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AJNR Am J Neuroradiol 1994, 15 (8) 1569-1574

<http://www.ajnr.org/content/15/8/1569>

This information is current as
of August 24, 2025.

Magnetization Transfer: A Potential Method to Determine the Age of Multiple Sclerosis Lesions

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PURPOSE: To determine whether magnetization transfer contrast can differentiate acute from chronic lesions in multiple sclerosis. **METHODS:** Thirteen patients with multiple sclerosis and eight healthy patients were studied with MR using a 0.1-T system. Relatively T2-weighted spin-echo images were obtained without and with magnetization transfer contrast. The magnetization transfer effect of multiple sclerosis lesions was calculated and compared with the ages of the lesions. The magnetization transfer effect of normal-appearing white matter in patients with multiple sclerosis was calculated and compared with the magnetization transfer effect of white matter in healthy volunteers. Statistical analysis was performed. **RESULTS:** White matter in the healthy volunteers had values from 0.40 to 0.45. Normal-appearing white matter in the patients with multiple sclerosis had magnetization transfer effect values ranging from 0.41 to 0.45. Multiple sclerosis plaques of less than 1 year's duration had magnetization transfer effect values ranging from 0.05 to 0.26; older plaques had values from 0.25 to 0.41. The difference in the distributions of these values for acute and chronic multiple sclerosis plaques is statistically significant. **CONCLUSION:** Current imaging modalities do not differentiate acute multiple sclerosis lesions from chronic ones. Our data on magnetization transfer show a statistically significant difference in magnetization transfer effect values between lesions of less than 1 year's duration and older lesions. The different values may correspond to the histologic changes of multiple sclerosis plaques over time. Magnetization transfer may be a reliable method for determining the age of multiple sclerosis lesions.

Index terms: Sclerosis, multiple, Magnetic resonance, technique; Magnetic resonance, tissue characterization; Brain, magnetic resonance

AJNR Am J Neuroradiol 15:1569-1574, Sep 1994

Multiple sclerosis is a demyelinating disorder typified by relapsing and remitting neurologic symptoms. Magnetic resonance imaging (MRI) is the most sensitive modality for the detection of multiple sclerosis lesions but lacks specificity (1). Gadolinium-enhanced MRI demonstrates multiple sclerosis lesions that are active in terms of a disrupted blood-brain barrier (2, 3) but does not differentiate demyelination from edema (4). No current imaging modality can determine the age, and by inference the histopathologic state, of multiple sclerosis lesions.

Magnetization transfer contrast is a method of creating a unique type of tissue contrast in MRI based on the transfer of magnetization between free protons in water and bound protons associated with macromolecules such as proteins (5-8). In a magnetization transfer sequence, an off-resonance pulse is applied before a standard imaging sequence to saturate the magnetization of bound protons. The bound proton pool interacts with the free proton pool by chemical exchange and cross-relaxation mechanisms to transfer saturation (6), the extent of which is dependent on the protein content of the tissue and on the efficiency of the protein/water interactions (9). The net effect is signal suppression in all tissues to varying degrees in relation to macromolecular structure and water content (7, 9, 10). Signal suppression in a given area can be quantified as the magnetization transfer effect. We evaluated the potential of mag-

Received June 11, 1993; accepted after revision December 16.

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AJNR 15:1569-1574, Sep 1994 0195-6108/94/1508-1569

