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AJNR Am J Neuroradiol 1995, 16 (9) 1771-1778

<http://www.ajnr.org/content/16/9/1771>

This information is current as
of August 20, 2025.

Improved Detection of Enhancing and Nonenhancing Lesions of Multiple Sclerosis with Magnetization Transfer

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PURPOSE: To determine whether magnetization transfer imaging can improve visibility of contrast enhancement of multiple sclerosis plaques. **METHODS:** Fifty-nine enhancing and 63 nonenhancing lesions in 10 patients with multiple sclerosis were evaluated to calculate contrast-to-noise ratios on conventional T1-weighted and T1-weighted magnetization transfer images. The signal intensity of the lesion and the background (white matter) were measured on precontrast T1-weighted and T1-weighted magnetization transfer images (800/20/1 [repetition time/echo time/excitations]) and on postcontrast T1-weighted and T1-weighted magnetization transfer images. Mean contrast-to-noise ratios was calculated for all lesions. **RESULTS:** The contrast-to-noise ratio was significantly higher for enhancing and nonenhancing lesions on T1-weighted magnetization transfer images than on conventional T1-weighted images. For enhancing lesions, the contrast-to-noise ratio was significantly higher on postcontrast T1-weighted magnetization transfer images, 32 ± 2 compared with 21 ± 2 on conventional T1-weighted images. Fifty of the 59 enhancing lesions were seen on both the T1-weighted and the T1-weighted magnetization transfer images. Nine enhancing lesions were seen only on the postcontrast T1-weighted magnetization transfer images. In addition, of 63 nonenhancing lesions seen on proton-density, T2-weighted, and T1-weighted magnetization transfer images, 16 were not seen on the conventional T1-weighted images. Seven of the 63 nonenhancing lesions and 7 of the 59 enhancing lesions had high signal intensity on the precontrast T1-weighted magnetization transfer images suggestive of lipid signal, a finding not seen on the conventional precontrast T1-weighted images. **CONCLUSION:** Magnetization transfer improves the visibility of enhancing multiple sclerosis lesions, because they have a higher contrast-to-noise ratio than conventional postcontrast T1-weighted images. High signal intensity on both nonenhancing and enhancing lesions noted only on precontrast T1-weighted magnetization transfer suggests a lipid signal was unmasked. If magnetization transfer is used in multiple sclerosis patients, a precontrast magnetization transfer image is necessary.

Index terms: Sclerosis, multiple; Magnetic resonance, contrast enhancement; Magnetic resonance, magnetization transfer

AJNR Am J Neuroradiol 16:1771–1778, October 1995

Multiple sclerosis (MS) is a complex disease with a relapsing and remitting course. Often the extent of the disease seen on magnetic resonance (MR) examination is more dramatic than the clinical symptoms suggest. This indicates

that not all plaques seen on MR images contribute to clinical symptoms, and not all are active (1, 2). The sensitivity of MR for white matter abnormalities has made it the imaging modality of choice for MS. With MR, one can assess the number, size, and location of MS lesions. MR can characterize lesions with T1-weighted, T2-weighted, and now with magnetization transfer relaxation parameters. An underlying assumption is that acute lesions represent potentially reversible disease, whereas chronic lesions (demyelinated) do not. Differentiating these lesions, therefore, has clinical importance in assessing various treatment modalities. On long-

Received October 26, 1994; accepted after revision April 19, 1995.

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AJNR 16:1771–1778, Oct 1995 0195-6108/95/1609–1771

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repetition-time/long-echo-time pulse sequences, both active and nonactive lesions of MS have a hyperintense signal. In vitro relaxation studies indicate an increase in T1 and T2 relaxation times as plaques age (3), but there is no simple correlation between relaxation times and lesion activity. Thus relaxation times do not allow clear distinction between acute and chronic MS lesions (4, 5). New white matter lesions may not be significantly demyelinated and thus may be poorly seen on T1-weighted images but appear as high signal intensity on the T2-weighted images. In addition, lesions may exhibit contrast enhancement and not be visible on T2-weighted images. At present, this highly sensitive technique lacks the specificity to characterize the stage of the disease process, but the combination of multiple parameters may offer the opportunity to separate inflammation and edema from demyelination to assess disease burden.

Contrast enhancement is an important criteria for acuteness and inflammatory activity. The use of gadopentetate dimeglumine allows the differentiation of inflammatory and presumably active from nonactive lesions by revealing disruption of the blood-brain barrier. In MS, the breakdown of the blood-brain barrier is a localized phenomenon and can occur in active plaques or at the periphery of chronic reactivated plaques. Plaques are not homogenous in their stage of disease. The information gained with gadolinium enhancement is thus useful in gauging the activity of MS (1, 2). The ability to distinguish active from nonactive plaques could help in understanding the natural course of the disease and assessing the effect of treatment. Efforts to improve the detection of contrast-enhancing lesions and their differentiation from background white matter on MR imaging have recently led to magnetization transfer imaging (6).

