AJNR

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AJNR Am J Neuroradiol 1996, 17 (6) 1041-1049
http://www.ajnr.org/content/17/6/1041

Multiple Sclerosis Lesions: Relationship between MR Enhancement Pattern and Magnetization Transfer Effect

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PURPOSE: To investigate the relationship between the enhancement pattern of a multiple sclerosis lesion and its magnetization transfer effect. **METHODS:** Fifty-four lesions were chosen from 29 patients with multiple sclerosis on the basis of enhancement pattern on contrast-enhanced T1-weighted MR images. They included 14 homogeneously enhancing lesions, 26 nonenhancing lesions, and 14 ring-enhancing lesions. Magnetization transfer ratios of the homogeneously enhancing lesions, nonenhancing lesions, and central portion of the ring-enhancing lesions were measured. Means were calculated and compared. **RESULTS:** The magnetization transfer ratios for homogeneously enhancing lesions were higher (mean, 32.2%; SD, 3.4%) than those for nonenhancing lesions (mean, 29.4; SD, 4.3%) and for the central portion of ring-enhancing lesions (mean, 24.5%; SD, 4.0%). Significant differences were found between the ring-enhancing lesions and the homogeneously enhancing lesions and between the ring-enhancing lesions and the nonenhancing lesions. **CONCLUSION:** We found a relationship between decreased magnetization transfer ratios and those enhancement patterns in which myelin is known to be decreased histopathologically. Thus, use of the magnetization transfer technique may increase the specificity of MR imaging in assessing the extent of residual myelination in multiple sclerosis lesions.

Index terms: Sclerosis, multiple; Magnetic resonance, magnetization transfer; Magnetic resonance, contrast enhancement

AJNR Am J Neuroradiol 17:1041–1049, June 1996

Multiple sclerosis lesions are heterogeneous in nature. Pathologically, in acute lesions, the inflammatory component predominates and there are variable degrees of demyelination (1), whereas in chronic lesions there is an absence of inflammation, usually with complete myelin loss and gliosis (2). All these changes are associated with increased water content, which leads to a similar appearance of high signal intensity on conventional long-repetition-time magnetic resonance (MR) imaging sequences (3).

Magnetization transfer is an MR imaging technique that is thought to be sensitive to the exchange of magnetization from immobile protons, bound in a macromolecular matrix, to free water protons. The magnetization transfer rate is thought to be related to several characteristics of the macromolecular matrix, including the concentration of the macromolecules as well as the surface chemistry and biophysical dynamics of the matrix (4). It is further thought that myelin-bound cholesterol has a surface structure that is ideal for cross relaxation (magnetization transfer) between water protons and cholesterol protons and thus is a prime determinant in magnetization transfer contrast. Accordingly, magnetization transfer imaging may be useful as an in vivo probe to the extent of myelination in the brain by providing a density map of the spatial distribution of myelin-bound cholesterol (5). Although relatively little work has been done in analyzing the composition of multiple

Received October 20, 1995; accepted after revision January 5, 1996.

Funded in part by grant R01 NS29029–0lA1 from the National Institutes of Neurological Disorders and Stroke, National Institutes of Health.

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AJNR 17:1041–1049, Jun 1996 0195-6108/96/1706–1041

sclerosis lesions with magnetization transfer imaging, it has been suggested that it may be possible to differentiate the components of multiple sclerosis lesions (edema versus demyelination) on this basis (6).

It has been shown from pathologic correlation studies that there is a correspondence between the pattern of contrast enhancement and the pattern of histologic changes in multiple sclerosis lesions, suggesting that enhancement indicates the presence of inflammation with some myelin loss and nonenhancement suggests scarring with almost complete loss of myelin (7, 8). Ring-enhancing lesions, which have a central nonenhancing portion and peripheral enhancing rim, reflect the presence of peripheral inflammation and complete central demyelination (8).

Relatively little work has been done in analyzing the composition of multiple sclerosis lesions with magnetization transfer imaging. A few previously published studies have looked at lesions using magnetization transfer ratios, an index of the magnetization transfer effect, and suggested that magnetization transfer ratios may be used as an index of demyelination (6, 9, 10). In this study, we compared the magnetization transfer ratios of homogeneously enhancing lesions, nonenhancing lesions, and the central, presumably completely demyelinated portion of ring-enhancing lesions to see whether we could detect a pattern of magnetization transfer ratios consistent with what is known about the histopathology, specifically the myelin content, of these lesions.