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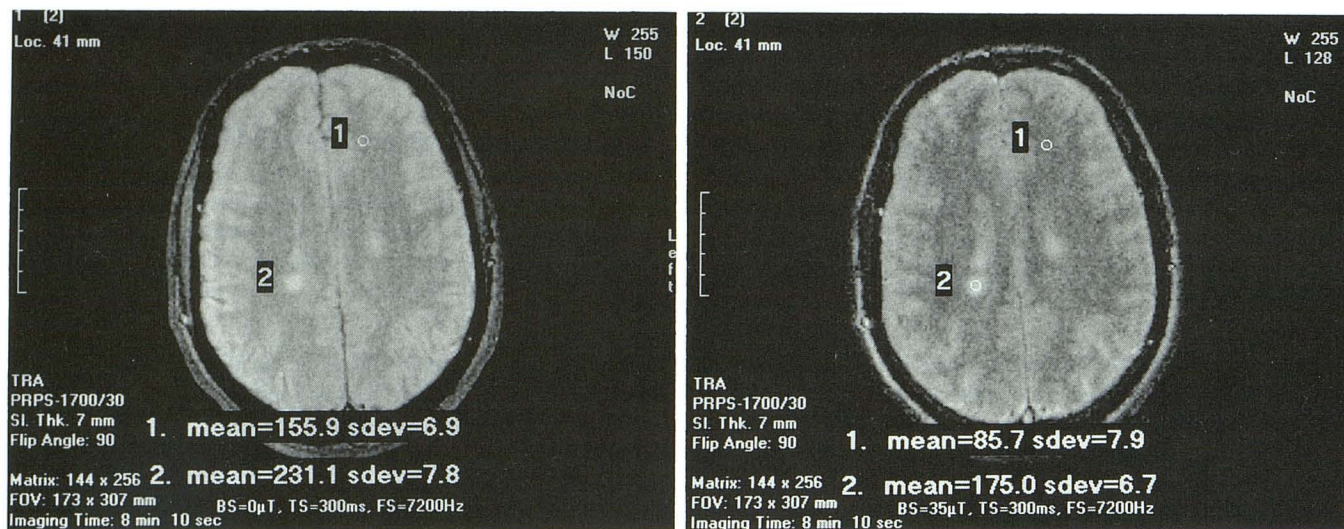


Fig 1. Example of a "mask" image in a patient with multiple sclerosis. The scan was taken at a level just superior to the lateral ventricles. Region of interest cursors have been placed on normal-appearing white matter in the left frontal lobe and on a plaque in the right parietal lobe. Each region's mean signal intensity value and standard deviation is shown at the bottom of the image.

Fig 2. Corresponding magnetization transfer image. Signal intensity in plaques is suppressed less than in surrounding brain tissue, making plaques appear relatively brighter. (The apparently increased signal intensity of cerebrospinal fluid on the magnetization transfer image relative to the mask image is an artifact of the computer software used in image processing.)

netization transfer to differentiate acute multiple sclerosis lesions from chronic lesions.

Methods

Subjects

Eight healthy volunteers, 4 women and 4 men ages 25 to 44 years, and 13 patients with known multiple sclerosis, 8 women ages 21 to 51 and 5 men ages 26 to 50, were evaluated. Diagnoses were based on clinical symptoms and MR findings, with additional evidence from cerebrospinal fluid analysis, visual evoked-potential testing, and electromyography testing. Some of the patients with multiple sclerosis were already part of a double-blind interferon study.

All patients with multiple sclerosis had multiple prior annual high-field (1.5-T) MR exams, performed according to a protocol used at our institution for evaluation of patients with multiple sclerosis (T2-weighted spin-echo images with parameters 2200/35–90/1 [repetition time/echo time/excitations] in standardized axial and coronal planes). Some patients had additional exams, the shortest interval between exams being 2 months. All patients had high-field exams within 1 day to 1 week of the magnetization transfer study. These exams were used to estimate ages of the multiple sclerosis plaques. The most recent prior exam on which a lesion was not seen on either axial or coronal images was used to determine the maximum possible age of a lesion. An arbitrary separation of lesions into those less than 1 year's duration and greater than 1 year's duration was used for purposes of analysis.

