Correlation of Magnetization Transfer Ratio with Clinical Disability in Multiple Sclerosis

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We performed spin echo magnetic resonance imaging with and without application of an off-resonance saturation pulse in 43 patients with multiple sclerosis (MS), 10 age-matched controls, and 4 elderly asymptomatic patients with the radiological diagnosis of small-vessel disease. Magnetization transfer (MT) ratio images were obtained from these. All MS subgroups (primary progressive, secondary progressive, benign, early relapsing–remitting) showed significantly lower average lesion MT ratios than small-vessel disease patients. Secondary progressive MS patients showed significantly lower lesion MT ratios than those with benign disease, and there was an inverse correlation of disability with average lesion MT ratio. The degree of reduction of MT ratios is an indicator of the extent of tissue destruction. Thus, reduced MT ratios in MS may provide an indication of the degree of demyelination and axonal loss, both of which are likely to cause functional deficits in MS. We conclude that MT measurement is (1) a robust quantitative method that may increase the pathological specificity of magnetic resonance imaging, (2) has the potential to differentiate demyelination in MS from less destructive pathological changes, and (3) may be useful in monitoring modifications in tissue structure brought about by treatment.

Gass A, Barker GJ, Kidd D, Thorpe JW, MacManus D, Brennan A, Tofts PS, Thompson AJ, McDonald WI, Miller DH. Ann Neurol 1994;36:62–67

The ready visualization of white matter plaques by conventional brain magnetic resonance imaging (MRI) helps to establish an accurate and early diagnosis in multiple sclerosis (MS) [1–3]. However, there is little or no correlation between total MR brain lesion load and clinical disability [4–6]. Possible explanations for this discrepancy include variations in disease duration, inaccuracies in the techniques for quantitating brain lesion load, the presence of spinal cord lesions that may account for much of the patient's locomotor disability, and finally, pathological heterogeneity of the MR visible brain lesions [7].

Proton density, T1 and T2 relaxation times are the main determinants of tissue contrast in conventional MR images. Only relatively mobile or *free* water protons are MR "visible" on conventional T1- or T2-weighted images. Immobile water protons, which are tightly bound to macromolecular structures such as proteins and lipid membranes, have extremely short T2 relaxation times (<1 msec) and are therefore not visible [8]. On conventional T2-weighted brain MRI, MS lesions are seen by virtue of an increase in concentration and mobility of free water. This may occur, directly or indirectly, as a consequence of any of the major pathological features of MS lesions, i.e., edema, inflammation, demyelination, gliosis, and axonal loss. It is not possible to distinguish these features individually on a standard image. Persistent functional disability in MS is likely to be due to demyelination and axonal loss, and therefore, it is of particular relevance to develop nuclear magnetic resonance (NMR) techniques that monitor these features specifically.

Exchange of magnetization between free water and *bound* water after selectively saturating the bound water pool reduces T1 and the equilibrium magnetization. The magnitude of this effect is an indicator of the amount and complexity of macromolecular structure present in the observed volume unit and is called the magnetization transfer (MT) ratio [9–11]. Myelin is the most complex macromolecular structure in normal white matter and it has therefore been suggested that the extent of demyelination in MS might be quantified by measuring MT ratios [12]. We therefore performed MT imaging on a group of MS patients to investigate the relationship of MT ratio abnormalities and the patients' clinical features. We also investigated a small group of patients with a radiological diagnosis of small-vessel disease.

Patients and Methods

We obtained proton density, T2-weighted, and MT images of the brain in 43 patients with clinically definite MS [13]

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Received Oct 26, 1993, and in revised form Dec 21. Accepted for publication Dec 22, 1993.

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who attended the National Hospitals for Neurology and Neurosurgery; 10 had a primary progressive course, 11 secondary progressive, 11 benign, 11 early relapsing–remitting disease course.

