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PURPOSE: To compare proton MR spectroscopic alterations with the degree of contrast enhancement in multiple sclerosis (MS) lesions. METHODS: Thirty-five patients with clinically diagnosed MS were studied with MR spectroscopy. A total of 47 lesions were examined. Solvent-suppressed proton spectra were acquired with an echo time of 16 milliseconds using the point-resolved spectroscopic localization method from 1.5 cm³ voxels. Marker peaks/creatinine (Cr) ratios obtained from these spectra were plotted against the relative enhancement of the lesion seen after administration of contrast material. The relative enhancement was defined as $S_{\text{contrast}} - S_0$, where $S_0$ is the signal intensity of a T1-weighted image and $S_{\text{contrast}}$ is the signal intensity after administration of gadopentetate dimeglumine. RESULTS: We found a positive linear relationship between the marker peaks/Cr ratio and the degree of enhancement of the lesion. That is, the marker peaks/Cr ratio was higher in the lesions that showed the greatest enhancement. CONCLUSION: The MR/Cr ratio obtained with the use of short-echo-time proton MR spectroscopy correlates with the degree of contrast enhancement. This ratio may therefore serve as a means for evaluating and quantifying the level of inflammatory activity within the plaques of patients with MS.

Index terms: Brain, magnetic resonance; Magnetic resonance, spectroscopy; Sclerosis, multiple

Multiple sclerosis (MS) is a disease of the central nervous system found in approximately 0.1% of the population in North America. Magnetic resonance (MR) imaging is the imaging method of choice in the diagnosis of MS (1, 2). However, the use of conventional MR imaging to characterize MS plaques is complicated by the heterogeneity of these lesions. Specifically, it is probable that acute, subacute, and chronic plaques will be present in the same patient, and all these different types of plaques may have similar signal intensities on MR images.

Contrast enhancement can be discerned before a lesion is visible on an unenhanced MR image (3). This observation suggests that the presence of inflammation is an early stage in the evolution of an MS plaque. It has been shown that the presence of enhancement can persist for 2 to 4 weeks (4) and may correlate with active demyelination for a short period of time (5). The utility of magnetization transfer (MT) in MS has been reviewed recently (6), and this technique may allow the subcategorization of MS lesions into those with a very low MT ratio (demyelinated lesions) and those with a slightly decreased MT ratio (edematous lesions) (7, 8).

Solvent-suppressed proton MR spectroscopy provides a noninvasive method with which to monitor metabolism in vivo (9–11). Chronic plaques show reductions in the level of N-acetylaspartate (NAA), a marker of neuronal viability. Acute plaques show transient elevations in choline (Cho) (12) and myo-inositol (13, 14) and the presence of free lipids (14–16). Lactate resonances have been observed in a small number of acute plaques and is probably a result of inflammation, since the dominant bioenergetic pathway in activated macrophages has been shown to be glycolysis (17, 18).
We have previously reported a correlation between a composite set of resonances between 2.1 and 2.6 ppm and the presence of contrast enhancement in a study of 14 patients (six with enhancing lesions) (19). At the time, we called these resonances marker peaks and speculated that these peaks might represent myelin degradation products or products of inflammatory reaction. More recently, we found a negative correlation between the levels of these marker peaks and the MT ratio present in the plaques of 11 patients with MS (20). That is, plaques with high levels of these marker peaks showed reduced MT ratios. Although there was a slight trend for the NAA/creatine (Cr) to be lower in plaques with a decreased MT ratio, this trend was not statistically significant. Since reduced MT ratios are consistent with loss of myelin structure, the findings described above suggest that the marker peaks may in fact represent the products of demyelination.

Having correlated MR spectroscopic findings with MT ratios in MS plaques and compared MT ratios with contrast enhancement, we undertook the present study to determine which, if any, spectral alterations correlate with the degree of contrast enhancement in MS lesions.

