Characterization of Multiple Sclerosis Plaques with T1-Weighted MR and Quantitative Magnetization Transfer

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PURPOSE: To investigate the relationship between the appearance of multiple sclerosis lesions identified on unenhanced T1-weighted images and their corresponding magnetization transfer ratios. **METHODS:** A total of 119 white matter lesions seen on T2-weighted images in 17 patients with multiple sclerosis were evaluated. Axial T1-weighted images were used to classify the lesions as isointense to white matter (10 lesions), hypointense to white matter but hyperintense to gray matter (44 lesions), hypointense to gray matter (59 lesions), and relatively isointense to cerebrospinal fluid (6 lesions). The magnetization transfer ratio of each lesion was calculated, and an average magnetization transfer ratio for each subcategory was determined. **RESULTS:** The magnetization transfer ratio values became progressively lower with increasing hypointensity of lesions on T1-weighted images. The average magnetization transfer ratio for lesions isointense to white matter, hypointense to white matter but hyperintense to gray matter, hypointense to gray matter, and relatively isointense to cerebrospinal fluid was 34.90 ± 2.67 (mean ± SD), 30.93 ± 3.57, 27.27 ± 3.56, and 23.62 ± 2.83, respectively. All groups were significantly different from each other. **CONCLUSION:** Lesions isointense to white matter exhibited higher magnetization transfer ratio values than lesions that were hypointense. These findings are consistent with relative preservation of the myelin structure in the former, perhaps indicating that these lesions are predominantly inflammatory (edematous) in nature. The proportionately lower magnetization transfer ratio values of lesions that appear progressively more hypointense on T1-weighted images may reflect varying degrees of demyelination, with increasing lesion hypointensity corresponding to more breakdown in the macromolecular structure. These results suggest that T1-weighted images may be useful in characterizing the underlying pathologic substrate in multiple sclerosis plaques.

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

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Magnetic resonance (MR) imaging is a very sensitive technique for detecting focal lesions in patients with multiple sclerosis. Serial MR examinations are helpful in distinguishing acute from chronic lesions, and lesion enhancement after administration of gadolinium may show transient blood-brain barrier abnormalities (1). Enhancing lesions may resolve or may progress to chronic plaques, and older lesions may be reactivated, as evidenced by recurrent enhancement (1). However, MR is not specific in showing disease stage and does not distinguish between edema, demyelination, and gliosis within tissue (1–3).

Classification of multiple sclerosis lesions could potentially serve as a rationale for therapeutic interventions. Identification of lesions with myelin loss may be important, because they may be less responsive to treatment than edematous and inflammatory lesions. Several investigators have noted a wide range of elevated T1 and T2 relaxation times in multiple sclerosis lesions and have speculated that the spectrum of values may denote histologic differences among lesions (4–7).

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Magnetization transfer imaging is a relatively new technique that may generate contrast that reflects structural variation within tissue. Magnetization transfer is observed through the application of off-resonance radio-frequency irradiation designed to saturate preferentially immobile protons of macromolecules, which subsequently exchange with mobile protons in the aqueous phase (8, 9). Exchange of the saturated proton spins into the pool of aqueous spins tends to decrease the observed signal intensity on the subsequent MR image when compared with the reference image obtained without saturation. This effect may be quantitated by determining the magnetization transfer ratio.

Dousset et al (10) measured the magnetization transfer ratio (expressed as percentages) of white and gray matter in healthy volunteers and found average values (mean ± SD) of 41.8 ± 1.3 and 38.9 ± 1.7, respectively. Cerebrospinal fluid (CSF) had an average magnetization transfer ratio of approximately 2%. In patients with multiple sclerosis, these investigators found a wide range of reduced magnetization transfer ratios in focal white matter lesions identified on T2-weighted images, with small to marked decreases, and speculated that these reflected edematous lesions without significant myelin loss and demyelination, respectively (10). In experimental allergic encephalomyelitis in guinea pigs, they found small decreases in the magnetization transfer ratios of lesions that histologically had edema but no demyelination (10). These authors found the decrease in the magnetization transfer ratio in edematous lesions without demyelination to be less than the decrease in the magnetization transfer ratio in those lesions suspected of being demyelinated. Although hyperintensity is seen with both types of lesions on T2-weighted images, T2-weighted images are unable to differentiate them.