Data

The magnetization transfer exams were performed on a 0.1-T system. For each patient, preliminary relatively T2-weighted spin-echo (1700/30/1) axial images of the whole brain were obtained as in the high-field exams to localize areas of interest. For the actual magnetization transfer exam, a single-section "mask" image was obtained without the magnetization transfer parameters followed by a magnetization transfer image with the parameters applied. (Figs 1 and 2) Both images used the same relatively T2-weighted sequence (1700/30/1), with a section thickness of 7 mm and a 162×256 matrix. For the magnetization transfer images an off-resonance pulse was applied to every other repetition time during image acquisition. Parameters for the off-resonance pulse were 7.2 kHz offset, amplitude $0.35 \mu\text{T}$, and duration 300 milliseconds.

Signal-intensity values were measured for comparable regions of interest on the mask image and on the magnetization transfer image. Regions of interest were at least 4×4 pixels and placed such that measured signal intensities had standard deviations less than 10 U. In the healthy volunteers, regions of interest were selected in deep white matter at multiple sites. In the patients with multiple sclerosis, regions of interest were selected in plaques and in normal-appearing white matter. All plaques were less than 1 cm. The magnetization transfer effect value for a given region of interest was calculated using the equation $(M_O - M_S)/M_O$, where M_O is the measured signal intensity on the mask image and M_S is the measured signal intensity on the magnetization transfer image. This magnetization transfer effect value represents the percentage by which signal intensity is decreased by the off-resonance pulse.

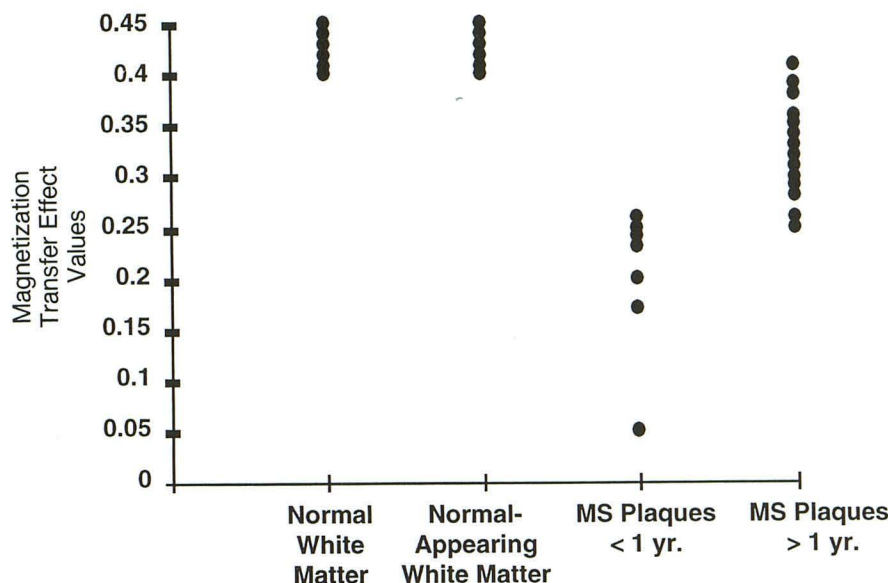


Fig 3. Scattergram plotting of magnetization transfer effect values (vertical axis) for white matter in healthy volunteers, normal-appearing white matter in patients with multiple sclerosis (MS), plaques less than 1 year old in patients with multiple sclerosis, and plaques more than 1 year old in patients with multiple sclerosis.

Statistics

We interpreted our data from the perspective of receiver operating characteristic analysis, which describes the ability of a diagnostic procedure to differentiate two complementary states of truth (11). In our study, the two states of interest were lesion age less than 1 year and lesion age greater than 1 year. We used the area under the receiver operating characteristic curve as an index to summarize the accuracy of magnetization transfer effect in classifying multiple sclerosis lesion age into these two groups. This index can be interpreted as the average sensitivity that a diagnostic procedure provides if its specificity is chosen randomly between 0% and 100%, or, equivalently, as the average specificity of the procedure if sensitivity is chosen randomly (11). The value of the A_z (area under the curve) and its standard error were estimated by techniques described by Hanley and McNeil (12). However, this standard error cannot be used to test the null hypothesis that magnetization transfer effect provides no information in classifying multiple sclerosis lesion age (ie, that the true value of the area under the curve is 0.5), because the standard error of estimates of the A_z depends on the true value. Therefore, in a supplementary analysis, we used a nonparametric method described by Hanley and McNeil (12) to calculate the amount by which estimates of the A_z would vary if the population distributions of magnetization transfer effect values were the same in both groups. We then used the resulting standard deviation in a normal-deviate test to evaluate the null hypothesis that the true value of the area under the curve was 0.5, which is equivalent to the normal approximation of the Mann-Whitney test for two independent samples (13).