Subjects and Methods

Thirty-five patients with clinically diagnosed MS were examined with MR imaging. Locations for single-voxel spectral acquisitions were identified on the axial long repetition time (TR)/long echo time (TE) images. In all, 41 lesions were examined with proton MR spectroscopy. Of these, 10 enhanced after administration of contrast material.

In all the patients, MR imaging of the brain was performed using a 1.5-T scanner. The imaging technique included a sagittal short-TR/short-TE sequence (600/20/1 [repetition time/echo time/excitations]), an axial conventional or fast spin-echo long-TR/short-TE/long-TE sequence (2500/18.90/1), followed by an axial short-TR/short-TE sequence (600/20/1) after injection of gadopentetate dimeglumine (0.1 mL/kg body weight). The postcontrast sequence was always performed last in order to standardize the period of time after injection of the contrast material; that is, no intervening sequences delayed the period of time between contrast administration and image acquisition. The elapsed time from injection to imaging was approximately 5 minutes in each case.

Localized solvent-suppressed proton spectra were acquired using the point-resolved spectroscopy (PRESS) (P. A. Bottomley, “Selective Volume Method for Performing Localized Spectroscopy,” US Patent 4 480 228: 1984) localization method (90°-180°-180°) with digitally crafted Shinnar-LeRoux radio frequency pulses (21). By using this method, we could sample voxels as small as 1.5 cm³ with a TE of 16 milliseconds. After choosing the voxel location for MR spectroscopy, we adjusted the homogeneity over this voxel with the linear x, y, and z shims (the typical width at half-height of the water resonance was 3 to 4 Hz). Solvent suppression was achieved by using three chemical-shift selective pulses, each followed by a spoiler gradient on each orthogonal axis to remove any transverse magnetization, resulting in an average suppression of between 500 and 800. The spectra were acquired with a TR of 2 seconds, a 1000-Hz sweep width, and 1024 complex points. An eight-step phase-cycling scheme was used to reduce spectral artifacts.

The spectra were processed with 1-Hz line broadening followed by zero-filling to 4096 points, Fourier transformation, and zero-order phase adjustment. The area under each peak was determined by using a nonlinear least squares minimization algorithm based on the Marquardt method using ProNMR software (Gueph, Ontario, Canada). We used Lorentzian line shapes to fit the real part of the spectra in the frequency domain. The fitting was performed blinded to the results of any of the MR imaging analyses. The peaks that were fit included marker peaks (seven peaks were fit in this range for all of the spectra, 2.1 to 2.6 ppm), NAA, and Cho. The concentration of the marker peaks was determined by calculating the area under the composite curves that resonated between 2.1 and 2.6 ppm and by subtracting two thirds of the area of the NAA methyl resonance at 2.03 ppm to correct for contributions of the β CH₂ of the aspartate moiety of NAA.

We defined a variable of the relative enhancement of these lesions that can be calculated by subtracting the signal intensity on the short-TR/short-TE sequence from the signal intensity seen after administration of contrast material. The relative enhancement was defined as \( \frac{S_{\text{contrast}} - S_0}{S_0} \), where \( S_0 \) is the signal intensity of a T1-weighted image and \( S_{\text{contrast}} \) is the signal intensity after administration of gadopentetate dimeglumine. One of the investigators, blinded to the results of the spectral analysis and working at an independent console, verified the lesion location on the long-TR/long-TE sequences. Regions of interest 4 mm² were placed on the noncontrast and contrast-enhanced short-TR/short-TE T1-weighted images at the lesion site. The signal intensity of fat and the contralateral normal-appearing white matter were used as controls for these measurements.

Results

Selected MR images, including the voxel location chosen for spectroscopy and the solvent-suppressed spectrum, are shown in Figure 1. The patient in this figure had patchy hyperintense regions in the periventricular white matter.
Fig 1. A, Axial T2-weighted (3000/90/1) image obtained with a fast spin-echo sequence and a 22-cm field of view, 256 × 192 matrix, and 5-mm contiguous sections.