Materials and Methods

A total of 54 lesions were chosen from 29 patients in a multiple sclerosis cohort entered in a National Institutes of Health study in which patients were followed up with serial MR studies. All patients satisfied the Poser diagnostic criteria for multiple sclerosis (11). The selection criteria included lesions that were all well defined on long-repetition-time images and at least 5 mm in diameter. Lesions were considered to enhance if they showed significant hyperintensity relative to the surrounding white matter on post-contrast T1-weighted MR images. Studies of the brain were performed on a 1.5-T magnet using a quadrature head coil. The following pulse sequences were used: sagittal spin-echo images (600/11/1 [repetition time/echo time/excitations], 5-mm-thick sections at 2.5-mm intervals, 256 × 192 matrix, and 22-cm field of view); axial fast spin-echo images (2500/18,90/1, 3-mm-thick contiguous sections, 256 × 192 matrix, 22-cm field of view, echo train length of 8, and echo spacing of 18); axial magnetization transfer images (described below); and unenhanced and contrast-enhanced spin-echo images (600/27/1, 3-mm-thick contiguous sections, 256 × 192 matrix, and 22-cm field of view). Gadopentetate dimeglumine was given at a dose of 0.1 mmol/kg body weight up to a maximum dose of 20 mL.

Magnetization transfer images were obtained by using a modification of a gradient-echo pulse sequence described by Schnall et al (M.C. Schnall, L. Dougherty, E. Outwater, "Technique for Magnetization Transfer Imaging at 1.5 T using Steady State Pulsed Saturation," *Book of Abstracts*, Society of Magnetic Resonance in Medicine, 1991). Contiguous axial 5-mm-thick images were acquired with a three-dimensional gradient recalled acquisition in a steady state (GRASS) pulse sequence at 100/5/1 with a 12° flip angle and a 256 × 128 matrix. The pulse sequence was designed to minimize T1-weighted and T2-weighted contrast. A control image was acquired before the magnetization transfer saturation pulses were applied, yielding a proton density–weighted image. The magnetization transfer–weighted images were obtained by the application of a pulsed off-resonance saturation with a single 19-millisecond sinc-shaped radio frequency pulse during the interpulse delay period every repetition time. The frequency offset of the pulses was 2 kHz off-peak water resonance with the average B_1 intensity 3.67×10^{-6} T. The magnetization transfer effect for a lesion was measured over a region of interest (ROI) (defined below) using these two sets of images by calculating a magnetization transfer ratio (MTR) defined as:

$$\mathrm{MTR} = \frac{M_o - M_s}{M_o} \times 100\%$$

where M_o represents the average pixel intensity in a region with the saturation pulse off and M_s represents the corresponding signal intensity with the saturation pulse on. Thus, the magnetization transfer ratio can be thought of as the percentage drop in signal intensity from the saturation effects of the off-resonance pulse.

The lesions were divided into three groups: nonenhancing lesions, homogeneously enhancing lesions, and ring-enhancing lesions on the basis of their enhancement configuration on contrast-enhanced T1-weighted images. Average pixel intensity values were then obtained from ROIs drawn around the corresponding lesions on the magnetization transfer images. ROIs were placed around the entire lesion in the case of the nonenhancing lesions and homogeneously enhancing lesions (Figs 1 and 2), but only around the central, nonenhancing portion of the ring-enhancing lesions (Fig 3). Mean magnetization transfer ratios for lesions in all three categories were calculated.

Comparison of the categories was done using a nonparametric analysis (rather than a parametric one) for two reasons: first, the number of patients in the various groups was relatively small, and second, a nonparametric analysis is relatively insensitive to outliers (extremely large or small values) (12).

