with a volumetric gradient-echo pulse sequence (three-dimensional gradient-recalled acquisition in a steady state, 106/5/1, 12° flip angle, 256 × 128 matrix). A prolonged, off-resonance, broad-bandwidth saturation pulse was applied before each excitation pulse to achieve partial saturation of the “macromolecular matrix” in the steady state (19-millisecond single-cycle pulse; 2-kHz off-peak water resonance; average B1 intensity, 3.67 × 10−6 T). A reference image (unsaturated) was also obtained with the amplitude of the off-resonance saturation pulse set to zero. Parameters for the reference image were otherwise identical (prescan parameters were held constant). The MTR of a given region of interest was then calculated by subtracting the average signal intensity of the region of interest on the saturated image, Ms, from the average signal intensity of the same region of interest on the unsaturated image, M0, and dividing by the average signal intensity of the region of interest on the unsaturated image (Fig 1):

\[ \text{MTR} = 100 \left(1 - \frac{M_s}{M_0}\right) \]

This is an adaptation of the rate equation for magnetization transfer described by Eng et al (7, 9). Throughout our discussion, we will refer to the general technique of magnetization transfer imaging as magnetization transfer and actual quantified results as MTR.

In addition to calculating a MTR for each white matter lesion, each lesion was categorized according to its appearance on the T1-weighted image. For the initial phase, only postgadolinium images were available and lesions were characterized as (a) isointense nonenhancing, (b) hypointense nonenhancing, (c) uniform or nodular enhancement, or (d) hypointense ring-enhancing, based on their appearance on the postgadolinium T1-weighted image relative to the surrounding white matter (Table 1).

Because our first group of patients did not have pregadolinium T1-weighted imaging and we thought that some minimally enhancing hypointense lesions might be misclassified as isointense nonenhancing lesions, we revised our methods in the second phase of the study to include precontrast T1-weighted images. For these patients, lesions were categorized based on their signal intensity on pregadolinium T1-weighted images (Table 2) and their enhancement on postgadolinium T1-weighted images (Table 3). Lesions were categorized as isointense, slightly hypointense, or definitely hypointense relative to surrounding white matter, based on appearance on the
pregadolinium T1-weighted images. The intermediate category of slightly hypointense lesions included lesions that were subtle, but discernible as discrete lesions on the pregadolinium T1-weighted images, knowing that there was a corresponding hyperintensity on the T2-weighted images. Examination time limitations did not permit acquisition of quantitative T1 relaxation times and, because prescan parameters for the T1-weighted images varied from patient to patient, region-of-interest measurements of signal intensity on T1-weighted images were not comparable among patients. Therefore, lesions were assessed visually. In addition, we measured region-of-interest values of lesions (from the T1-weighted images) and normalized the region-of-interest measurement of each lesion to the signal intensity of the cerebrospinal fluid (CSF) of that patient (normalized region-of-interest measurement equals T1-weighted image of the region of interest of lesion divided by average CSF region of interest from lateral ventricle in same patient). CSF was used as a standard because the T1 of CSF should be relatively constant between patients. The type of enhancement (nonenhancing, uniform or nodular enhancement, or ring enhancement) was assigned based on the postgadolinium T1-weighted images. Because the primary goal of this phase was to compare MTR to lesion appearance on pregadolinium images, enhancement was not a criterion for either patient or lesion selection. Therefore, because the number of nonenhancing lesions far outnumbered the enhancing lesions in these 17 patients, there are relatively few enhancing lesions in the second phase.

All calculations and lesion characterizations were performed by one author (J.F.H.), who was not blinded to the imaging or patient data.

Statistical significance was calculated using the Student’s t test. Significance of MTR differences between lesion groups was calculated using a two-tailed Student’s t test. Significance of correlation coefficients was calculated using an adaptation of the t test (10).

### Table 1: Phase 1: MTR of lesions categorized by postgadolinium T1-weighted MR appearance

<table>
<thead>
<tr>
<th>Group</th>
<th>T1-Weighted Image Appearance</th>
<th>Enhancement?</th>
<th>MTR*, mean, %</th>
<th>Standard Deviation, %</th>
<th>Number of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isointense</td>
<td>No</td>
<td>30.5</td>
<td>2.6</td>
<td>31</td>
</tr>
<tr>
<td>2</td>
<td>Hypointense</td>
<td>No</td>
<td>23.9</td>
<td>5.4</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>Hypointense*</td>
<td>Yes (nodular)</td>
<td>30.2</td>
<td>3.3</td>
<td>22</td>
</tr>
<tr>
<td>4</td>
<td>Hypointense</td>
<td>Yes (ring)</td>
<td>17.5</td>
<td>8.0</td>
<td>8</td>
</tr>
<tr>
<td>1, 3</td>
<td>Isointense†</td>
<td>...</td>
<td>30.4</td>
<td>2.9</td>
<td>53</td>
</tr>
<tr>
<td>2, 4</td>
<td>Hypointense</td>
<td>...</td>
<td>22.4</td>
<td>6.6</td>
<td>34</td>
</tr>
<tr>
<td>1, 2</td>
<td>Isointense</td>
<td>No</td>
<td>27.5</td>
<td>5.3</td>
<td>57</td>
</tr>
<tr>
<td>3, 4</td>
<td>Hypointense</td>
<td>Yes</td>
<td>26.8</td>
<td>7.5</td>
<td>30</td>
</tr>
</tbody>
</table>