Prior investigators have suggested that lesions that are hypointense on T1-weighted images represent older plaques with more demyelination and gliosis compared with lesions that show minimal or no hypointensity (11, 12). The purpose of this study is to investigate the relationship between the appearance of white matter lesions on unenhanced T1-weighted images and their corresponding magnetization transfer ratios. The particular intensity of lesions on T1-weighted images may provide additional information regarding their pathologic substrate.

Materials and Methods

A total of 119 circumscribed white matter lesions (high signal abnormalities on T2-weighted images) were studied in 17 patients with multiple sclerosis (4 chronic progressive and 13 relapsing remitting). To avoid artifacts related to volume averaging, lesions were selected for evaluation only if they were well defined and measured at least 5 mm. The patients (11 women and 6 men) ranged in age from 24 to 48 years (mean, 34.2 years). All studies were performed with a 1.5-T scanner using a quadrature head coil. Each patient's head was secured between sponge wedges and taped to prevent motion both during and between the acquisition of images. Patients were evaluated with conventional spin-echo sequences, which included unenhanced 5-mm-thick sagittal T1-weighted images (600/11/1 [repetition time/echo time/excitations]), contiguous 3-mm-thick axial T1-weighted images (600/11–17/1), and 3-mm-thick interleaved axial T2-weighted fast spin-echo images (2500/18,90/1). Other imaging parameters included a 22-cm field of view and a 256 × 192 matrix.

Unenhanced magnetization transfer imaging in the axial plane was performed with a modified three-dimensional gradient-recalled acquisition in the steady state (General Electric Medical Systems, Milwaukee, Wis). The pulse sequence was chosen to minimize both T1 and T2 weighting (106/5/1, 12° flip angle) with 5-mm-thick sections and a 256 × 128 matrix. Magnetization transfer contrast was achieved by the application of 19-millisecond sinc-shaped saturation pulses with an average amplitude (B1 intensity) of 3.7×10^{-6} T at a frequency 2 kHz less than water resonance. The interval between the end of the saturation pulses and the beginning of each excitation was approximately 1 millisecond. Corresponding reference images were obtained using identical acquisition parameters but no saturation pulses.

Image analysis consisted of identifying focal, well-defined plaques on T2-weighted images (all lesions measured 5 to 15 mm). These lesions were then evaluated on the corresponding unenhanced axial T1-weighted images and divided into categories based on increasing hypointensity relative to brain tissue. Plaques were subcategorized as isointense to white matter (10 lesions), hypointense to white matter but hyperintense to gray matter (44 lesions), hypointense to gray matter (59 lesions), and approaching the intensity of CSF (6 lesions) (Fig 1). T1-weighted intensity values in the center of each lesion were obtained from the axial images using a 0.04-cm^2 round cursor. We obtained normalized T1 intensity data by dividing the lesion T1-weighted intensity value by the average ventricular CSF intensity value in the same patient. On magnetization transfer images, a region of interest also using a 0.04-cm^2 round cursor (eight pixels were encompassed in this region of interest) was positioned at the same axial level (to within 1 mm) as the apparent center of each plaque identified on T1-weighted images. This was because the section thickness on the T1-weighted images was 3 mm compared with 5 mm on the magnetization transfer images, and it was not always possible to get the