The subgroups were defined as follows: (1) early relapsing–remitting, a history of relapses and remissions of less than 5 years' duration without gradual deterioration; (2) benign, relapsing–remitting disease of at least 10 years' duration and with disability on the Kurtzke expanded disability status scale (EDSS) [14] ≤3; (3) secondary progressive, an initial relapsing–remitting course, with subsequent progressive deterioration for at least 6 months, with or without superimposed relapses; and (4) primary progressive, progressive deterioration from the onset, without any relapses or remissions [15].

In addition, we studied 10 age- and sex-matched normal controls (3 male/7 female) and 4 asymptomatic patients with white matter lesions and a radiological diagnosis of small-vessel disease. These 4 patients were older, had neither symptoms nor signs of previous neurological disease, but all had vascular risk factors (e.g., hypertension or smoking).

Each patient gave a full history and underwent a full neurological examination at the time of the MRI examination, from which Kurtzke Functional Systems and EDSS scores were obtained. The study was approved by the National Hospitals medical ethics committee and informed consent was obtained from each subject involved in the study.

Magnetic Resonance Imaging

Imaging was performed on a 1.5-T unit (Signa, General Electric, Milwaukee, WI). After 3 localizing scans in the axial, coronal, and sagittal planes, 8 axial slices through the hemispheres were obtained aligned with the bicommissural line.

Dual echo images were obtained using a spin echo sequence (SE = 1,500/32/80, 8 slices, 5-mm thickness, 2.5-mm gap, 256 × 128 matrix, scan time = 10 min) both with and without application of a saturation prepulse to saturate the broad resonance of immobile macromolecular protons. The applied pulse was a four-lobed, 64-msec sinc pulse, 2-kHz off-water resonance. The energy deposited by this pulse provided measurable differences between saturated and unsaturated images and ensured a good signal-to-noise ratio in the calculated MT image. To ensure exact coregistration of the saturated and unsaturated images, scans with and without saturation were interleaved for each phase encoding step.

From the 2 images, i.e., without (Mo) and with (Ms) saturation pulse, quantitative MT ratio images were derived pixel by pixel according to the equation: MT ratio = (Mo − Ms)/Mo. Signal intensities in the calculated image represented the amount of MT between the free and bound water pool.

In healthy controls, MT ratios were calculated from a 22-mm^2 region of interest in 5 white matter (frontal, parietal, and occipital lobes, genu and splenium corpus callosum) and 2 gray matter (frontal cortex and putamen) areas in each hemisphere, and from a single area of ventricular cerebrospinal fluid (CSF). White matter regions of interest were selected at a maximum distance from gray matter and ventricle to avoid partial volume contamination. The regions of interest were placed anterolateral to the frontal horn in the frontal lobes, posterior to the trigones in the occipital lobes, and in the centrum semiovale in the parietal lobes slightly above the level of the lateral ventricles.

In all patients the total lesion area was calculated from the proton density–weighted images using a semiautomated lesion detection program [16]. This technique has been shown to have an intrarater reliability of 5% [16]. The average MT ratios of the total lesion area were calculated from every patient. MT ratios were also calculated from 22-mm^2 regions of interest in the patients' normal appearing white matter (NAWM) in the frontal, parietal, and occipital lobes and from the genu and splenium of the corpus callosum.

Quality assurance scanning was undertaken using a phantom containing 10% and 20% bovine ovalbumin at weekly intervals and in a human volunteer at the beginning and end of the study. Total lesion areas and average MT ratios of lesions and NAWM were compared between the clinical subgroups and controls using the two-sample Student's t test. Spearman's rank correlation coefficient was used to assess the relationship between other clinical and MR parameters.

Results (See Table)

Quality Assurance

Phantom MT ratios were measured over a 4-month period, during which time they varied by less than 1%.

Controls

Gray matter MT ratios were all between 23% and 24%. White matter MT ratios varied slightly according to site, with the following mean values: genu corpus callosum 33.1%, splenium corpus callosum 32.2%, frontal white matter 31.8%, occipital white matter 30.1%. The SD was below 1% in all brain regions studied, and the MT ratio of ventricular CSF was 0%.

