MR Proton Spectroscopy in Multiple Sclerosis

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PURPOSE: To elucidate the natural history of visualized MR abnormalities in patients with multiple sclerosis using proton spectroscopy. METHODS: MR imaging and proton spectroscopy (¹H spectroscopy) were performed on 16 patients with clinically definite multiple sclerosis. All patients received gadopentetate dimeglumine (Gd-DTPA). RESULTS: Decreased levels of N-acetylaspartate (NAA) were demonstrated in 17 out of 21 lesions. No correlation was found between decreased NAA and Gd-DTPA enhancement. In five out of seven enhancing lesions, abnormal ¹H spectra with extra peaks (termed marker peaks) at 2.1–2.6 ppm (ranging in absolute concentration from 10–50 mM protons) were observed. In nine out of 14 unenhancing lesions, no elevated marker peaks were observed. In the five other unenhancing lesions, the levels of these marker peaks were generally lower than the enhancing group. No correlation was found between the NAA levels and the levels of the marker peaks. We suggest two distinct biochemical processes: 1) decreased NAA reflecting neuronal cell loss, and 2) elevated marker peaks reflecting ongoing demyelination. CONCLUSIONS: Based upon these observations we infer that 1) the majority of enhancing lesions are demyelinating and represent a marker of this process, 2) enhancing lesions without this marker most likely represent edematous regions without significant demyelination, and 3) demyelination may be long in duration compared with transient blood-brain barrier disruption manifested by Gd-DTPA enhancement. Our results suggest that ¹H spectroscopy has the ability to further categorize MR-demonstrated enhancing and unenhancing lesions in patients with multiple sclerosis and that it may be more sensitive than contrast enhancement in revealing the true time course of demyelination.

Index terms: Sclerosis, multiple; Demyelinating disease; Magnetic resonance, spectroscopy


Magnetic resonance (MR) has made a significant impact with its sensitivity in detection of lesions in multiple sclerosis (MS) (1–4). Such lesions appear as high-intensity abnormalities on long TR images. Further insight into these lesions has been gained with the use of gadopentetate dimeglumine (Gd-DTPA) to subcategorize these lesions into those that enhance, ie, possess a transient abnormality in the blood-brain barrier and those that do not display enhancement, ie, in which the blood-brain barrier is intact (5). Thus, MR has the ability to both detect MS lesions and relate them according to their enhancement characteristics. A recent report has correlated histopathologically active lesions with contrast enhancement (6). From previous serial MR studies we have learned that MS lesions are dynamic; both active and inactive lesions may change over time (7). Such changes suggest that: 1) some lesions may be purely edematous with very little demyelination, and 2) some lesions may demyelinate and subsequently remyelinate (7). However, MR imaging lacks the capability for defining the precise biochemical nature of these lesions, and cannot easily separate edematous regions from those that are demyelinating or incompletely remyelinating. This information would be extremely useful in elucidating the natural history of visualized MR abnormalities, as well as perhaps serving as a rationale for proposed therapeutic interventions.
Localized proton (1H) spectroscopy provides a probe to study certain biochemical constituents of MS lesions (8, 9). This technique in combination with MR imaging and Gd-DTPA enhancement offers potential insights into MS that are not obtainable with either technique alone. Our report will focus on a cohort of patients with clinically definite MS who were studied with a combination of 1H spectroscopy and MR imaging with Gd-DTPA enhancement.

Subjects and Methods

Sixteen patients, five women and eleven men, aged 27 to 64, with clinically definite MS, were imaged in the axial plane on a GE 1.5 Sigma MR imager using 3000/30/90/1 (TR/TE/excitations) with a 256 x 192 matrix, section thickness = 5 mm with a 2.5-mm intersection gap. The study was approved by the Committee on Studies Involving Human Beings at the University of Pennsylvania and informed consent was obtained in all patients. In the 16 patients, 1H spectroscopy was performed on 21 hyperintense lesions presumed to be MS lesions. We generally chose lesions that were large enough to fill the spectral voxel. The patients were then asked to return in 48 hours for the 1H spectroscopic examination.