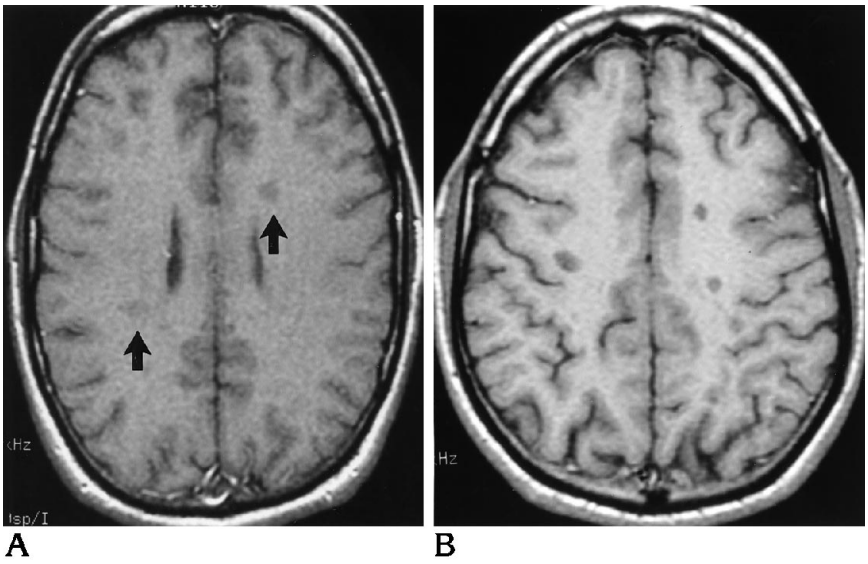

Fig 1. Examples of white matter lesions on T1-weighted images in two patients with multiple sclerosis.

A, Lesions hypointense to white matter are noted in the corona radiata (*arrows*) in this 29-year-old man.

B, Multiple lesions hypointense to gray matter in the centrum semiovale in a 27-year-old man.

exact axial level; however, the same axial level to within 1 mm was achievable for all measurements. The average intensity in the region of interest was measured in the same location on images with the saturation pulses on and off. The magnetization transfer ratio defined as (Mo − Ms)/Mo, where Mo is the average intensity of pixels within a region of interest on an image without saturation, and Ms is the average intensity of pixels corresponding to the same region of interest on an image with saturation, was determined for each lesion. The calculated magnetization transfer ratio was then multiplied by 100 to yield a percentage (Fig 2). An average magnetization transfer ratio for each subcategory of lesions identified on T1-weighted images was then determined. The relationships between (*a*) lesion appearance on T1-weighted images and magnetization transfer ratio and (*b*) normalized lesion T1 intensity values and magnetization transfer ratio were examined. All lesion characterizations and calculations were performed by the same radiologist (L.A.L.).

Statistical analysis of the data was performed. Comparison of the magnetization transfer ratio data among the four groups of white matter lesions subcategorized by their

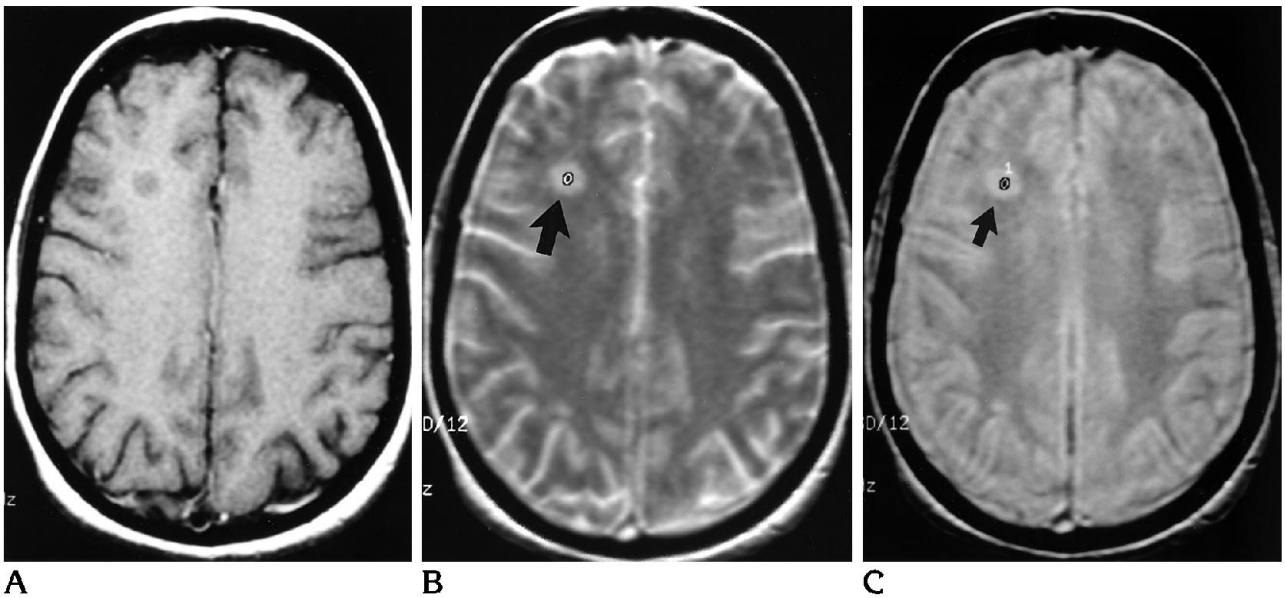

Fig 2. Demonstration of region of interest intensity measurement in a white matter lesion.