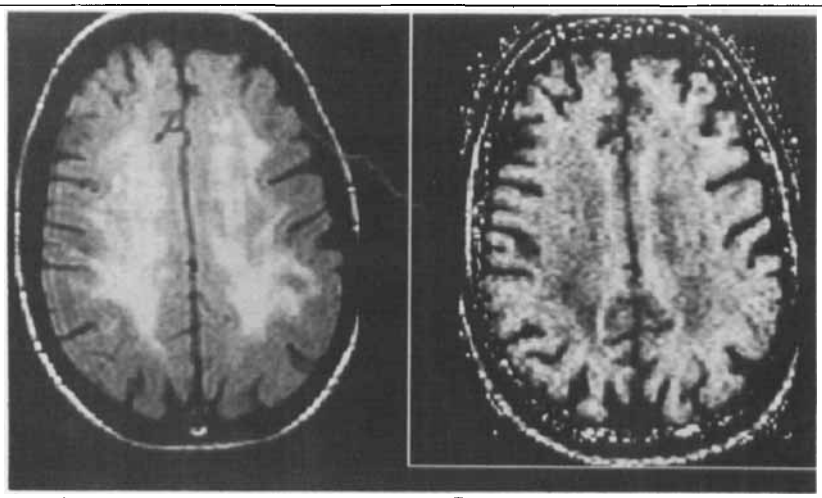
Patients

The total lesion areas were not significantly different between any of the MS subgroups and the small-vessel disease group. However, consistent with previous reports, the primary progressive MS subgroup had a lower mean total lesion area than either the benign or secondary progressive subgroup [15].

The average MT ratios of lesions were significantly lower in all MS groups than in the small-vessel disease group (primary progressive MS compared with small-vessel disease, $p = 0.008$; secondary progressive MS compared with small-vessel disease, $p = 0.0001$; benign MS compared with small-vessel disease, $p = 0.017$; early relapsing–remitting MS compared with small-vessel disease, $p = 0.0012$) (Figs 1–3).

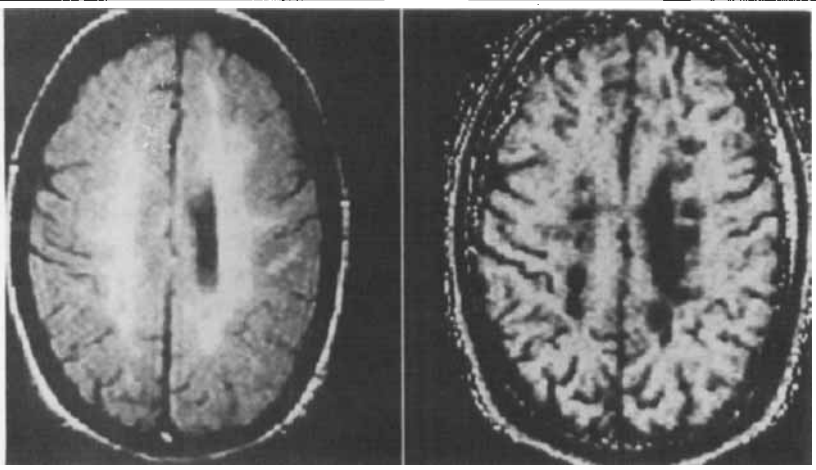
The average lesion MT ratio was significantly higher in the subgroup of benign MS compared with the secondary progressive MS subgroup ($p = 0.01$) and in mildly disabled (EDSS ≤3) compared with severely disabled (EDSS ≥5) MS patients ($p = 0.001$) (see Figs 1, 2).

In the whole MS cohort, there was an overall correlation of total lesion area with disability (EDSS) (SRCC



A B

Fig 1. A 49-year-old female, benign multiple sclerosis, disease duration of 24 years, expanded disability status scale score of 3.0. (A) Proton density–weighted image with extensive confluent white matter abnormalities. (B) Corresponding magnetization transfer (MT) ratio image shows only mildly decreased intensity in most lesion areas. Average lesion MT ratio = 24.8%.