Results

White matter in the healthy volunteers had magnetization transfer effect values ranging

from 0.40 to 0.45. Normal-appearing white matter in all of the patients with multiple sclerosis had magnetization transfer effect values ranging from 0.41 to 0.45. The magnetization transfer effect value of cerebrospinal fluid was less than 2%, corresponding to minimal bleed-over of saturation on free-water protons.

Nine plaques of less than 1 year's duration were identified in 4 patients with multiple sclerosis. These had magnetization transfer effect values ranging from 0.05 to 0.26. Thirty-two plaques of greater than 1 year's duration were identified in 10 patients with multiple sclerosis. These had magnetization transfer effect values ranging from 0.25 to 0.41. These results are shown graphically in Figure 3.

By using techniques described by Hanley and McNeil (12), we estimated the receiver operating characteristic area index and its standard error to be 0.993 and 0.02, respectively. A nonparametric calculation described by the same authors (12) indicated that, with 9 and 32 lesions in samples for the two groups, estimates of the A_z would vary with a standard deviation of 0.11 if the true value of the area were 0.5 (ie, according to the null hypothesis that magnetization transfer provides no information in classifying multiple sclerosis lesion age). Thus an appropriate statistic for testing the null hypothesis is $(0.993 - 0.5)/0.11 = 4.48$, which corresponds to $P < .00001$ according to the Mann-Whitney test for two independent samples (13). Although this calculation does not take into account possible correlation between magnetiza-

tion transfer effect values of different lesions in a given patient, a similar calculation, which assumes that correlation to be perfect, yields $P < .01$. We conclude with high confidence that magnetization transfer effect value is associated with the age of a multiple sclerosis lesion.

Discussion

The transverse (T2) relaxation of the central nervous system has been shown in animal models to consist of distinct components corresponding to extraaxonal water protons, axonal water protons, intramyelinic water protons, and protons possibly associated with mobile lipids in the myelin sheaths (14). In multiple sclerosis, the T2 relaxation times of plaques are increased and show predominantly biexponential decay curves (15, 16), as opposed to the monoexponential distribution of normal white matter (17). The faster-relaxing T2 component probably represents the more-bound, myelin-associated water compartment in white matter; the second compartment probably represents the less-bound interstitial water (18). This suggests that contributions to T2 relaxation come from demyelinated fibers, remaining myelinated fibers, edema, and gliosis (16). That the prolongation of transverse relaxation in multiple sclerosis corresponds to alterations in central nervous system water compartmentalization is further supported by the fact that water-diffusion coefficients are increased in patients with multiple sclerosis (19). This increase is greater in acute lesions than in chronic ones, possibly reflecting predominance of demyelination acutely and gliosis chronically (20). Normal-appearing white matter in patients with multiple sclerosis also has been shown to have transverse relaxation times longer than normal (15–17); however, the values overlap considerably with normal values (15), and the decay curves are more likely to be monoexponential (17). This may reflect the early histopathologic changes of multiple sclerosis at a microscopic level.