A, Axial T1-weighted images shows a lesion in the right frontal white matter.

B and *C*, On magnetization transfer images, a region of interest (*cursors*) was positioned in the apparent center of the plaque. The intensity value was measured in the exact same location on images with the saturation pulses on (Ms) and off (Mo) (*B* and *C*, respectively). The magnetization transfer ratio, defined as (Mo − Ms)/Mo, was determined.

T1 weighting and magnetization transfer ratio data for lesions

Lesion Category on T1 Weighting	Number of Lesions	Average Magnetization Transfer Ratio ± SD
Isointense to white matter	10	34.90 ± 2.67
Hypointense to white matter but hyperintense to gray matter	44	30.93 ± 3.57
Hypointense to gray matter	59	27.27 ± 3.56
Approaching intensity of CSF	6	23.62 ± 2.83

appearance on T1-weighted images was performed using a one-way analysis of variance and an unpaired *t* test with Bonferroni's correction. A *P* value of less than .05 was considered a significant difference.

Results

All patients had focal, circumscribed lesions. The number of plaques per patient ranged from 2 to 16. There was a strong correlation between lesion hypointensity on T1-weighted images and magnetization transfer ratio values. Specifically, the magnetization transfer ratio values were progressively lower with increasing lesion hypointensity on T1-weighted images. The average magnetization transfer ratio for lesions isointense to white matter, hypointense to white matter but hyperintense to gray matter, hypointense to gray matter, and relatively isointense to CSF were 34.90 ± 2.67 (mean ± SD), 30.93 ± 3.57, 27.27 ± 3.56, and 23.62 ± 2.83, respectively. The recorded SDs were calculated on the range of average magnetization transfer ratios that were obtained for each subcategory of plaques. The mean SD for the signal intensity measurements of all the individual region of interests within the plaques was 2.8 (range, 0.4 to 5.3; median, 2.6). All groups were compared with each other by statistical analysis and found to be significantly different from each other with $P < .01$ in all comparisons. These results are summarized in the Table.

Comparison of normalized lesion T1 intensity values with their corresponding magnetization transfer ratios showed a good correlation, with lower signal intensity on the T1-weighted images having proportionately lower magnetization transfer ratios. To reduce the effects of volume averaging, only lesions larger than 6 mm were evaluated by a scatter plot, which demonstrated a regression correlation coefficient of .62 (Fig 3).

Discussion

To evaluate the efficacy of various treatment protocols in patients with multiple sclerosis, a sensitive indicator of disease burden is necessary. Clinical symptoms depend not only on physiologic activity, but also, perhaps more importantly, on lesion location (1, 13). Numerous lesions are usually identified on MR imaging, many of which are clinically silent. Studies have suggested that MR is a sensitive indicator of disease burden and activity (1, 14, 15). T2-weighted imaging is sensitive in identifying focal plaques in patients with multiple sclerosis; however, it does not distinguish histologic differences (edema, demyelination, and gliosis) among lesions, most of which are similar in appearance on T2-weighted images (1).

To evaluate long-term prognosis as well as to establish the subset of patients most likely to benefit from a particular therapeutic intervention, it would be useful to be able to subcategorize total disease burden into those lesions that