A B

Fig 2. A 31-year-old female, early relapsing–remitting multiple sclerosis, disease duration of 4 years, expanded disability status scale score of 6.5. (A) Proton density–weighted image demonstrates extensive, confluent white matter abnormalities. (B) Corresponding magnetization transfer (MT) image shows markedly reduced intensities (i.e., very low MT ratios) in multiple, well-circumscribed lesion areas. Average lesion MT ratio = 21.7%.

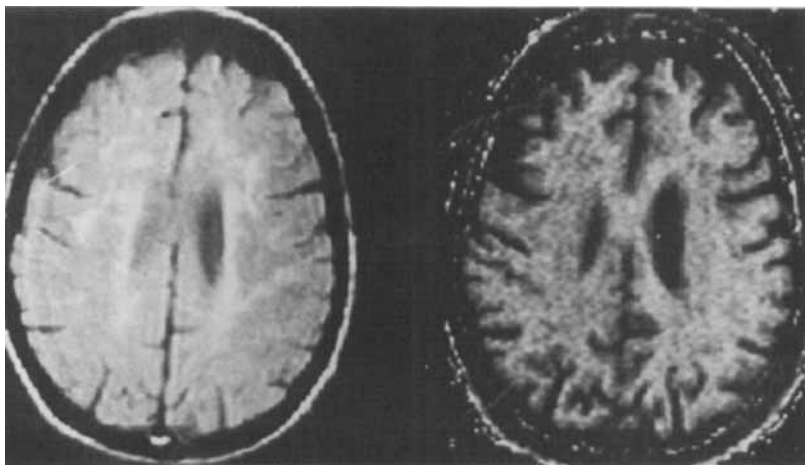
= 0.33, $p = 0.03$) and a stronger inverse correlation of average MT ratio with EDSS (SRCC = −0.44, $p = 0.006$) (Fig 4); there was a weaker inverse correlation between total lesion area and average lesion MT ratio (SRCC = −0.32, $p = 0.04$).

The individual MS lesions displayed a much wider range of MT ratios (MT ratio range, 0–28%) than lesions in the small-vessel disease group (MT ratio range, 20–28%). Very destructive lesions (MT ratios <10%) were seen only in MS patients.

The NAWM MT ratio in all MS patients (31.0%) was slightly lower than in healthy controls (31.4%) and patients with small-vessel disease (31.2%), but the difference was not statistically significant. In MS patients, the average NAWM MT ratio was correlated with total lesion area (SRCC = −0.495, $p = 0.001$), but not with EDSS (SRCC = 0.044, $p > 0.2$) or disease duration (SRCC = 0.1, $p > 0.2$).

Discussion

Previous cross-sectional studies have generally shown little or no correlation between the extent of MRI brain lesions and clinical disability in MS. Although the present study shows a moderate correlation between total lesion area and disability, it confirms that lesion extent in the cerebral hemispheres is not the sole ex-



A B

Fig 3. A 67-year-old asymptomatic female, radiological diagnosis of small-vessel disease. (A) Proton density–weighted image with extensive white matter abnormalities. (B) Corresponding magnetization transfer (MT) ratio image shows only mildly reduced intensities in all lesion areas. Average lesion MT ratio in (A) = 27.6%.

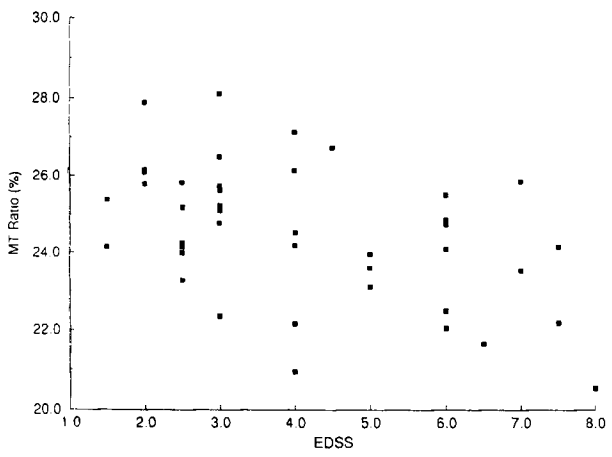


Fig 4. Multiple sclerosis: regression plot of average lesion magnetization transfer ratios (%) versus expanded disability status scale (n = 43).

planation of disability, i.e., some disabled patients had small total lesion areas, and some nondisabled patients had large total lesion areas (Table).