B, The same section as in A with the voxel location and voxel size (1.5 cm³) as indicated for the solvent-suppressed MR spectroscopic study.

C, Solvent-suppressed proton spectrum plotted from 0 to 4 ppm obtained using the PRESS method from the voxel shown in B. The spectrum was acquired with a TR of 2 seconds and a TE of 16 milliseconds, a 1000-Hz sweep width, and 1024 complex points. An eight-step phase cycling scheme was used to reduce spectral artifacts. The spectrum was processed with 1-Hz line broadening followed by zero filling to 4096 points, Fourier transformation, and zero-order phase adjustment.

D, Solvent-suppressed proton spectrum plotted from 0 to 4 ppm obtained using the PRESS method from the centrum semiovale of a healthy volunteer. The spectrum was acquired and processed using the same parameters as indicated for C.

E, An example of the results of the Marquardt fitting algorithm. The bottom spectrum is the experimental spectrum shown in C and the top spectrum is the computer-generated best-fit spectrum.
on the T2-weighted images. The voxel, which was located in the left posterior region of the section, was chosen for MR spectroscopy. The spectrum in Figure 1C shows increased levels of the marker peaks with relatively normal levels of NAA, Cr, and Cho as compared with the spectrum obtained from the centrum semiovale of a healthy control subject (shown in Fig 1D). An example of results of the fitting algorithm is shown in Figure 1E. The lesion selected for MR spectroscopy exhibited a fractional enhancement of 0.06 after administration of gadopentetate dimegiolamime.

Selected MR images from another patient, including the voxel location chosen for spectroscopy and the solvent-suppressed spectrum, are shown in Figure 2. This patient had multiple hyperintense lesions on the long-TR/long-TE sequences. As indicated, the largest of these lesions located in the left periventricular white matter was chosen for spectroscopy. This lesion showed significant enhancement after injection of contrast material. The spectrum in Figure 2E shows increased levels of the marker peaks with relatively normal levels of NAA, Cr, and Cho. There is also a large peak centered at 1.6 ppm. The lesion selected for MR spectroscopy exhibited a fractional enhancement of 0.33 after administration of contrast material.

The results obtained from an analysis of MR spectra of the 10 enhancing lesions are summarized below. Marker peaks (2.1 to 2.6 ppm) were shown in all the patients who had enhancing lesions. The variation in the marker peaks/Cr ratio with the fractional enhancement seen after administration of contrast material is illustrated in Figure 3. We used linear regression analysis (SPSS version 6.1 for the MacIntosh; SPSS Inc, Chicago, Ill) to fit the variation in the marker peaks/Cr ratio with the fractional en-

Fig 2. A, Axial T2-weighted image (2500/90/1) obtained with a conventional spin-echo sequence and a 22-cm field of view, a 256 × 192 matrix, and 3-mm contiguous sections. B, The same section as in A with the voxel location and voxel size (1.5 cm³) as indicated for the solvent-suppressed MR spectroscopic study. C, Contrast-enhanced T1-weighted image (600/27) of same section as in A. Note the enhancement visible on this image. D, Solvent-suppressed proton spectrum plotted from 0 to 4 ppm obtained using the PRESS method from the voxel shown in B. The spectrum was acquired with a TR of 2 seconds and a TE of 16 milliseconds, a 1000-Hz sweep width, and 1024 complex points. An eight-step phase cycling scheme was used to reduce spectral artifacts. The spectrum was processed with 1-Hz line broadening followed by zero filling to 4096 points, Fourier transformation, and zero-order phase adjustment.
enhancement observed. The marker peaks/Cr ratio shows a positive, statistically significant, linear relationship with the fractional enhancement observed after administration of contrast material (slope = 5.5, intercept = 0.8; $r^2 = .59$; $P < .05$). In general, the NAA levels were slightly decreased and appeared to have a negative trend with respect to the level of enhancement. However, this relationship was not statistically significant. Choline was generally increased. The ratio of Cho/Cr was increased in seven of the 10 enhancing plaques. No correlation was found between the fractional enhancement after administration of contrast material and the Cho/Cr ratio. Peaks that may reflect free lipids (0.9 to 1.6 ppm) were observed in two of 10 cases. We did not observe a distinct resonance for lactate in any of the lesions studied.