* Signal intensity on T1-weighted image not discernable because of enhancement of lesion.
† Including nodular enhancing plaques whose T1-weighted image appearance was not discernable.
‡ Average MTR of all lesions in group.
§ Standard deviation of MTR measurements.

### Table 2: Phase 2: MTR as a function of appearance on pregadolinium T1-weighted images

<table>
<thead>
<tr>
<th>T1-Weighted Image Appearance</th>
<th>MTR*, mean, %</th>
<th>Standard Deviation, %</th>
<th>Number of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isointense</td>
<td>33.1</td>
<td>3.5</td>
<td>40</td>
</tr>
<tr>
<td>Slightly hypointense</td>
<td>30.6</td>
<td>4.1</td>
<td>22</td>
</tr>
<tr>
<td>Hypointense</td>
<td>27.3</td>
<td>4.2</td>
<td>71</td>
</tr>
</tbody>
</table>

* Average MTR of all lesions in group.
† Standard deviation of MTR measurements.
All patients had lesions with abnormal high signal intensity on the T2-weighted images, although there was marked variability in the number of lesions per patient. There was also variability in the conspicuity of these lesions and in their degree of enhancement on the T1-weighted images. All of the lesions had decreased MTR (mean, 28.6%; N = 220), compared with normal white matter in healthy control subjects (mean, 41.8%; standard deviation, 1.3%) (6).

In the first group of 18 patients, lesions with central hypointensity on T1-weighted images (groups 2 and 4) had decreased MTR relative to isointense or uniformly enhancing lesions (groups 1 and 3) (Table 1; Fig 2). There was also correlation between MTR and signal intensity on the postgadolinium images, which was best for the “nonenhancing” lesions, including both nonenhancing lesions with central hypointensity on postgadolinium T1-weighted images and nonenhancing lesions that were isointense to surrounding gray matter on the postgadolinium T1-weighted images (r = .64, P < .001) (Fig 3). There was no significant difference in the MTR of enhancing lesions (groups 3 and 4) and nonenhancing lesions (groups 1 and 2) (Table 1; Fig 2).

In the second group of 17 patients and 133 lesions, there was again no difference in the MTR as a function of enhancement (Table 3). The MTR of hypointense lesions (27.3%), however, was significantly lower than the MTR of isointense lesions (33.1%; P = .0001, two-tailed

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**TABLE 3: Phase 2: MTR as a function of gadolinium enhancement on T1-weighted images**

<table>
<thead>
<tr>
<th>Enhancement</th>
<th>MTR*, mean, %</th>
<th>Standard Deviation, †, %</th>
<th>Number of Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>29.8</td>
<td>4.7</td>
<td>117</td>
</tr>
<tr>
<td>Nodular</td>
<td>27.1</td>
<td>3.7</td>
<td>10</td>
</tr>
<tr>
<td>Ring</td>
<td>26.6</td>
<td>5.6</td>
<td>6</td>
</tr>
</tbody>
</table>

* Average MTR of all lesions in group.
† Standard deviation of MTR measurements.
unpaired Student's t test) (Table 2; Fig 4). Furthermore, this significant difference held up when the intermediate group of slightly hypointense lesions was pooled with either the hypointense lesions or the isointense lesions ($P < .0001$ for both comparisons, two-tailed Student's $t$ test). There was a large variability in the measured signal intensities of lesions on the T1-weighted images, probably attributable in part to variabilities in the prescan routine between patients. The correlation between these region-of-interest measurements from the T1-weighted images and MTR by regression analysis was $r = .46$ ($P \leq .01$). When the lesion region-of-interest measurements were normalized to CSF, however, there was much better correlation ($r = .60, P \leq .01$) (Fig 5).