These patients received Gd-DTPA (0.1 mmole/kg) which was intravenously administered after the long TR images were performed, and imaging repeated using a T1-weighted pulse sequence either a spin echo (800/30/11) (13 patients) with a 256 x 192 matrix, 5-mm section, thickness with a 2.5-mm intersection gap) or a volumetric spoiled grass (34/14/1.5, flip angle = 45° with contiguous 1.5-mm sections) sequence (three patients). Lesions were assessed for enhancement on the T1-weighted sequences, as well as intensity on standard T2-weighted spin-echo sequences. In each patient, suitable T2 lesions were identified for spectroscopy.

Solvent-suppressed proton spectra were obtained using the stimulated echo acquisition mode (STEAM) sequence reported by Frahm et al. (9). In our particular implementation, solvent suppression was achieved by the application of three consecutive chemical shift-selective pulses (CHESS) (25-Hz bandwidth) centered on the water resonance each followed by a single 8-msec gradient spoiler pulse (1 G/cm) successively applied on the x, y, and z axis, respectively. The pulse sequence employed for STEAM localization is shown in Figure 1. Depending upon the size of the lesion, the voxel location was selected from the MR image with dimensions between 1.5X1.5X1.5 cm3 and 2X2X2 cm3. MR images (300/19/11) of each voxel were then obtained to ensure the correct location of each voxel. This acquisition took 1 min 19 sec per voxel. The homogeneity of the field for each voxel was adjusted by shimming on the resonance of water in each voxel. Our experience was that the width at half-height of the water resonance was between 4-6 Hz after shimming. The resulting water FID was stored for use in computing the absolute concentration of the compounds. After the amplitudes of the saturation pulses were adjusted for maximum solvent suppression, a spectrum was obtained from each voxel using a TE of 19 msec, TM 10.6 msec, 1000-Hz sweepwidth, 2K points, 2-sec repetition time, eight-step phase cycle (a similar approach employing an eight-step phase cycling scheme has been reported by Griffey and Flaming (10)), and 256 averages per spectrum. Each spectrum required about 8 min of acquisition. The total time for the spectroscopy portion of the study was about 35 min; 5 min for shimming each voxel, 5 min for optimization of solvent suppression, and 8 min of acquisition per voxel. The resulting free induction decay was processed by zero-filling to 4K data points, applying an exponential filter of 1 Hz, Fourier transformation, and phase correction.

The spectra were analyzed by an experienced spectroscopist (R.E.L.) who was blinded to the patient and whether or not the particular spectrum was from an enhancing or unenhancing lesion. For each lesion studied with 1H spectroscopy, assessment was made as to Gd-DTPA enhancement. The data analyzed included MR images without and with Gd-DTPA enhancement, as well as the determination of the relative and absolute levels of the compounds present in the MR spectra.

The absolute concentration of the compounds present were calculated in two different ways. The relative areas under each peak were determined by numerical integration of the spectrum. The concentrations were then determined from the relative areas by assuming the total creatine concentration as 10.5 mM (11, 12). The details of this approach have been described by Frahm et al (12).
In addition, we employed the method of Thulborn and Ackerman to determine the concentrations based on the areas of the peaks referenced to the area of the unsuppressed water peak (13). The concentration of the compounds present can be calculated from

\[
S_A/S_{H_2O} = (D \cdot nC_A/C_{H_2O})
\]  

(A)

where \(S_A\) and \(S_{H_2O}\) are the signal intensities of the compound and water, respectively, \(C_A\) is the concentration of the compound expressed in moles/liter, \(n\) is the number of protons present in the resonance detected, \(C_{H_2O}\) is the concentration of water present, and \(D\) is a proportionality constant. This equation can be rearranged to give

\[
C_A = (S_A \cdot C_{H_2O})/(D \cdot S_{H_2O} \cdot n)
\]  

(B)

In phantoms containing pure solutions of water the value of \(C_{H_2O}\) is 2\(\times\)55.5 moles/liter. We can obtain estimates of \(C_{H_2O}\) in the voxels sampled by spectroscopy by employing a method similar to the one described by Wehrli and coworkers in MR imaging (14, 15). Regional signal intensities obtained on long TR/short TE images were referenced to cerebrospinal fluid to obtain values of the proton densities, i.e., the concentration of water in the regions sampled spectroscopically for each voxel. These values were used in equation B. Equation B is valid only if the signals were acquired under fully relaxed conditions, with no differential relaxation effects. Our approach has been to acquire the spectra with short TEs cognizant that the T2s of the compounds present are quite long (14). We believe that the effects of differential T2 relaxation are negligible, thus, no corrections were made for T2 relaxation. Corrections for differential T1 relaxation effects were made after peak areas were corrected for difference in receiver settings. The relative saturation corrections were made based on estimates of the T1 values obtained in three normal volunteers for the different compounds present. The results of these two methods (referencing to total creatine or the Thulborn and Ackerman approach (13)) were in good agreement in all of the cases.