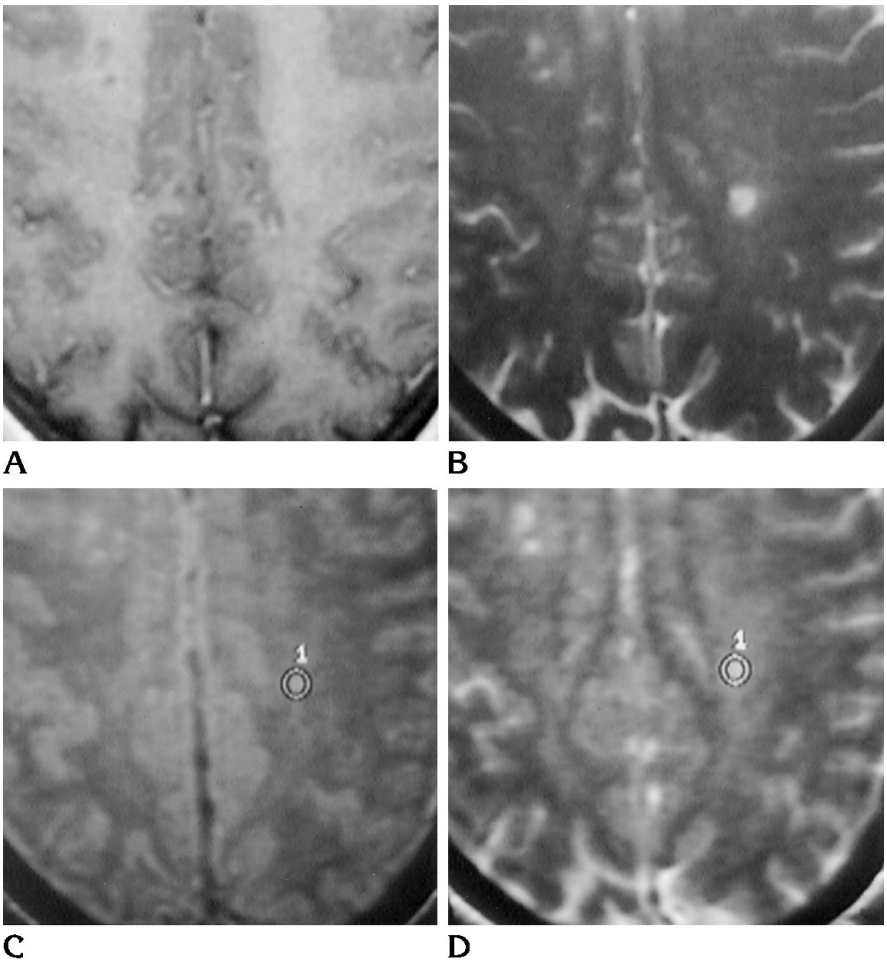

Fig 1. *A*, Example of a nonenhancing lesion on contrast-enhanced T1-weighted MR image.

B, The same lesion as seen on a T2-weighted image.

C and *D*, Placement of the ROI is around the entire corresponding lesion area on the presaturation and postsaturation magnetization transfer images.

All patients had lesions in either one or two categories, and none had lesions from all three categories. To address this issue of repeated measures, a combination of two analyses for each of the three category comparisons (homogeneously enhancing lesions versus nonenhancing lesions, homogeneously enhancing lesions versus ring-enhancing lesions, nonenhancing lesions versus ring-enhancing lesions) was used to maintain the statistical assumption of independence of each measurement. It was crucial to assume here that the presence or absence of one type of lesion in a patient had no effect on the magnetization transfer ratio of another type of lesion in that same person. A between-category correlation analysis was performed on the paired patient data (ie, patients who had lesions in both categories) to make sure no such effect could be found for any of the three comparisons. If a patient had more than one lesion in the same category, the average magnetization transfer ratio was obtained and reported as a single independent measurement to maintain strict statistical independence of measurements, an underlying assumption of the analysis.

For each comparison there were a number of patients (N) who had lesions in both categories (paired) and there were others in whom only one of the two categories was present (unpaired, m for one category and n for the other). A Wilcoxon's signed rank test was performed on the paired data and a Wilcoxon's rank sum test on the unpaired data. A weighted z value of the two tests was then obtained for the comparison and was defined as:

$$z = (a/c)z_p + (b/c)z_u,$$

where z_p was the standard normal statistic for the paired (Wilcoxon's signed rank) test and z_u was the standard normal statistic for the unpaired (Wilcoxon's rank sum) test. The ratios a/c and b/c were weights, where a = 2N/(2N + m + n), or the proportion of paired measurements, and b = (m + n)/(2N + m + n), or the proportion of unpaired measurements in the comparison. The proportions were normalized by a factor c, where $c = \sqrt{(a^2+b2)}$, to obtain the weights. Thus the new *z* value also had a variance of 1 and a mean of 0 under the null hypothesis, and could be compared, therefore, with the standard normal table.

For the small samples, the exact *P* values for the test were obtained first and then adjusted to the corresponding *z* values on the standard normal curve. Since all three pairs of lesions (homogeneously enhancing lesions versus non-

