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Magnetization Transfer Imaging in Patients with Clinically Isolated Syndromes Suggestive of Multiple Sclerosis

Peter A. Brex, Siobhan M. Leary, Gordon T. Plant, Alan J. Thompson, and David H. Miller

BACKGROUND AND PURPOSE: In patients with multiple sclerosis (MS), reduced magnetization transfer ratios (MTRs) have been reported in white matter that appears normal on studies obtained with conventional imaging techniques. The stage in the disease when this first becomes detectable is unclear. The purpose of this study was to measure the MTR of normal-appearing white matter (NAWM) and lesions in patients with clinically isolated syndromes (CIS), many of whom are at the earliest stages of MS, and to determine the prognostic value of any observed changes.

METHODS: Twenty-seven CIS patients and 13 matched control subjects were studied. The mean MTR was measured from 10 regions of NAWM and, when present, from lesions. The patients were followed-up clinically for a median of 12 months.

RESULTS: There was no significant difference in the mean MTR between NAWM in control subjects (38.5% units) and that in CIS patients (38.4% units). After 12 months' follow-up, MS developed in 26% of the patients. The MTR of NAWM in these patients did not differ from that of the other patients or the control subjects.

CONCLUSION: The reduced MTR in NAWM, described in established MS, was not detectable in patients with CIS. MTR did not provide prognostic information for this short period of follow-up.

Magnetization transfer imaging (MTI) has proved to be a sensitive and robust method for detecting and quantifying pathologic changes in multiple sclerosis (MS) (1). The derived magnetization transfer ratio (MTR) is believed to reflect characteristics of protons bound to macromolecules, such as myelin (2). Significant reductions in MTR have been found in the white matter that appears normal on studies obtained with conventional imaging techniques (3-7). This finding is consistent with histopathologic studies, which have confirmed that abnormalities may occur in macroscopically normal-appearing white matter (NAWM) in MS (8). In

vivo detection of these abnormalities that are invisible by MR imaging is important, as they may play a role in disease pathogenesis and have an impact on disability. Possible causes of NAWM abnormalities include microscopic lesions, shadow plaques, edema, astrocytic proliferation, microglial activation, perivascular inflammation, and wallerian degeneration.

The stage of the disease at which NAWM abnormalities first appear is not clear. The time of onset, particularly in relation to lesion development, is relevant in understanding disease pathogenesis. The earliest clinical event in many patients with MS is a clinically isolated syndrome (CIS) affecting the optic nerve, brain stem, or spinal cord. Over 60% of CIS patients already have disseminated cerebral white matter lesions on MR images at presentation that are indistinguishable from those found in MS (9, 10). The presence and extent of such lesions are strong predictors of the future risk for developing MS (11-13); a 10-year follow-up study found that over 80% of CIS patients with abnormal brain findings on MR images developed clinically definite MS (14, 15). The present study, therefore, evaluated MTR from NAWM in patients with CIS to determine whether any abnormality was already detectable and whether any observed

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TABLE 1: Demographics

	Control Group	Patients with Clinically Isolated Syndromes	
		Total	Those with Four or More Lesions
No.	13	27	13
Sex (male/female)	6/7	13/14	5/8
Mean age, years (range)	34 (25–47)	34 (21–51)	37 (21–48)
Median T2 lesion volume, cm ³ (range)	0	0.3 (0–6.8)	1.1 (0.2–6.8)

changes were of prognostic value for the risk of developing MS. The MTR of focal lesions was also investigated.

Methods

Patients

MTI was introduced into a prospective, longitudinal multisquence MR imaging study of patients with CIS (16) after January 1998. A CIS was defined by the occurrence of an acute, presumed inflammatory demyelinating event in any part of the CNS in an individual without a history suggestive of previous demyelinating episodes. In all patients, appropriate investigations were performed to exclude alternative diagnoses. All patients with optic neuritis were seen by a neuroophthalmologist, who confirmed that the clinical picture was compatible with idiopathic optic neuritis. The study was approved by local ethics committees. Informed consent was obtained from all patients before entry.

Twenty-seven CIS patients with a median age of 34 years (range, 21–51 years) were studied a median of 18 weeks (range, 14–24 weeks) after the onset of symptoms; 14 of the patients were women and 13 were men. Seventeen (63%) of the patients had lesions on proton density—and T2-weighted images. The median total lesion volume for all patients was 0.3 cm³ (range, 0–6.8 cm³). Thirteen age- and sex-matched control subjects were also studied. These included six men and seven women with a median age of 34 years (range, 25–47 years) (Table 1).