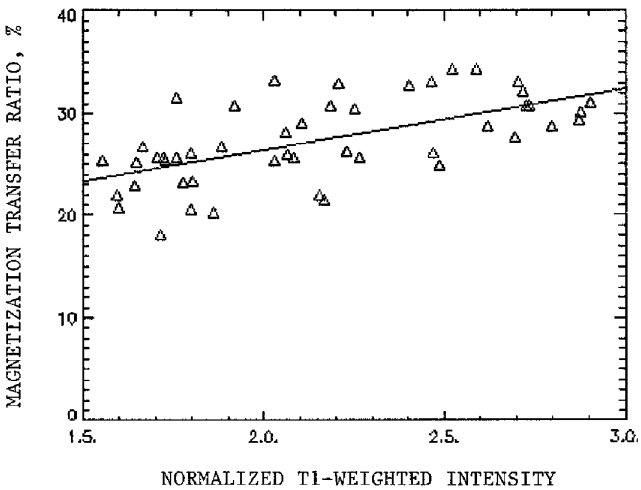

Fig 3. Scatter plot correlating lesion T1-weighted signal intensity values (normalized using the ratio lesion T1-weighted intensity value over mean CSF intensity value in the same patient) with magnetization transfer ratios in lesions larger than 6 mm. Regression analysis showed a correlation with a coefficient $r = .62$.

are edematous and inflammatory with relative preservation of myelin structure and those lesions in which there has been significant breakdown of myelin. Pathologic evaluation of multiple sclerosis plaques has established the heterogeneous nature of these lesions. Not only is there histologic variation from lesion to lesion within a patient, but individual lesions themselves are often complex, having central demyelination and gliosis with more peripheral edema (16). Therefore, imaging techniques that reflect structural variations within tissue would be useful in subcategorizing lesions based on their predominant underlying pathologic substrate.

Investigators have studied a variety of MR imaging techniques in an attempt to classify white matter plaques based on their underlying histology. Lacomis et al (7) demonstrated increased T1 relaxation times in lesions compared with normal-appearing white matter. Larsson et al (5, 6) found a range of prolonged T1 and T2 values in both stable and active multiple sclerosis lesions. Armspach et al (4) found a wide distribution of increased T2 relaxation values in lesions as well as changing T2 values within lesions over serial examinations, supporting the concept that multiple sclerosis is an evolving disease. Prolongation of T1 and T2 values have also been noted in lesions of unfixed postmortem brains (17). Increased relaxation times may be related to an increase in the free water–to–bound water ratio in abnormal tissue (18, 19). In multiple sclerosis, this may be secondary to a decrease in lipid bound water accompanying demyelination with an increase in extracellular free water that fills in areas of tissue loss (20, 21). Investigators have speculated that the spectrum of increased relaxation values reflects pathologic differences in tissue; however, they have not been able to assign specific values to particular histologies (4–6, 17).

Magnetization transfer imaging is a technique that may generate contrast based on the exchange of magnetization between bound protons and free water, thus reflecting structural variation within tissue (8, 9). In 1963, Forsen and Hoffman exploited the exchange of magnetization in a spectroscopy experiment to quantify chemical exchange rates (22). Although the exact physical mechanism of magnetization transfer contrast has not been completely delineated, a model that has been proposed incorporates two distinct pools of water protons within biological tissues: bound immobile protons associated with macromolecules (such as myelin and cell membranes) and mobile protons associated with bulk water. Magnetization transfer imaging is achieved through the application of off-resonance radio-frequency irradiation designed to saturate preferentially immobile protons of macromolecules, which subsequently cross-relax with mobile protons in bulk water through chemical exchange and/or dipole interactions (9, 23). The result is decreased signal intensity on the magnetization transfer image, which may be quantitated by the magnetization transfer ratio. The magnetization transfer ratio reflects structural variations in tissue. Low magnetization transfer ratios, corresponding to a decreased exchange between spin pools, are thus consistent with a breakdown in macromolecular structure.

Dousset et al (10) found mildly reduced magnetization transfer ratios (36.3% to 37.8%) in focal white matter lesions in guinea pigs with experimental allergic encephalomyelitis. On histologic evaluation these lesions were edematous without demyelination. In white matter lesions identified on T2-weighted images in patients with multiple sclerosis, these investigators found even lower magnetization transfer ratios with small to marked decreases and hypothesized that these reflected edematous lesions without significant myelin loss and demyelination, respectively (10). Gass et al (24) demonstrated lower average magnetization transfer ratio values in lesions identified on T2-weighted images in all subgroups of patients with multiple sclerosis (benign, progressive, and relapsing remitting) and found an inverse relationship between the lesion magnetization transfer ratio and disability (24). These authors suggested that reduced magnetization transfer ratios in multiple sclerosis lesions might correspond to varying degrees of demyelination and axonal loss, both of which are likely to result in functional disability. Tomiak et al (25) found that lesions identified on T2-weighted images of less than 1 year's duration had higher average magnetization transfer ratios than older plaques and suggested that the different values may reflect histologic changes over time (25).