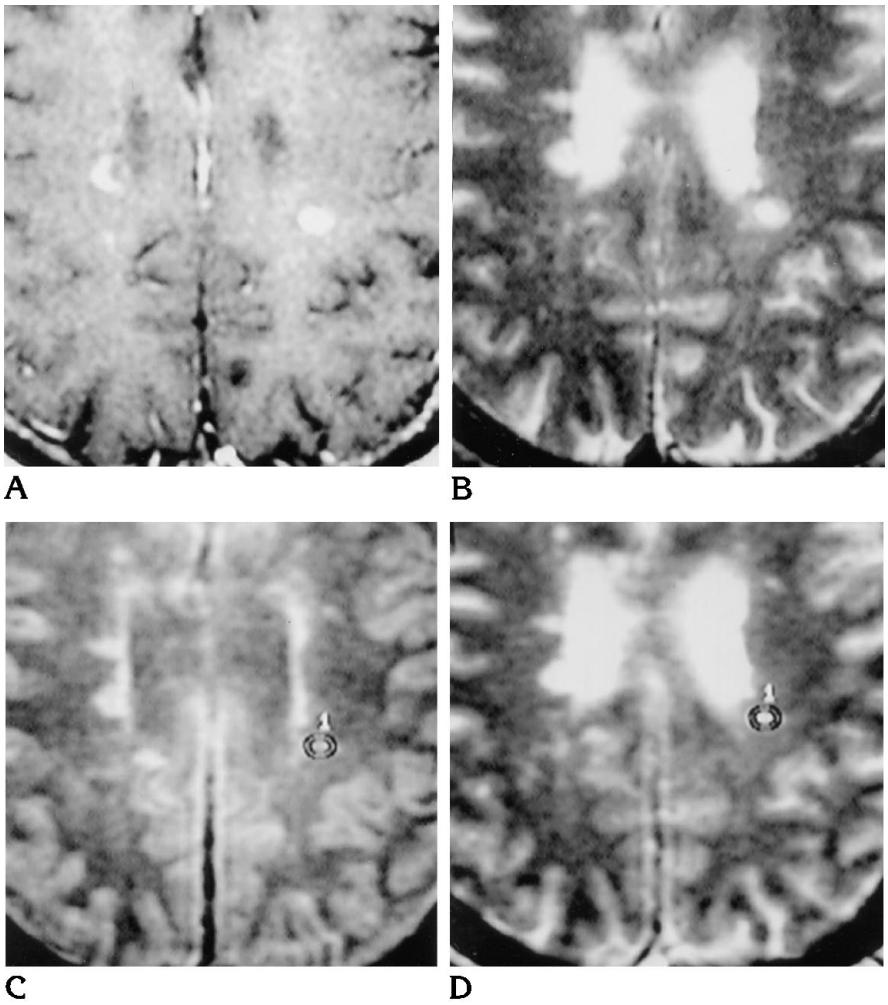

Fig 2. *A*, Example of a homogeneously enhancing lesion on a contrast-enhanced T1-weighted MR image.

B, The same lesion as seen on a T2-weighted image.

C and *D*, Placement of the ROI is around the entire corresponding lesion area on the presaturation and postsaturation magnetization transfer images.

enhancing lesions, homogeneously enhancing lesions versus ring-enhancing lesions, nonenhancing lesions versus ring-enhancing lesions) were compared, a Bonferroni adjustment (multiplicative factor of three) was incorporated in all reported *P* values.

Results

Among the 54 lesions chosen, we obtained a total of 42 independent measurements after averaging repeated measurements for lesions in the same patient and in the same category. The mean magnetization transfer ratios are shown in Table 1. There was evidence of a significant difference in the mean magnetization transfer ratio between the homogeneously enhancing lesions and the central portion of the ring-enhancing lesions ($P < .001$) as well as between the nonenhancing lesions and the central portion of the ring-enhancing lesions ($P < .05$). No significant difference was found between the mean magnetization transfer ratios of the homogeneously enhancing lesions and the nonenhancing lesions (Table 2). The largest range and standard deviation of magnetization transfer ratios were obtained in the nonenhancing lesions category. The range and standard deviation of magnetization transfer ratios for the homogeneously enhancing lesions and the ring-enhancing lesions were about equal (Fig 4).

No significant correlations were found in the paired data between categories for any of the three comparisons. Thus, the assumption that the presence of one type of lesion in a patient had no effect on the magnetization transfer ratio of a different type of lesion in that same patient appeared valid.

Discussion

It has been shown from pathologic correlation studies that there is a correspondence between