The concentrations of metabolites were compared for enhancing and unenhancing lesions and the results were subjected to a two-tailed Student's \(t\)-test for independent variables with separate variances.

**Results**

Seven enhancing and 14 unenhancing lesions were studied in our 16 patient cohort (Table 1; Figs. 2 and 3). Decreased levels of N-acetylaspartate (NAA) were demonstrated in 17 out of 21 lesions for 14 of the 16 patients (Fig. 4). Figure 4 also shows the absolute concentration of NAA relative to Gd-DTPA enhancement. There is no separation between these groups, as indicated by a \(P\) value of .7. The majority of enhancing lesions \((n = 5)\) had abnormally high levels of peaks at 2.1–2.6 ppm which we have termed marker peaks. The ratio of the integrated areas of these peaks relative to the creatine peaks ranged between 0.1–5. Note that the area under the creatine peak at 3.0 ppm corresponds to a total proton concentration of 31.5 mM. Nine out of 14 unenhancing lesions had relatively normal levels of marker peaks (Fig. 5). The absolute mM concentrations of the proton containing compounds are given in Table 1. Figure 5 provides the ratio of the areas of the marker peaks (between 2.1–2.6 ppm) to the creatine peak for the unenhancing and enhancing lesions. These groups separate much better, with the Student's \(t\)-test showing a \(P\) value <.05 (.0003).

To determine whether there was any correlation between the levels of NAA and marker peaks present, we examined the cross-correlation plots shown in Figures 6 and 7. From these plots, it is clear that there is no significant correlation between the decreases in the levels of NAA and increased levels of the marker peaks in these patients.

**Discussion**

The advent of MR ushered in a new era of sensitivity in detection of white matter disease. It

### Table 1: Spectroscopic findings of MS lesions

<table>
<thead>
<tr>
<th>Gd-DTPA Enhancement</th>
<th>NAA (mM)</th>
<th>Resonances between 2.1–2.6 ppm (mM protons)</th>
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<td>9</td>
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<td>-</td>
<td>10.2</td>
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Note.—Six enhancing lesions (denoted +) showed a mean concentration of 30 mM (SD = 13.8%) for peaks resonating between 2.1 and 2.6 ppm, compared to thirteen unenhancing lesions (denoted -) which had a mean of 9.6 mM (SD = 6.5%). For statistical analysis, the Student’s \(t\)-test was performed, resulting in a \(P\) value <.05 (.0003), indicating a significant difference between the two groups. The mean NAA value for enhancing lesions was 11.6 mM and 10.9 for unenhancing lesions. There was no discernable difference in these groups, evidenced by the \(P\) value of .7.
Fig. 2. Images and spectrum from a 33-year-old man with known MS and exacerbation of right-sided sensory deficits.

A, Image (3000/90) showing lesion in left hemisphere within the spectroscopic voxel localizer.

B, Spoiled grass (34/14/45 μ) image showing enhancement of the lesion after administration of Gd-DTPA.

C, Spectrum of the lesion area showing increased resonances (arrow) in the 2.1–2.6 ppm range.

was clear very early in its development that MR would have a major impact in the diagnosis of MS. Gd-DTPA, just as iodinated contrast media in CT, further refined our insight into the MS lesion by demonstrating the abnormal blood-brain barrier associated with some lesions. There are a few serial imaging studies that shed further light on the dynamic nature of this disease. Preliminary evidence indicates that, in relapsing MS patients studied over a 6-month interval, disease activity identified by MR imaging appeared to be more frequent than predicted by clinical exami-