MT Imaging Sequence

All imaging was performed on a 1.5-T imager provided by the Multiple Sclerosis Society of Great Britain and Northern Ireland. A dual-echo spin-echo sequence was performed with and without presaturation pulses using an interleaved sequence described by Barker et al (17). The presaturation pulse was a Hamming apodized three-lobe sinc pulse, with a duration of 16 milliseconds and a peak amplitude of 23.2 μ T, giving a nominal bandwidth of 250 Hz, applied 1 kHz off-water resonance. MTR was calculated for each pixel using the formula

$$[(M_0 - M_S)/M_0] \times 100\% \text{ units}$$

where, M_0 and M_S represent signal intensities with and without presaturation, respectively. Thus, 28 inherently coregistered 5-mm-thick axial proton density-weighted images (1720/30/0.75 [TR/TE/excitations]), T2-weighted images (1720/80/0.75), and calculated MTR images were produced and then displayed on a Sun workstation (Sun Microsystems Inc, Mountain View, CA), using image display software (18).

NAWM MTR Analysis

Although MTR analysis was performed by the same observer who followed the patients clinically, he was unaware of the attribution of the MTR images because of blinding of the images. Regions of interest (ROIs) were outlined on the proton density-weighted images with reference to the T2-weighted

images. A standard template was used to ensure the amount of white matter studied in each region of the brain was the same for each subject. The ROIs were positioned in each designated region of white matter taking care not to include CSF or gray matter (or lesions, in the case of patients) and leaving a surrounding rim of white matter to minimize partial volume effects. Adjacent slices were examined to ensure the ROI was completely in the white matter. The ROI size was 77.3 mm² in the pons and 22.9 mm² in the genu of the corpus callosum. For bilateral regions, the mean ROI size was 40.9 mm² in parietooccipital white matter, 49.2 mm² in frontal white matter, 59.8 mm² in the posterior limb of the internal capsule, and 77.3 mm² in the centrum semiovale. Once all the ROIs had been identified, they were applied to the calculated MTR images. For bilateral regions of white matter, the mean of the measurements from the right and left hemisphere was taken to average any (minimal) effects of asymmetry between the hemispheres (19). The reproducibility of the technique was assessed by duplicating five images before the blinding process and comparing the MTR values of each pair after unblinding.

Lesion Identification and MTR Analysis

Lesions, when present, were contoured on the proton density-weighted images using a semiautomated local thresholding technique (18). Lesion volume was calculated automatically as the computed area multiplied by the slice thickness. The regions were then applied to the inherently coregistered MTR image, enabling the mean lesion MTR to be calculated for each patient.

Statistical Analysis

Reproducibility was quantified using the coefficient of variation, after determining the mean and standard deviation (SD) of the duplicate measurements of NAWM MTR. Comparison was made between the MTR in NAWM and lesions in the patients with that in the control subjects using two-sample *t*-tests. Owing to the number of statistical comparisons made, a *P* value of less than .01 was considered to be significant.

Results

The mean coefficient of variation of the technique was calculated as 0.6% (range, 0.2% to 0.9%). In the control subjects, significant differences were found in the MTR among different regions of the brain, with the highest MTR recorded in the corpus callosum. There were no significant differences between the MTR in control subjects and that in patients in any of the white matter regions or between the overall mean values for white matter. Comparison of NAWM in the control group with that in the subgroups of patients with one or more T2 lesions and with four or more T2 lesions also did not reveal any statistically significant differences (Table 2). In the 17 patients with lesions

TABLE 2: Magnetization transfer ratios (MTRs)

	Control Group	Patients with Clinically Isolated Syndromes			
		Total	Those with one or more lesions	Those with four or more lesions	MS Group
Mean MTR, percentage units (SD)					
Pons	38.8 (0.7)	38.6 (1.1)	38.7 (0.9)	38.8 (0.9)	38.6 (0.5)
Parietooccipital lobe	37.0 (0.7)	37.4 (0.6)	37.4 (0.5)	37.5 (0.5)	37.7 (0.5)
Frontal lobe	39.5 (0.7)	39.4 (0.6)	39.4 (0.6)	39.3 (0.7)	39.6 (0.4)
Posterior internal capsule	37.1 (0.7)	36.9 (0.7)	36.8 (0.5)	36.8 (0.6)	36.7 (0.2)
Corpus callosum	41.0 (0.9)	40.4 (0.9)	40.5 (0.9)	40.3 (1.0)	40.6 (0.7)
Centrum semiovale	37.8 (0.5)	37.9 (0.9)	38.1 (0.9)	37.9 (0.9)	38.0 (0.8)
Normal-appearing white matter (total)	38.5 (0.6)	38.4 (0.5)	38.5 (0.4)	38.4 (0.4)	38.5 (0.3)
Lesions (total)	NA	NA	33.1 (2.3)*	33.9 (1.2)*	34.1 (0.8)*

* $P < .001$ as compared with control normal-appearing white matter MTR.

(median, 6; range, 1–51), the mean MTR of the lesions was significantly lower than that of control NAWM (Table 2).