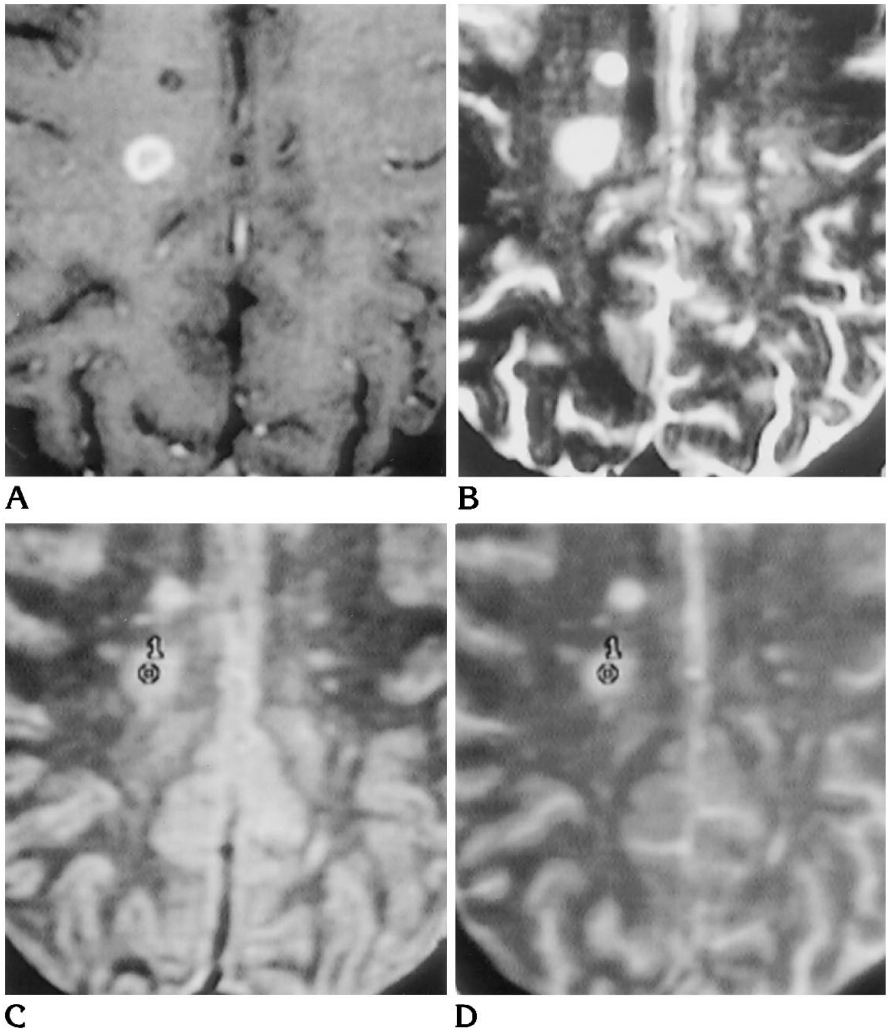

Fig 3. *A*, Example of a ring-enhancing lesion on a contrast-enhanced T1-weighted MR image.

B, The same lesion as seen on a T2-weighted image.

C and *D*, Placement of the ROI is only in the portion of the lesion on the presaturation and postsaturation magnetization transfer images that corresponds to the nonenhancing area on the contrast-enhanced T1-weighted image.

the pattern of enhancement and the pattern of histologic changes in multiple sclerosis lesions, suggesting that enhancement indicates the presence of inflammation. Enhancement in multiple sclerosis lesions is caused by disruption of the blood-brain barrier with extravasation of contrast material into the edematous central nervous system parenchyma (13, 14). Microscopically, enhancing areas show intense perivascular inflammation with some demyelination and myelin breakdown products, whereas nonenhancing areas show minimal inflammation with a fibrous astroglial response and nearly complete loss of myelin (7, 8).

TABLE 1: Summary of data from all independent measurements

Lesion Type	n	Mean Magnetization Transfer Ratio, %	Range (%)	SD, %
Homogeneously enhancing	14	32.2	28.5–41.0 (12.5)	3.4
Nonenhancing	19	29.4	19.5–35.8 (16.3)	4.3
Ring-enhancing (center)	9	24.5	15.9–28.5 (12.6)	4.0

Magnetization transfer is a technique that is thought to be sensitive to the exchange of magnetization from immobile protons, bound in a macromolecular matrix, to free water protons. The technique involves applying a radio frequency pulse or pulse train designed to selectively saturate the broad resonance peak of the macromolecular bound protons (15). As the macromolecular pool approaches and reaches a stable condition of partial saturation, the saturation is transferred to the free pool, so that the free pool also reaches a stable condition of partial saturation, resulting in lower signal intensity. The higher the rate of magnetization transfer, the greater the degree of signal suppression in the tissue voxel, given all other factors influenc-

TABLE 2: Statistical comparison of the magnetization transfer ratios from three groups of lesions

Comparison	N	m	n	Paired Difference	W_s	z_p	Unpaired Difference	W_r	z_u	a	b	z	*P**
Homogeneously enhancing vs ring-enhancing	2	12	7	2.69	3	0.674	8.79	150	3.507	0.174	0.826	3.57	<.001
Nonenhancing vs ring-enhancing	3	16	6	5.92	6	1.150	4.10	214	2.175	0.214	0.786	2.40	<.05
Homogeneously enhancing vs nonenhancing	8	6	11	3.66	29	1.447	0.98	56	0.151	0.432	0.568	1.00	Not significant

Note.—N indicates number of patients with a lesion in both categories; m, number of patients with a lesion in first category only; n, number of patients with a lesion in second category only; paired difference, mean difference in magnetization transfer ratios for paired patients; W_s, value of Wilcoxon's signed rank test; z_p, standard normal value for the paired (Wilcoxon's signed rank) test; unpaired difference, mean difference in magnetization transfer ratios for unpaired patients; W_r, value of Wilcoxon's rank sum test; z_u, standard normal value for the unpaired (Wilcoxon's rank sum) test; a and b, proportion factors, defined in text; z, weighted combination of z_p and z_u, defined in text.