One explanation for the weak association between cerebral total lesion area and disability might be pathological heterogeneity of lesions. On conventional MRI, which probes free water only, it is not possible to determine the amount of demyelination and/or axonal loss, the pathological substrates of disability. However, MT images provide a direct indication of the amount of bound water, and hence, the amount of structured material in tissue [9, 10]. In normal white matter, the MT contrast effect is likely to be significantly influenced by the concentration, chemical structure, and mobility of myelin constituents [17, 18]. It is therefore possible that measurement of MT ratios provides an indication of the amount and integrity of myelin.

The absolute MT ratios observed depend on the exact imaging sequence parameters [19] and differences in the technique can account for the different MT ratios obtained from normal white and gray matter when the present results are compared with an earlier study [12]. However, the excellent internal reproducibility of the quantitative MT ratio measurements was clearly demonstrated using phantom measurements for quality assurance (<1% variation).

In normal controls, the same region in either gray or white matter showed very little interindividual variation in MT ratio with a standard deviation below 1% in all regions studied. There were, however, differences in MT ratios between different white matter regions, the highest ratio being in the genu of the corpus callosum and the lowest in occipital white matter. Possible explanations for the observed variation could be differences in fiber density, the extent of myelination, or varying amounts of bound water in myelin.

Low MT ratios imply a major loss of tissue structure. In MS, this could be due to either demyelination or axonal loss, and a correlation might therefore be predicted with disability. A strong inverse correlation between lesion MT ratios and EDSS was indeed seen in the present study, the correlation being stronger than that between total lesion area and EDSS. While the weak inverse correlation between lesion MT ratios and total lesion area may indicate that the former is influenced by partial volume effects, it may also indicate that extensive disease is associated with more tissue destruction.

While the results suggest that more disabled patients have a more destructive pathology, the relationship of lesion MT ratio and EDSS is not absolute, with some overlap in the range of lesion MT ratios seen in minimally and severely disabled groups. This observation

Clinical and Magnetic Resonance Imaging Findings in Patient Subgroups

	ERR (n = 11)	BE (n = 11)	SP (n = 11)	PP (n = 10)	SVD (n = 4)	NC (n = 10)
Age (range; yr)	28.7 (22–44)	45.8 (31–60)	42.1 (29–51)	42.4 (32–48)	63 (57–67)	41.2 (32–56)
DiDu (yr)	3 (1.5–4.5)	21.4 (14–32)	11.9 (4–22)	10.2 (5–22)	—	—
EDSS (range)	2.9 (1.5–6.5)	2.7 (1.5–3.0)	6.1 (5.0–8.0)	4.8 (3.0–7.0)	—	—
NAWM %	31.0	30.8	30.9	31.4	31.2	31.4
Range	29.8–31.8	29.9–31.8	29.7–32.3	30.4–32.8	30.8–31.9	30.7–32.2
TLA mm^2	2,824	3,490	5,003	2,696	3,138	—
Range	186–10,772	538–13,096	343–14,270	135–6,035	1,431–5,447	—
MTR %	24.8	25.4	23.7	24.2	26.7	—
Range	21.7–27.9	23.3–27.1	20.5–25.6	20.1–27.1	26.3–27.7	—

ERR = early relapsing remitting multiple sclerosis (MS); BE = benign MS; SP = secondary progressive MS; PP = primary progressive MS; SVD = small-vessel disease; NC = normal controls; DiDu = disease duration; EDSS = expanded disability status scale; NAWM = normal appearing white matter; TLA = total lesion area; MTR = average lesion magnetization transfer ratio.