Discussion

One difficulty in MR analysis of MS lesions has been poor specificity in characterizing the age and histologic substrate of lesions. Edema in acute lesions may be nearly impossible to differentiate from demyelination and gliosis in chronic lesions on routine spin-echo imaging. Gadolinium has proved sensitive in the detection of blood-brain-barrier breakdown, which often occurs in inflammatory or "active" lesions. Although the inflammatory change producing enhancement may precipitate or occur in concert with the demyelinating process, active plaques may either resolve or progress to chronic demyelinated lesions and gadolinium enhancement itself cannot be used to quantify myelin loss. Distinguishing myelin loss is, however, potentially useful because edematous or inflammatory lesions with relatively intact myelin may be more responsive to appropriate therapy than lesions that have already undergone myelin breakdown. Therefore, investigators have used a variety of MR techniques to evaluate myelin breakdown. Several investigators have looked at relaxation times of MS lesions compared with normal-appearing white matter. Lacomis et al found that T1 values were increased in MS lesions (11). Larsson et al found both T1 and T2 values lengthened in MS lesions in 10 patients with long-standing MS and no clinical symptoms over the preceding year (12), although the T1 and T2 values of lesions varied over a broad range. In a follow-up study of 10 patients with the acute onset of MS (13), there was a large overlap between the relaxation values of the acute lesions and the chronic lesions from their previous study (12). Armspach et al also studied T2 values in MS lesions and found a similarly wide range of values (14). In summary, multiple authors have suggested that the variability of relaxation times reflects biophysical differences in tissue composition, but it has been difficult to establish the relationship between plaque composition and prolongation of T1 or T2 (11, 13).

MR spectroscopy of MS has also been investigated and has yielded some promising results. Several investigators have demonstrated relatively decreased $N$-acetyl aspartate in MS lesions (15–21), most evident in chronic lesions (19). Other studies have found increased lipid or cholesterol peaks in MS lesions, usually in acute lesions (18, 22, 23). MR spectroscopy clearly has potential for better defining the pathologic substrate of MS lesions. Unfortunately, MR spectroscopy software is not widely available in the clinical setting, and spectroscopic examination is limited by volume location and time constraints.

Magnetization transfer was described in the physical chemistry literature in 1963 by Forsén and Hoffman as a means of measuring chemical exchange rates (24). Recently, Balaban et al have applied the technique to in vitro and in...
vivo MR imaging or magnetization transfer imaging (9, 25). The physical basis of magnetization transfer is complex and not completely understood. In one of the more commonly accepted theories, Eng et al have described two separate populations of protons, (a) the protons within freely mobile water molecules and (b) the restricted-motion protons bound within various macromolecules such as cell proteins and cell membranes (9). Experimental evidence suggests that the restricted-motion protons bound within the “macromolecular matrix” have a very broad resonance peak, and that there is rapid exchange of energy between the protons in this matrix, so that energy from a saturation pulse applied anywhere over the broad resonance peak will be quickly distributed among all the bound protons (25). When this broad peak of the macromolecular matrix has been saturated, there is exchange with the protons of the bulk water component via both chemical exchange and mutual spin-flip or dipole interactions, so that there will be some signal loss in the resulting image (26). The larger the macromolecular matrix, the larger the energy transfer to the free water protons and the greater the signal loss on the “saturated” image relative to the “unsaturated image.” In our technique, the MTR represents the ratio of signal intensities between the two images; therefore a high MTR occurs in more structured tissue where there is a large macromolecular matrix, and a low MTR occurs when there is a small macromolecular matrix.

Dousset used magnetization transfer to study a model of MS in both guinea pigs and human patients (6). In the guinea pigs with experimental allergic encephalomyelitis there was a mild decrease in MTR in lesions that had histologic evidence of edema, but no demyelination. In human patients with MS, however, MTR measurements of white matter lesions resulted in a broad range of values, mildly to markedly lower than normal. They hypothesized that mildly diminished MTR might correlate with edematous or inflammatory lesions that did not yet have significant demyelination (thus relative preservation of the highly structured myelin matrix), whereas more marked decrease in MTR might correlate with actual demyelination. Unfortunately, the lesions with low MTR were all in human subjects, so that no pathologic correlation was available to prove the coexistence of markedly diminished MTR and demyelination.

In more recent work, we demonstrated a correlation between MR spectroscopy findings and MTR (7). Decreased MTR correlated to increased spectroscopy peaks in the 2.1 through 2.6-ppm range, in which amino acid products including γ-aminobutyric acid and glutamate are known to resonate. We hypothesize that these peaks may represent myelin catabolites and that the MTR may be decreased as a result of disruption of the normal macromolecular matrix of myelin.

Our current study demonstrates an interesting correlation between the MTR of MS lesions and their signal intensity on the T1-weighted images. Data from an earlier study (7) had led us to suspect that enhancing plaques would have relatively low MTR, presumably because of an active process of inflammation and demyelination. Our current study, however, did not confirm this but rather demonstrated that most enhancing lesions had a relatively small decrease in MTR. Instead, the lowest MTR were in those white matter lesions that appeared hypointense to surrounding white matter on the T1-weighted image, including both hypointense nonenhancing lesions and the central, hypointense portions of ring-enhancing lesions. White matter lesions that were nonenhancing and relatively isointense to the surrounding white matter on the postgadolinium T1-weighted images also had a relatively modest decrease in the MTR.