* *P* denotes significance of difference in magnetization transfer ratios.

ing signal intensity are equal. The magnetization transfer rate is thought to be related to several characteristics of the macromolecular matrix in the tissue voxel being imaged, including the concentration of the macromolecules as well as the surface chemistry and biophysical dynamics of the matrix. All these factors will, of course, vary among tissues and are thought to be the basis for magnetization transfer contrast (4). It is thought that myelin-bound cholesterol has a surface structure that is ideal for cross relaxation (magnetization transfer) between water protons and cholesterol protons and thus is a prime determinant in magnetization transfer contrast. By providing a density map of the spatial distribution of myelin-bound cholesterol, magnetization transfer imaging may be an in vivo probe to the extent of myelination in the brain (5).

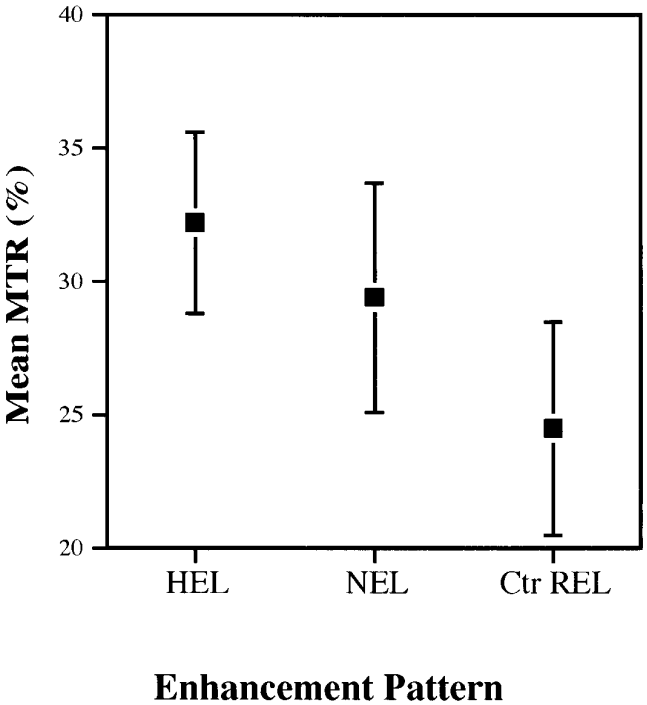

Fig 4. Scatter plot shows the mean magnetization transfer ratios (*MTR*) measured in ROIs drawn over homogeneously enhancing lesions (*HEL*), nonenhancing lesions (*NEL*), and at the center of ring-enhancing lesions (*Ctr REL*). Error bars denote the standard deviation of each mean.

Although relatively little work has been done in analyzing the composition of multiple sclerosis lesions with magnetization transfer imaging, magnetization transfer ratios have been published in the literature. Dousset et al (6) suggested that it may be possible to differentiate the components of multiple sclerosis lesions (edema versus demyelination) by using magnetization transfer ratios. Applying magnetization transfer techniques to an experimental model of multiple sclerosis in guinea pigs and to humans, these researchers showed that magnetization transfer ratios were highly reproducible in the normal-appearing white matter of both pigs and healthy human subjects. Magnetization transfer ratios of the experimentally induced lesions in pigs were slightly but significantly decreased relative to those of normal white matter. Pathologically, these lesions showed inflammatory changes without any evidence of demyelination. They also calculated magnetization transfer ratios in more than 200 lesions in humans and showed that the ratios were markedly decreased relative to normal white matter, although there was a wide range of values, pos-

sibly indicating lesions of different age and degrees of demyelination. In one lesion, the central portion had a very low magnetization transfer ratio, whereas the periphery of the lesion showed a much higher transfer ratio. The authors postulated that these values reflected substantial myelin loss at the center of the lesion with less denaturation of the myelin structures at the periphery, perhaps the active region of the disease. Thus, it was hypothesized that magnetization transfer techniques could enable characterization of multiple sclerosis lesions according to their myelin content, that is, subcategorize lesions into demyelinated lesions (very low magnetization transfer ratio compared with normal white matter) and edematous lesions (only slightly decreased magnetization transfer ratio compared with normal white matter).

In another study, Tomiak et al (9) measured the magnetization transfer ratios of multiple sclerosis lesions and looked for a difference in mean magnetization transfer ratios based on the age of the lesion. The authors divided lesions found on long-repetition-time sequences into two age categories, less than 1 year and more than 1 year, based on an analysis of previous examinations. They found a statistical difference in the magnetization transfer ratios of the lesions between the two groups, with the more recent lesions having a lower magnetization transfer ratio than the older lesions. In this work, the enhancement characteristics of lesions were not studied, and the age category of a lesion was determined by the time between the initial appearance of the lesion on T2-weighted images and the most recent prior examination when the lesion was not seen. The authors attributed the higher magnetization transfer ratios in older lesions (25% to 41%) to gliosis, whereas the lower magnetization transfer ratios in recent lesions (5% to 26%) were attributed to edema and demyelination, but they did not say why such pathologic substrates would cause the corresponding changes in magnetization transfer ratios.