nation (16). Uhlenbrock et al found, in MS patients with acute relapses, that most lesions were stable; however, new lesions could be detected in an interval of 4–6 weeks (3). In a serial study of nine patients with mild relapsing-remitting MS, Willoughby et al found that new lesions had a characteristic temporal profile reaching a maximum size in approximately 4 weeks and then waning to leave a small residual lesion that could not be distinguished from chronic lesions (17). Miller et al noted that Gd-DTPA enhancement disappeared in approximately 78% of MS patients with acute relapses within 3–5 weeks and no enhancement persisted for more than 6 months (18). It has also been suggested that Gd-DTPA enhancement may precede high-intensity changes on long TR images (19). Harris et al reported on a series of six patients with relapsing remitting MS. Most lesions in this series enhanced for approximately 4 weeks, while a few revealed enhancement for greater periods of time (1–4 months). They also observed that new enhancement could occur without clinical worsening, and new Gd-DTPA enhancing lesions might shrink in size over one month on T2-weighted images (20).

The observation that both enhancing and unenhancing lesions may change (some decreasing or resolving) over time suggests that: 1) certain lesions, most often those that are active, may just represent edema with very little demyelination, and/or 2) significant remyelination may occur. In addition, clinical neurologic deficits may be transient, partially improve, or remain fixed. This again suggests that the MS lesion is heterogeneous. Presently, MR imaging is incapable of distinguishing these possible cohorts of lesions. 1H spectroscopy offers a biochemical probe to further extend our knowledge of individual MS lesions.

There have been several clinical spectroscopic studies carried out on patients with MS. Naranya et al monitored 28 plaques in 13 patients with MS (21). A solvent suppressed (STEAM) sequence with a TE of 50 msec, TM of 90 msec, and repetition time of 3 sec was employed. The plaques were identified on long TR/long TE MR imaging sequences prior to performing localized proton spectroscopy. The authors reported that resonances consistent with the presence of cholesterol and/or fatty acids were observed in five of 21 interpretable spectra. In one of the patients that was followed serially, these additional resonances disappeared after 2 weeks. The authors concluded that these results indicated the dy-
A, Long TR/TE image, showing lesion that did not enhance following Gd-DTPA administration.
B, Spectrum obtained from the same area.

Leasing, Grouped According to Enhancement

Fig. 4. Plot of NAA concentration in enhancing and unenhancing lesions. Statistical analysis showed no separation between enhancing and unenhancing lesions in terms of NAA concentration. Numbers in parentheses indicate number of lesions with the same NAA concentration.

The chronic nature of the disease with respect to the demyelinating process and the need for serial monitoring of MS plaques in patients. These authors did not employ Gd-DTPA enhancement as a means of distinguishing active from inactive plaques. The sensitive volume employed in this study was not specified.

Arnold et al examined seven patients with MS (22–24). A refocused STEAM sequence was employed with TEs of 68, 136, and 272 msec. The sensitive volumes sampled ranged from 44–160 cm³. In three patients with moderate to severe chronic disability, the NAA/creatine ratio was lower (1.6–2.0) than observed in normals (2.4–2.9). In three of four patients with minimal or no disability, the NAA/creatine ratio was normal. No lipid resonances were observed in any of the patients studied. The authors attributed the decrease in the NAA/creatine ratio to cumulative irreversible tissue damage rather than a response to acute inflammation. Based on these results, the authors suggested that: 1) in hyperacute plaques, the metabolite ratios would be unchanged; 2) demyelinating plaques would exhibit increased choline/creatine; and 3) subacute to chronic plaques would have decreased NAA/creatine ratios. The protocol employed in this study did not include Gd-DTPA-enhanced MR.

Bruhn et al examined six children with mild to moderate disease. A STEAM sequence with sensitive volumes ranging from 2–8 cm³ was employed with a TE of 20 msec and an unspecified TM (25). There was a 50%–80% decrease observed in the levels of NAA. The creatine pool was also decreased. Increases in the levels of choline and inositol were observed. The authors noted that there were no differences observed in the metabolite levels of plaques that exhibited Gd-DTPA enhancement and nonenhancing plaques. No changes in the level of lactate were observed.

Den Hollander et al (26) employed a chemical shift imaging (CSI) technique based on a 90/180/
Lesions, Grouped According to Gd-DTPA Enhancement

Fig. 5. Plot showing ratio of marker peaks resonating at 2.1–2.6 ppm to creatine between enhancing and unenhancing lesions. Numbers in parentheses indicate lesions with the same concentration of peaks (mM protons) between 2.1–2.6 ppm.