Discussion

There have been relatively few MR spectroscopic studies of acute MS plaques. Narayana et al (15) observed prominent resonances in the 0.5 to 2.0 ppm region in six of nine enhancing lesions. They speculated that these resonances arose from lipids and other myelin breakdown products. In their cohort of enhancing lesions, there was no significant decrease in NAA.

Davie et al (22) recently reported the results of a serial MR spectroscopic study of eight patients with large, acute MS plaques. All the spectra obtained from these acute lesions showed two distinct broad resonances between 0.9 and 1.5 ppm, which were tentatively assigned to mobile lipids. In seven of these patients, the lipid resonances resolved to normal levels within 4 to 8 months. The lesions also showed elevations in myo-inositol and reversible changes in NAA. Resonances assigned to lactate were observed in two of the eight plaques. These authors discussed their findings in terms of the histopathology of myelin degradation. Note that the lipid found in demyelination is in the form of triglycerides and cholesterol esters (23). Cholesterol esters exhibit a broad amorphous nuclear MR spectrum at 1.5 T. The nuclear MR spectrum of a lipoma shown by Davie et al (22) also indicates that the resonance at 0.9 ppm is about one third the area of the resonance centered at 1.3 ppm. In the examples of spectra of acute plaques shown by Davie et al (22), the ratios of intensities observed for the resonances at 0.9 and 1.3 ppm are inverted relative to those shown in the spectrum of the lipoma. These observations suggest that these resonances may arise from compounds other than mobile lipids.

The authors point out that the variability in detection of lipid resonances in other studies may be a result of the short T2 of the lipid resonances and that sequences with echo delays of 10 milliseconds may be required. We and others have observed these resonances in some of the acute plaques studied. The variability in the detection of lipid resonances may in part be due to differences in technique; it may also be due to the criteria used in lesion selection. Davie et al restricted their study to large lesions that occupied between 4 and 12 cm³. The other studies included smaller lesions. Thus, as Davie et al (22) point out, there may be partial volume effects that hamper the detection of lipid resonances. It is also possible that the biochemical behavior of large focal lesions may be different from that of smaller plaques.

Roser et al (24) used stimulated-echo acquisition mode (STEAM) at a TE of 30 milliseconds and a voxel size of 8 cm³ to study 22
patients with enhancing plaques at 2.0 T. These authors reported decreased NAA/Cr and NAA/Cho ratios in the plaques. No resonances associated with lactate were observed in the spectra obtained at 30 or 135 milliseconds. The authors found no increase in the marker peaks/Cr ratio, although they pointed out that the choice of acquisition or processing parameters would influence the detectability of these resonances. No attempt was made to quantitate resonances observed between 0 and 1.4 ppm.

The results of this study support our earlier observation of increased marker peaks in enhancing lesions. In the present study, we used PRESS localization, which is less susceptible to the effects of J-modulation than the STEAM sequence. The observation that the levels of these resonances correlate with the degree of enhancement is intriguing. If these marker peaks are products of myelin breakdown or arise from molecules that bring about demyelination, then our findings suggest that lesions with higher degrees of enhancement should show more demyelination. The observation made by Hiehle et al (20) that the MT ratio was not statistically different in enhancing versus none-enhancing lesions appears to argue against this interpretation. However, the duration of the elevations in marker peaks and the time course of demyelination may be quite different. These marker peaks appear to be present much longer than the transient breakdown in the blood-brain barrier would suggest a priori, which reinforces the meaningful relationship between the degree of inflammatory response and marker peak levels.