In this study we have attempted to determine whether the appearance of lesions on T1-weighted images might be helpful in subcategorizing lesions based on myelin loss. Lesions on unenhanced T1-weighted images were subcat-

egorized as isointense to white matter but hyperintense to gray matter, hypointense to white matter, hypointense to gray matter, and approaching the intensity of CSF (Fig 1). We found that magnetization transfer ratios were progressively lower as lesion hypointensity increased. Using regression analysis, we found a correlation between observed lesion T1 intensity values and magnetization transfer ratios, consistent with the proposed multisite exchange model for magnetization transfer. In McConnell's two-site model (26), in which the time rate of change of the longitudinal magnetization of observable "a" spins is given by:

$$dM_{za}/dt = -(M_{za} - M_{oa}/T1) - M_{za}k_{for} + M_{zb}k_{rev},$$

the T1 on the right side of this equation is the intrinsic T1 of material "a." However, the observed T1 will reflect all processes that affect the return of magnetization to equilibrium, including exchange. If there is a net decrease in longitudinal magnetization recovery resulting from the exchange process, as might be the case if magnetization is held in saturation, the approach to equilibrium of the "a" magnetization will be less rapid. This will result in a longer observed T1, even though the intrinsic T1 is constant. The modulation of observed T1 is related to the pseudo–first-order exchange constant, k_{for}, and therefore to the magnetization transfer effect. Comparing magnetization transfer experiments with materials of different k_{for} magnitudes, the expectation is that magnetization transfer ratio will have a correlation with observed T1 values, consistent with our observations.

From our understanding of magnetization transfer imaging together with results from previous studies using magnetization transfer to evaluate multiple sclerosis, we speculate that lesions identified on T1-weighted images may represent varying degrees of demyelination, with the most hypointense lesions representing chronic, demyelinated plaques. We speculate that T1-weighted images may be better than T2-weighted images in indicating myelin loss. Little has been published on the appearance of lesions on T1-weighted images; however, other investigators also support the potential utility of T1-weighted images in evaluating patients with multiple sclerosis. Hiehle et al (11) showed lower magnetization transfer ratios for lesions hypointense to white matter on T1-weighted images when compared with lesions that were isointense. Shah et al (12) compared a T1-weighted gradient-echo technique and T2-weighted images in evaluating lesions in multiple sclerosis and found that the gradient-echo technique better identified lesions in the corpus collosum and pons. The improved contrast for lesion detection in these locations using the gradient-echo technique may be secondary to increased magnetization transfer effects.

Results recently obtained with MR spectroscopy also tend to support conclusions regarding a pathologic substrate obtained in the present study. Investigators have shown decreases both in *N*-acetyl aspartate as well as the *N*-acetyl aspartate–to–creatine ratio in chronic plaques (27–30). Spectra of active enhancing lesions have demonstrated increases in lactate, the choline-to-creatine ratio, and mobile lipid and cholesterol peaks (27, 28, 30, 31). Grossman et al (29) found an association between composite peaks at 2.1 to 2.6 ppm and lesion enhancement. Because these extra peaks are in a region in which γ-aminobutyric acid, glutamate, and other amino acids resonate, the authors suggested that these peaks might represent myelin byproducts. Recently, Hiehle et al (32) noted a linear, inverse correlation between decreased magnetization transfer ratio and increased spectral composite peaks at 2.1 to 2.6 ppm in multiple sclerosis plaques identified on T2-weighted images, supporting the contention that extra peaks and very low magnetization transfer ratios may be good markers of demyelination.

In conclusion, the higher average magnetization transfer ratio values of lesions only readily identified on T2-weighted images (on corresponding T1-weighted images the lesions were not readily apparent as they were isointense to white matter) is consistent with the relative preservation of the macromolecular structure, perhaps indicating that these lesions are predominantly edematous with little demyelination. The lower magnetization transfer ratio values of lesions conspicuous on T1-weighted images as evidenced by increasing hypointensity may reflect a breakdown of the macromolecular structure, representing demyelination. These results suggest that T1-weighted images may provide additional information useful for characterization of lesions in which myelin loss has occurred.

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