180 spin echo sequence (PRESS) to study nine patients with MS (three chronic progressive and six in the relapsing-remitting stage). The total echo time employed was 272 msec and the nominal voxel size was about 1 cm$^3$. The plaques exhibited decreased levels of NAA and increased levels of choline. Focal increases in lactate were observed in some of the patients who were in the active stage of disease. In two patients, decreased creatine was observed.

Van Hecke et al studied 18 patients with MS using the STEAM method (8). These patients showed a significant reduction in the area of the NAA resonance as compared to normals. These investigators did not employ Gd-DTPA to separate the enhancing from the unenhancing lesions. The STEAM sequence was carried out with a TE of 272 msec, which in our experience will lead to a differential suppression of the peaks between 2.1–2.6 ppm.

Richards has demonstrated that there are lipid signals present in the single voxel localized proton spectra of the brains of monkeys with the experimental allergic encephalomyelitis (27). The presence of mobile lipids was confirmed by histochemical oil red O staining. The author suggested that since the spectroscopic methods were performed under conditions that were sensitive only to mobile lipids, the lipids detected were associated with demyelination. These authors have also employed a CSI technique based on the stimulated echo (STEAM) method to study the same model system (28). A decrease in creatine and choline and slight changes in NAA were observed. The precise TE and TM values employed in this CSI study were not specified. The observation of lipid resonances in the model system support the hypothesis that proton spectroscopy is sensitive to the presence of demyelination. Preece et al have carried out in vitro high-resolution proton studies on extracts of the spinal cord of a chronically relapsing encephalomyelitis mouse model of MS (29). This model showed decreased inositol to creatine ratios and increased taurine to creatine ratios. A slight trend to NAA depletion was reported.

Koopmans et al studied seven plaques in four patients (two new lesions, two chronic-active, and three chronic) using the STEAM method with TEs as short as 20 msec and sensitive volumes of between 8–32 cm$^3$ (30). A decrease in the NAA/creatine ratio was observed in five/seven of the lesions. Six of the lesions demonstrated reduced NAA/choline. Lipid signals were observed in both chronic and new lesions. The authors pointed out that these lipid signals were not detected when TEs longer than 120 msec were employed. Christiansen et al employed the STEAM method in a serial study of 15 patients with MS (31). In this study, the TE employed was 50 msec, the TM was 30 msec, and the sensitive volume was 27 cm$^3$. Lipid signals were observed in seven/22 of the examinations performed. These lipid signals were observed in both relatively new plaques (7–10 days) as well as older plaques (70–85 days). The level of NAA was
found to be lower in the patients as compared to a control group. The levels of creatine were not significantly different as compared with controls. The ratio of NAA/choline decreased with time after occurrence of the plaque. This decrease was attributed to gliosis or axonal degeneration.

In reviewing the results of these literature reports, as well as our own experimental results, it became clear that there are some general trends that have been observed in the MS studies. There is consensus that the NAA/creatine ratio decreases in MS plaques. This finding is consistent with the view that the level of NAA is an indicator of neuronal integrity and, therefore, should be decreased in patients with chronic disease. Some groups have found resonances in the region of the spectrum where lipids resonate; others have not. We have found elevated levels of the compounds that resonate between 2.1–2.6 ppm. Moreover the levels of these compounds appear to statistically correlate with whether the lesion exhibits enhancement after administration of Gd-DTPA. We believe that the variability in the results presented in the literature may arise from two sources. First, differences in the manner in which the spectroscopy portion of the examination is carried out and analyzed may lead to variations in the sensitivity and accuracy in measuring the levels of the compounds present. Second, MS is a dynamic disease with results dependent on the particular phase of the disease being sampled when the patient is studied.

As indicated in the Subjects and Methods section, our investigation was performed using the STEAM method of localization. This method was chosen for several reasons. With STEAM it is possible to achieve excellent solvent suppression (suppression factors greater than 1000) even at short echo times. Good section profiles can be achieved by using simple sinc pulses for the section-selective 90° pulses so that it is possible to implement STEAM with relatively short echo times. Griffey and Flamig have reported a version of STEAM called VAPOR which has a minimum echo time of 10 msec (10). The multipulse nature of the STEAM technique and its associated affects of spin-spin coupling may complicate the quantification of spectra. This is especially true in situations with small spin-spin couplings that may not be resolved in vivo. The difficulties arise because of the modulation of the signal due to spin-spin coupling or the creation of multiple quantum coherences that are converted to observable signal. Both of these effects may distort the spectra. We have chosen to acquire spectra with TE and TM intervals set as short as possible, because these effects are minimal at short TEs and TMs.