An alternative explanation is that the marker peaks reflect immune activation or inflammatory response. This possibility is supported by the fact that, as pointed out in the introduction, the presence of contrast enhancement showed a better correlation with macrophage infiltration and astroglial response than with perivascular lymphocyte infiltration (25).

As mentioned above, the ability to detect these resonances may depend in large part on the precise acquisition parameters and methods used. If the resonances arise from coupled spin systems, then the choice of TE and mixing time in the STEAM sequence may be critical (26). It has been shown that it may be possible to choose a mixing time and TE in which a particular multiplet structure is preferentially affected (26).

Several studies have demonstrated that macromolecular resonances can be detected in the proton spectra of guinea pigs in vivo with the use of spin-echo sequences (27–30). Those authors compared the spectra obtained from different fractions of high-performance liquid chromatography separations of perchloric acid extracts of cerebral tissue with authentic samples and spectra of intact tissue. On the basis of these methods, these authors assigned the macromolecular resonances to thymosin β4, which is a polypeptide found in macrophages and a subset of oligodendrocytes. The concentration of this polypeptide was found to be about 250 μg per gram of extract dry weight in the acid extracts (NAA was 500 μg per gram of extract dry weight in the acid extracts).

Behar et al (31) analyzed the macromolecular resonances of human brain in healthy volunteers at 2.1 T. In vivo spectra edited to obtain macromolecular resonances were compared with spectra acquired on cytosol and dialyzed cytosol obtained from biopsy tissue samples of patients with temporal lobe epilepsy. Two-dimensional nuclear MR studies showed multiplet structures and connectivities in some of these resonances. The T1 and T2 values of the peak at 0.93 ppm were reported to be 250 ± 36 milliseconds and 44 ± 4 milliseconds, respectively. These values are consistent with relaxation data for polypeptides and low-molecular-weight proteins. The value of 44 milliseconds corresponds to a line width of about 7 Hz for this resonance. This resonance most likely originates from methyl groups undergoing relatively rapid internal rotation. The line widths of other resonances that arise from more rigid moieties within the same molecule should be significantly broader.

Davie et al (22) pointed out that this polypeptide can give rise to the resonances close to those (1.4 ppm) that have previously been assigned to the resonances of mobile lipids (between 0.9 and 1.3 ppm). These authors also suggested that resonances from myelin basic protein may also occur in the same region of the spectrum.

Inspection of the spectra published for these molecules from the three different laboratories indicates that resonances may also occur in the region that we have designated as marker peaks. In fact, Behar et al (31) assigned two of the macromolecular resonances, M5 and M6, to glutamate and glutamine residues in the amino acid.
acid chains. These two resonances are significantly broader than the methyl resonances in the macromolecular spectrum, presumably for the reasons discussed above. This observation is consistent with the spectra shown in Figures 1 and 2. In general, we have found that the marker peaks are significantly broader than the resonances observed for NAA, Cr, Cho, and myo-inositol. It is quite likely that the detection of all or any of the resonances from macromolecules is very sensitive to both the particular localization sequence used and to the precise acquisition parameters used to obtain spectra. This may in part explain the fact that these resonances have not been observed in all of the studies of acute MS plaques reported to date.

By using PRESS localization with a short TE, we were able to detect marker peaks/amino acids in all of the enhancing lesions. We found a positive correlation between the levels of these peaks and the degree of enhancement observed after injection of gadopentetate dimeglumine. We suggest that these peaks can be assigned to resonances associated with low-molecular-weight polypeptides and proteins, such as thyro-mosin β4 or glutamine/glutamate. Since the detectable concentrations of these peaks are increased in acute MS lesions, these peaks may be indicative of the degree of inflammatory activity and/or demyelination present. The quantitation of these peaks may further serve as a method to define lesional activity. MR spectroscopy may aid in detecting the in vivo chain of biochemical events that lesions undergo. Further technical developments will lead to more precise localization and better spatial resolution. MR spectroscopy may therefore provide new insights into the pathogenesis of MS plaques.

References