To date, the median follow-up is 12 months (range, 11–15 months), during which time seven patients (26%) have developed clinically definite (four patients) or clinically probable (three patients) MS (20). As in other studies, progression was most likely in those with a greater number of T2 lesions (five of 13 patients with four or more lesions developed MS), although two of the patients who developed MS had normal baseline imaging findings. The NAWM MTR of those in whom MS developed was not significantly different from that of the control subjects (Table 2).

Discussion

In contrast with findings in established MS using similar techniques (3–6), we did not find the MTR in the NAWM of patients with CIS to be reduced. In particular, using an identical MTI sequence and ROI approach in our unit, we found significant reductions in the NAWM MTR of patients with primary progressive MS (6) and of patients with early relapsing-remitting clinically definite MS (21). By contrast, in only one patient in the present CIS study was the mean MTR value of NAWM below the 95% confidence interval of control NAWM MTR.

Our CIS cohort is representative of those previously reported in the literature in terms of the frequency and extent of T2 lesions on brain MR images at presentation. CIS patients with T2 abnormalities have a high risk of developing clinically definite MS, probably on the order of 80% after 10 years (14, 15). Our finding of a normal NAWM MTR in this high-risk group, and in those who developed clinical MS in the short follow-up period, suggests that widespread NAWM tissue abnormality is not usually present at the earliest clinical stages of MS. Our results concur with those reported in MR spectroscopy studies in CIS patients, in which the major metabolites, including *N*-

acetyl aspartate, were found to be normal in NAWM (22, 23).

A limitation of selecting regions of white matter is that only a small percentage of the total white matter is examined. A more comprehensive assessment of tissue MTR can be achieved using a histographic analysis technique (24–26). Such studies have been performed in CIS patients, but with conflicting results (1, 27, 28). Two of these studies, both administered by the same group of investigators, selected only CIS patients with at least four T2 lesions, thus concentrating on a group with a high likelihood of developing clinically definite MS (1, 27). In the first of their studies (1), 21 CIS patients were seen within 3 months of symptom onset. Global whole-brain histographic analysis showed no significant difference between CIS patients and 20 age- and sex-matched control subjects. However, in their second study, these investigators analyzed MT histograms of segmented normal-appearing brain tissue (incorporating white and gray matter after the extraction of lesions) of 24 CIS patients and found that the average MTR and peak position were significantly lower in patients than in control subjects (27), suggesting that small focal abnormalities beyond the resolution of conventional imaging might be present. The discrepancy in the results of these two studies is unexpected, since the inclusion of lesions, which have a lower MTR than normal-appearing tissue, would be expected to produce a more abnormal histogram. A third study, by another group of investigators, included 11 CIS patients (median T2 lesion load of 1.0 cm³; range, 0–7.6 cm³) and found no differences in MT histographic parameters between patients and control subjects (28).

The difference between the study of Iannucci et al (27), the only authors to report abnormal MTR histograms, and our study, which found normal NAWM MTR using an ROI approach, may have several explanations. First, we did not examine the MTR of gray matter, so it could be that this is where these subtle changes lie. Second, the lesion volumes in the present study were much smaller,

even when only patients with four or more lesions were considered (median T2 lesion volume: present study, 1.1 cm³; study by Iannucci et al, 5.1 cm³), suggesting that the latter study included patients with more pathologically advanced disease (27).

The MTR of the T2 lesions was significantly reduced as compared with control NAWM. For individual patients, the mean lesion MTR ranged from 26.5% units to 36.8% units, implying histologic heterogeneity between patients. Whether patients with a lower mean lesion MTR (which implies more tissue damage, such as demyelination and axonal loss [29]) will have a poorer prognosis will need to be determined by further follow up; the study by Iannucci et al (27) suggested that, after a mean of 33 months' follow-up, they do not.

Conclusion

The present study suggests that focal lesions are the predominant pathologic feature in CIS patients, many of whom are in the early stages of MS. This would be consistent with a hypothesis that focal lesions rather than diffuse NAWM abnormalities are the primary event in MS patients who present with CIS. However, it is possible that MTR is insensitive to subtle NAWM pathologic changes, and that an investigation of NAWM in CIS with other techniques (eg, T1 relaxation, diffusion) would be of interest. It is also possible that subtle focal NAWM changes occur that precede the frank appearance of a lesion, as has been suggested by the occurrence of MTR and diffusion abnormalities in prelesional NAWM for several weeks or months before lesion appearance in patients with clinically definite MS (30–32). Continued follow-up of CIS patients is necessary to determine when the widespread decrease in NAWM MTR that has been found in established MS occurs and whether its development correlates with the extent and nature of focal lesion pathology. The prognostic value of lesion MTR at this early stage also needs to be determined.

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