We have employed the STEAM method as a single voxel rather than a multivoxel method. This decision was based on our initial experience with STEAM that indicated that we could obtain quantitatively reliable, reproducible, precisely localized spectra at short TE and TM when the
method was employed as a single-voxel localization technique. We have also found that spectra obtained using this method can be analyzed by using the approach of Thulborn and Ackerman to give precise and accurate estimates of the concentrations of amino acids present in phantoms (32). While there have been some preliminary reports that have indicated that it is possible to implement STEAM as a chemical shift imaging technique at short echo times, there has been no data presented that provide indications of the quantitative reliability of this approach.

Tofts and Wray have critically reviewed the methods employed to analyze spectral data in terms of the concentration of compounds present (33). We chose to employ the method described by Thulborn and Ackerman in the analysis of our data because this method has several attractive features particularly when applied to the analysis of proton data (32). There is no correction necessary for coil loading since the same coil is used for the water referencing and spectral acquisition. Also, the acquisition of the water signal is extremely easy since a spectrum can be obtained from the STEAM voxel after shimming by acquiring the signal without CHESS suppression pulses. We also have validated this method in phantoms by analyzing samples in a blinded fashion. Our experience indicates that this method is both accurate and precise in providing estimates of the absolute concentrations of the compounds present (34). There are some limitations in this method, particularly when the resonance cannot be assigned unambiguously to a particular compound. Under these circumstances, the value of \( n \) in equation B cannot be determined and, as a result, the method gives values of the total concentration of protons present. Also, it becomes difficult to correct for differential relaxation effects without making some assumptions about the identity of the resonances. In spite of these difficulties, we are confident in both of the concentrations reported in the present work. For example, the concentration range of NAA found in normal controls is in good agreement with the values reported by Frahm et al (12).

The most intriguing result of our study is the finding of elevated compounds that resonate between 2.1-2.6 ppm which we earlier termed marker peaks. These were noted in those plaques that displayed contrast enhancement. Amino acids, including GABA, glutamate, etc, are expected in this spectral region. We hypothesize that the lesions with these extra spectral peaks may consist of myelin catabolites and thus provide marker peaks for demyelination. The ability to detect these products provides us with new information on the substrate of MS lesions. \(^1\)H spectroscopy may contribute to understanding the natural history of a particular plaque. Lesions without these marker peaks may either be old gliotic areas or active edematous regions. The levels of NAA present in these lesions may provide an indicator of the extent of tissue viability in these lesions. Two of our patients revealed Gd-DTPA enhancement, but had rather low levels of marker peaks present. We suggest that these represent active, primarily edematous lesions. On the other hand, lesions with myelin catabolites are most likely undergoing active demyelination and thus most likely to display Gd-DTPA enhancement.

Another situation we hypothesize is that demyelination may be seen without Gd-DTPA enhancement. This was observed in five of 14 lesions where marker peaks are present without enhancement. This also suggests that demyelination may have a broader time course than disruption of the blood-brain barrier. An alternative explanation, of course, is that not all demyelinating lesions need enhance.

Our results indicate possible clinical applications for \(^1\)H spectroscopy. Prognostication of symptoms referable to particular lesions may be possible with \(^1\)H spectroscopy. Lesions associated with edema presumably will have a better prognosis than those associated with demyelination. A rationale for treatment of MS could be based on \(^1\)H spectroscopic findings, ie, edematous lesions could be treated with steroids early in their course. Lesions in patients undergoing drug therapy protocols could be monitored serially with \(^1\)H spectroscopy to appreciate if those lesions with high levels of marker peaks change during the course of therapy. Clearly, many additional studies need to be performed; however, longitudinal studies utilizing \(^1\)H spectroscopy would offer further insight into the possible extent of remyelination in previously identified demyelinating lesions, as well as the extent to which edematous lesions evolve to demyelination. \(^1\)H spectroscopy may furnish an important biochemical window to view the inflammatory and immunologic features of this complex disease, as well as being more sensitive than enhancement as a gauge of continuing demyelination.
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