The magnetization transfer effect is dependent on field strength and pulse sequence; therefore, the magnetization transfer ratio should not be considered an absolute number and the magnetization transfer ratios from different studies cannot be compared if the techniques are different. The study by Tomiak et al was performed at a very low field strength, using a 0.1-T system with different acquisition parameters (spin echo 1700/30/1) and a different saturation pulse (300 milliseconds, 7.2 kHz offset, amplitude 3.5×10^{-7} T) than the current study, preventing comparison of absolute magnetization transfer ratios.

Hiehle et al (10) measured the magnetization transfer ratios of enhancing lesions, nonenhancing lesions, and ring-enhancing lesions and were unable to demonstrate a statistically significant difference among the groups. On analyzing a single ring-enhancing lesion, the authors found that the magnetization transfer ratio increased as one moved from the center to the periphery. Confirming similar findings by Dousset et al (6), the authors speculated that demyelination in multiple sclerosis lesions occurs centrifugally (10), leaving the central portion of the lesion the most demyelinated.

Our results show that the average magnetization transfer ratios of the homogeneously enhancing lesions and the nonenhancing lesions differed significantly from that of the central portion of the ring-enhancing lesions. The lack of a significant difference in mean magnetization transfer ratios between the nonenhancing lesions and the homogeneously enhancing lesions in both this study and that of Hiehle et al may be attributable to the wide variability in the macromolecular composition of nonenhancing lesions as well as the small number of lesions in the homogeneously enhancing lesions category (14 in this study compared with 10 in the study by Hiehle et al [10]). Perhaps the reason a difference was found between the ring-enhancing lesions and the other two lesion groups in this study and not in the study by Hiehle et al has to do with the placement of the ROI in the present study; that is, we included only the central, nonenhancing portion of the ring-enhancing lesions, presumably a uniform pathologic substrate where maximum demyelination has occurred. In the study by Hiehle et al, the incompletely demyelinated enhancing periphery of the lesion was most likely included in the ROI, possibly altering the magnetization transfer ratio.

Given what we know about the histopathology of different patterns of enhancement in multiple sclerosis lesions and what we know about the magnetization transfer process, our study supports the fact that magnetization transfer ratios may reflect differences in the chemical composition of the lesions or portions of lesions. The homogeneously enhancing le-

sions, in which there is evidence of breakdown of the blood-brain barrier and active inflammation, had the highest magnetization transfer ratio of the three groups. This could be the result of a greater degree of myelin preservation in these lesions. Conversely, the central portion of the ring-enhancing lesions had the lowest average magnetization transfer ratio, possibly reflecting the area of a lesion where the greatest degree of myelin loss has taken place. Nonenhancing lesions had an average magnetization transfer ratio that lay in between these two extremes and not significantly different from that of the homogeneously enhancing lesions. The standard deviation and range of magnetization transfer ratios were broadest among the nonenhancing lesions, which may be the result of greater variability in this group's tissue composition, reflecting different degrees of residual myelination.

The exact pathophysiologic evolution of multiple sclerosis lesions is still unknown, however. Experience with serial contrast-enhanced and T2-weighted imaging studies at short intervals has shown that new lesions enhance initially and may also become reactivated, reenhancing some time later in their evolution (16). The exact relationship between enhancement pattern (homogeneously enhancing lesions versus ring-enhancing lesions versus nonenhancing lesions) and lesion evolution needs further evaluation. Our results, combined with those of previous studies, may give clues to the nature of this relationship. On the basis of magnetization transfer ratio measurements, there is evidence to suggest that demyelination occurs centrifugally (from the center outward) (6, 10). We speculate that homogeneously enhancing lesions are early inflammatory lesions, with the greatest degree of myelin preservation. As the inflammatory component resolves and demyelination occurs from inside to outside, a homogeneously enhancing lesion may evolve into a ring-enhancing lesion or a nonenhancing lesion. Subsequently, as the peripheral enhancing portion of a ring-enhancing lesion deactivates or becomes demyelinated, the lesion may become a nonenhancing lesion. If a previously nonenhancing lesion, with residual T2-weighted abnormality, is reactivated, it is more likely to demonstrate peripheral enhancement, becoming a ring-enhancing lesion rather than a homogeneously enhancing lesion, since the central portion is more likely to be demyelinated and devascularized than is the periphery. If a nonenhancing lesion has lost enough myelination, the entire lesion will remain burned out and never go back to an enhancing pattern (Fig 5). Our magnetization transfer ratio measurements are consistent with this evolution of enhancement. This may explain the large variability in magnetization transfer ratios that we found for nonenhancing lesions (ie, wide range of residual myelination), hence the lack of a statistically significant difference from the homogeneously enhancing lesions category.