may have several explanations. First, the lesions studied were all in the cerebral white matter, where they were less likely to cause locomotor disability than lesions in the brainstem, cerebellum, or spinal cord. Second, the hypothesis that demyelination is the sole determinant of MT ratios may be an oversimplification; other pathological features such as gliosis and edema may also be important. Third, even if demyelination per se is the major determinant of low MT ratios, it may not necessarily be the major cause of fixed disability. Experimentally, it has been shown that continuous conduction can develop in demyelinated axons in both the peripheral [20] and central nervous system [21] and, despite complete demyelination within the optic nerve, vision can be retained in some patients [22, 23].

An alternative and likely cause of fixed disability is axonal loss, which is sometimes present to a considerable degree in chronic lesions [24]. However, MT ratios in areas of complete demyelination may well be similar, whether or not there is significant axonal loss. In the light of such uncertainties, direct correlation of MT imaging with pathology is clearly needed, both in appropriate experimental models and in MS.

Despite the caveats regarding pathological specificity and MT ratios, the present study nevertheless sheds some light on the mechanisms underlying different disease courses in MS. In 90% of patients, the early pattern is one of relapse and remission, which for most patients evolves eventually into either a benign course with few relapses and minimal disability or a secondary progressive course with increasing disability. The secondary progressive group in the present study displayed significantly lower lesion MT ratios than the benign group, consistent with a more destructive pathological process.

About 10% of patients have primary progressive MS [25], and despite being disabled, they usually have smaller total lesion areas than nondisabled benign patients [6]. A possible explanation for this discrepancy is that the primary progressive group has more destructive lesions. The present results support this hypothesis in that while primary progressive patients had a lower mean total lesion area than benign patients (2,696 mm^2 vs 3,490 mm^2), they also had lower average lesion MT ratios (24.2% vs 25.4%). However, these group differences were not statistically significant, and further study of a larger cohort is required to consolidate this preliminary observation.

In comparison with MS, the MT ratios were significantly higher in white matter lesions thought to be due to vascular disease. Postmortem studies in elderly patients who had displayed asymptomatic white matter abnormalities on MRI suggest a less destructive pathology, with atrophic changes in axons and myelin, associated with an increased extracellular space [26, 27], which is possibly also due to loss of glial cells [28], rather than the complete loss of myelin characteristically seen in MS [24, 29]. However, the number of patients with vascular disease in the present series was small, they were much older than the MS patients, and the influence of aging per se on MT ratios is not yet known. Further study of a larger, age-matched cohort is required to consolidate these preliminary observations.

Abnormalities in the NAWM have been identified using MR proton spectroscopy [30] and imaging studies analyzing T1 and T2 relaxation times [31, 32]. In addition, a recent study showed significantly lower MT ratios in NAWM [12] of MS patients compared with healthy controls. We found no significant differences between normal controls and MS patients, although the mean MT ratios were lower in the NAWM in MS patients. The different observation may reflect methodological differences, or that MT ratios are less sensitive than other MR parameters to the subtle pathological abnormalities known to occur in NAWM [33]. Further studies are needed that compare MT ratios, proton spectroscopy, and relaxation time measurements in NAWM.

The strong correlation of lesion MT ratios with dis-

ability suggests that MT imaging will be useful in assigning prognosis in MS. A prospective follow-up study of patients scanned close to clinical onset is needed to evaluate properly its prognostic role.

Because of the frequent detection of asymptomatic disease activity, conventional MRI is now widely used to monitor new treatments in MS [34–36]. MT imaging can be performed in clinically acceptable times on almost any scanner, and MT ratio measurements are quantitative, highly reproducible, and perhaps give an indication of pathological severity. Thus, MT imaging should have a particularly valuable role in therapeutic monitoring.

The NMR Research Group is funded by a generous grant from the Multiple Sclerosis Society of Great Britain and Northern Ireland, and supported by the Brain Research Trust.

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