Magnetization transfer contrast is a unique type of MR contrast based on the exchange of magnetization in tissues between the proton pool associated with free or mobile water and the proton pool associated with immobile water or macromolecules (6). An off-resonance pulse is applied before an imaging sequence to saturate the bound proton pool. Magnetization is

transferred to the free-proton pool by cross-relaxation and chemical exchange mechanisms (6). The net effect is signal suppression in all tissues, the degree of which is dependent on the efficiency of these mechanisms and varies with tissue composition (21). The surface structure of myelin consists of hydrophilic cholesterol hydroxyl groups projecting into the aqueous phase, with hydrophilic phosphate groups projecting out further, forming depressions that can hold water molecules. This geometry is ideal for magnetization transfer between the water protons and the hydroxyl protons (22). The final image contrast or magnetization effect is also affected by the amplitude, duration and frequency of the pulse (8), as well as by the field strength (21). Technical aspects for clinical applications of magnetization transfer have been discussed in detail by Hajnal et al (5).

The consistently narrow range of magnetization transfer effect values for white matter in the healthy volunteers indicates the reproducibility of the magnetization transfer effect in the brain. This has been shown by other investigators as well (4, 10). It is likely that magnetization transfer effect values are characteristic for normal brain (21). The data presented here show a statistically significant temporal distribution of magnetization transfer effect values for multiple sclerosis plaques, which suggests a relation to the temporal course of the disease's histopathologic changes. The early histologic stages of multiple sclerosis consist of swelling and fragmentation of the myelin sheath, followed by phagocytosis of the myelin (23). This is associated with an inflammatory reaction and edema (4). The chronic stages show absence of myelin, proliferation of astrocytes, and eventual development of fibrous gliosis (23). It is possible that these histologic changes disrupting the myelin structure are reflected in the magnetization transfer effect values, with lower values corresponding to edema and demyelination and higher values to gliosis. Although the changes in T2 relaxation values seem to be related to the histopathologic changes in multiple sclerosis plaques, such a relation has yet to be documented for magnetization transfer effect values.

In our study, values for normal-appearing white matter in the patients with multiple sclerosis were similar to those in healthy volunteers. This differs from a study by Dousset et al (4), in which the average magnetization transfer effect

values of normal-appearing white matter in 15 patients with multiple sclerosis were lower than values in healthy subjects. However, 3 of the patients in that study had normal-appearing white matter magnetization transfer effect values within the normal range. The discrepancy between the two studies may be explained by the small number of patients in both studies, possibly skewing results in either case. It also may be caused by sampling of white matter with microscopic disease in their study and white matter without involvement in our study. Some of our patients were involved in a double-blind study in which they may have been receiving either immunosuppressive therapy or placebos, possibly affecting the magnetization transfer effect values of their normal-appearing white matter. We do not have information regarding which patients were on actual therapy; however, it is unlikely that this affected magnetization transfer effect values, because values were the same as in the patients with multiple sclerosis who were not in the study.

Age assignment for the multiple sclerosis plaques was an arbitrary division of less than or greater than 1 year based on retrospective evaluation of prior high-field MR exams, as previously discussed. Lesions visible on the low-field exams were assumed to be visible on the high-field exams, because high-field MR has sensitivity equal to or greater than low-field MR for the detection of white matter abnormalities (24). Exams were limited to single-section acquisitions for the magnetization transfer images because of problems with cumulative saturation in multisection acquisitions. Consequently, only one or two images could be obtained for each patient.

Conclusion

The ability to discern the age, and thereby the histologic stage, of multiple sclerosis lesions is of clinical importance in that acute edematous lesions would be more likely to respond to medical therapy than chronic gliotic ones. No current imaging modality is able to show this distinction. Dousset et al speculated that the wide range of magnetization transfer effect values in their patients with multiple sclerosis indicated lesions of differing ages and grades of myelination (4). A search of the literature on magnetization transfer showed no other reports that at-

tempt to show a temporal correlation of magnetization transfer effect values in multiple sclerosis lesions. Our study shows a statistically significant difference in magnetization transfer effect values between lesions of less than 1 year's duration and older lesions. This suggests that magnetization transfer is a potential method for differentiating acute from chronic lesions in patients with multiple sclerosis.

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