A potential source of error in measuring magnetization transfer ratios may be in placement of the ROIs on the magnetization transfer images so that they correspond exactly to the lesions and areas of enhancement seen on the contrast-enhanced T1-weighted images. Although this was done as accurately as possible by careful visual comparison of the lesions on the two pulse sequences, the development of more sophisticated image registration techniques to ensure accurate placement of the ROI might improve the significance of our results. In addition, the use of smaller sections (3 mm) for the magnetization transfer images may also improve the accuracy of the measurements by reducing volume averaging, although this is limited by the specific absorption rate to the patient.

Different-sized rather than same-sized ROIs were used to evaluate lesions in the current study. This may introduce variability in the standard deviation of the individual measurements but it does not affect our conclusions. The standard deviation of an ROI measurement is influenced by the number of pixels in the ROI, given homogeneous signal throughout the region. Larger ROIs should have a smaller standard deviation because statistical noise is reduced. We used the largest ROIs possible, around the border of a homogeneously enhancing lesion, a nonenhancing lesion, or the nonenhancing portion of a ring-enhancing lesion while still attempting to maintain homogeneous signal within the ROI. This was done to minimize the standard deviation in the ROI. If, on average, the ROI size of the three groups was not the same, there would be a slightly larger standard deviation for the group with the smaller ROIs, in our case the ring-enhancing lesions. Despite this possible greater variability in the ring-enhancing lesions group mean, we were still able to show a significant difference between the magnetization transfer ratios of the ring-enhancing lesions and the two other groups; thus, our conclusions are not affected.

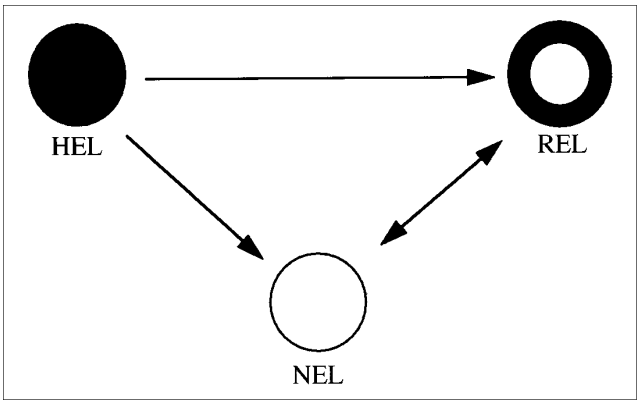

Fig 5. Speculation on the evolution of the enhancement pattern in multiple sclerosis lesions. Homogeneously enhancing lesions (*HEL*), the early inflammatory lesions, evolve into ring-enhancing lesions (*REL*) or nonenhancing lesions (*NEL*). As the peripheral portion of a ring-enhancing lesion deactivates, the lesion can become a nonenhancing lesion. Once a nonenhancing lesion, it may become reactivated to a ring-enhancing lesion, but usually not a homogeneously enhancing lesion, since the central portion is most likely demyelinated and devascularized. Eventually, the entire nonenhancing lesion may remain burned out, and not go back to an enhancing pattern.

The causes of the magnetization transfer effect are quite complex, and although magnetization transfer imaging holds promise in providing specific biochemical and biophysical information, it is still unclear exactly what biochemical properties of brain tissue affect the magnetization transfer rate and thus influence magnetization transfer ratios. Our study shows that there is a relationship between magnetization transfer ratios and the enhancement pattern of lesions; and we know the latter has been correlated with the histopathology of the lesions (7, 8). The relationship between the degree of demyelination in brain tissue and the magnetization transfer effect is not precisely known and awaits the development of a good animal model simulating the demyelination component of multiple sclerosis. In addition, the relationship between lesion age and enhancement pattern and lesion age and histopathologic changes is not precisely known and needs to be worked out with further studies. Our in vivo measurements of the magnetization transfer ratios of multiple sclerosis lesions combined with what we know about the histopathology of enhancement patterns does, however, suggest that we may be able to use the magnetization transfer ratio information in the development of an index of demyelination in multiple sclerosis lesions. This may be important in the future, as it may enable the use of MR imaging to track the histopathologic evolution of multiple sclerosis lesions over time to understand better the pathophysiology of this disease.

Acknowledgments

We thank Joseph Frank and Craig Bash of the Laboratory of Diagnostic Radiology Research, National Institutes of Health, for valuable discussion.

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