Given the underlying physics of magnetization transfer and earlier results suggesting an association between decreased MTR and demyelination, we conclude that hypointense plaques represent the most demyelinated lesions, including both hypointense nonenhancing lesions and the hypointense central portion of ring-enhancing lesions. On the other hand, the mildly diminished MTR of isointense nonenhancing and nodularly or uniformly enhancing lesions suggests an inflammatory or edematous reaction with less significant demyelination.

Ring-enhancing MS lesions produced some of the most interesting results. There is general consensus that the peripheral, enhancing portion of a ring-enhancing lesion represents the “active, inflammatory” and presumably most acute component, whereas the nonenhancing central portion represents an older and potentially demyelinated area or gliotic scar (13). Ring-enhancing lesions may represent either recrudescence of an old demyelinated or gliotic plaque, or a rapidly progressive acute plaque.
which has already demyelinated centrally. Most of the ring-enhancing lesions in our study were relatively hypointense centrally, with a relatively low central MTR. Although it was difficult to measure the MTR along the thin enhancing rim of many of these lesions, there seemed to be relatively less decrease in the MTR along the rim (Fig 6). These findings support the hypothesis that active demyelination occurs peripherally in ring-enhancing plaques, with the central portion corresponding to the most myelin loss.

Unfortunately, the variability in data, including both magnetization transfer results and T1-weighting images, coupled with the absence of pathologic correlation, makes it impossible to determine a threshold at which actual demyelination can be diagnosed. Pathologic correlation would be helpful to correlate degree of demyelination to decreases in MTR or hypointensity on T1-weighted images but is unlikely to be available given the low mortality rate of MS and the difficulty in justifying biopsy. We hypothesize that there is a spectrum of values for MTR. At the lower end, these would correlate with myelin loss; in the middle, there would be a combination of myelin loss and edema; and at the upper end, mostly edema with little myelin loss.

Our data are in agreement with some of the previous work done on relaxation time changes. Namely, a mild increase in T1 would be consistent with little to no perceptible change in the appearance of the lesion on T1-weighted images (ie, isointense to surrounding white matter); the greater increase in T1 would be consistent with myelin loss (27). We might have achieved better correlation between the magnetization transfer image and the T1-weighted image had we measured relaxation times instead of region-of-interest, but time constraints would not permit that experiment. Furthermore, unpredictable sources of T1 variance would be expected to affect relaxation time measurements as well as region-of-interest measurements (28).

Comparison to Koenig’s results is also helpful in understanding our data (29). Koenig hypothesizes that white matter appears bright because of rapid mixing of axonal water with the water of myelin, causing an unexpectedly short T1. He also suggests that this may be caused by cross-relaxation effects analogous to the magnetization transfer effects reported by Balaban’s group (9, 25). If cross-relaxation properties of myelin are indeed a major factor in the short T1 of white matter, it would explain our correlation between diminished MTR and decreased signal intensity on T1-weighted images in MS lesions and support our hypothesis that both of these changes are caused by demyelination.
Because of the high conspicuity of MS lesions on T2-weighted images, most protocols for the evaluation of MS have exploited the sensitivity of these images for the detection or volumetric quantification of plaques. Several investigators, however, have discussed the advantages of T1-weighted images in the evaluation of MS lesions. Edwards et al showed that heavily T1-weighted inversion recovery scans had a higher specificity for demyelinating lesions than standard T2-weighted images (Edwards MK et al, “Clinical Utility of Inversion Recovery MR in the Diagnosis of MS” [abstract], AJNR Am J Neuroradiol 1989;10[suppl]:898). More recently, Shah et al showed that although T2-weighted imaging was better in detecting gray matter lesions, heavily T1-weighted MP RAGE images actually detected more deep white matter lesions than the T2-weighted images (30).

Although the high sensitivity of T2-weighted images makes them ideal in the detection of plaques, their relatively low specificity limits their usefulness in determining the type of plaque. T1-weighted image contrast, on the other hand, may prove helpful in defining the inherent structure and myelin content of lesions, contributing information that may be used in the prognosis and evaluation of treatment regimens.

In conclusion, the MTR of MS plaques is uniformly lower than that of normal white matter. Previous reports suggest that myelin may serve as the substrate for the relatively large magnetization transfer of white matter, and that the cross-relaxation properties of myelin may contribute to the short T1 of normal white matter. Given these findings, we believe that diminished MTR may be a sensitive indicator of myelin loss. Furthermore, the correlation of T1 signal intensity with MTR suggests that T1-weighted images may be more useful and more specific than previously thought in the categorization of MS lesions and perhaps even patient cohorts.

References