Magnetization transfer imaging has been shown to improve the contrast-to-noise ratios in contrast-enhancing lesions and MS plaques (7-10). We prospectively studied the effect of magnetization transfer on precontrast and postcontrast T1-weighted with magnetization transfer images in MS patients to determine whether magnetization transfer imaging can improve the visibility of MS plaques as measured quantitatively with contrast-to-noise ratios.

Materials and Methods

The study population consisted of 10 patients (4 men, 6 women; age range, 25 to 65 years; average age, 40.2 years) with definite MS diagnosed clinically (Poser criteria) (11) with supporting laboratory data. MR imaging was performed on a 1.5-T unit. The protocol for imaging patients with MS was as follows: (a) sagittal T1-weighted (800/20/1 [repetition time/echo time/excitations]); 5-mm sections with 2.5-mm intersection spacing); (b) axial conventional proton-density and T2-weighted (2000/30,80/2; 4-mm sections with 1.0-mm intersection spacing); (c) axial precontrast T1-weighted, with and without magnetization transfer (800/20/1; 5-mm sections with 1.0-mm intersection spacing); and (d) axial postcontrast T1-weighted with and without magnetization transfer (800/20/1; 5-mm sections with 1.0-mm intersection spacing). The precontrast and postcontrast T1-weighted magnetization transfer sequences were incorporated into this imaging protocol for all patients suspected of having MS since September 1991. All patients signed a written consent form allowing the additional magnetization transfer sequence. Gadopentetate dimeglumine was used at a dose of 0.1 mmol/kg. The postcontrast T1-weighted and T1-weighted magnetization transfer imaging was done in random order. Each of the postcontrast sequences T1-weighted and T1-weighted magnetization transfer is 3 minutes 35 seconds. Thus, a total of approximately 8 to 9 minutes elapsed between infusion of contrast and completion of all postcontrast T1-weighted axial sequences. The patient population was a subset of 29 patients undergoing longitudinal MR examinations since early 1991 (12, 13). These 10 patients had both contrast-enhancing and non-enhancing lesions on conventional T1-weighted and T1-weighted magnetization transfer scans. A total of 20 MR examinations yielded 59 enhancing lesions and 63 nonenhancing lesions. The selection criteria for lesions was contrast enhancement on either T1-weighted or T1-weighted magnetization transfer images, where enhancement was defined as a signal intensity increase between precontrast and postcontrast images. Three to 4 enhancing lesions per MR scan were randomly selected. A similar number of nonenhancing lesions (comparable in size and location) also were selected if they were discrete lesions identified on the T2-weighted (echo time, 80) images and showed no change in signal intensity between precontrast and postcontrast images.

Magnetization transfer was performed with an on-resonance, 0° 1-2-1 binomial pulse (+90, -180, +90) to saturate the restricted hydrogen protons (H_r) pool (14, 15). This pulse has a broad passband with no significant saturation of free hydrogen protons (H_f) and is reasonably insensitive to the B_0 inhomogeneities. After testing a variety of binomial pulses, the 1-2-1 pulse was found to be the best compromise between H_r saturation and H_f bandwidth. A single binomial pulse is applied before each section-selective excitation in this multisection spin-echo sequence. An equal number of sections (18) were acquired in all studies, thereby providing equal saturation pulse

repetition times (800/20/1) (15). The specific absorption rate was well below the Food and Drug Administration limits; average specific absorption rate was 0.04 W/kg, and peak specific absorption rate was 2.53 W/kg for any gram of cranial tissue. Contrast enhancement was quantitatively assessed using contrast-to-noise ratio. The contrast-to-noise ratios were calculated using the following formula:

$$\text{Contrast-to-noise ratio} = \frac{\text{Signal}_{\text{lesion}} - \text{Signal}_{\text{background}}}{\text{Noise}_{\text{background}}}$$

Regular and irregular regions of interest measuring between 0.5 mm² and 25 mm² outlining the area of contrast enhancement were drawn to measure mean signal intensity. The identical region of interest was used for T1-weighted images with and without magnetization transfer and for precontrast and postcontrast images. Lesions were divided into enhancing and nonenhancing groups. Their signal intensities were measured on precontrast and postcontrast T1-weighted and T1-weighted magnetization transfer images. Contrast enhancement was measured as an increase in signal intensity on contrast-enhanced images over the precontrast images for both T1-weighted and T1-weighted magnetization transfer sequences. Nonenhancing lesions were those having a high signal abnormality on proton-density and T2-weighted sequences but no increase in signal intensity on contrast-enhanced images over the precontrast images on both T1-weighted and T1-weighted magnetization transfer sequences. Adjacent normal white matter was used as background to calculate the above two ratios. The signal intensity of the caudate nucleus also was measured to compare it with the signal intensity of the contrast-enhancing lesions. (Of all the normal gray matter structures in the brain, the caudate nucleus had the highest signal intensity.) Noise background was measured as the signal intensity of air (in a region not contaminated by the phase-encode artifact) and divided by the square root of pi (16). Tests for statistical significance (two-tailed *t* test) were applied.

Results

Enhancing Lesions

The average contrast-to-noise ratio of all the contrast-enhancing lesions (Figs 1 and 2) on postcontrast T1-weighted magnetization transfer images was 32 ± 2 (mean \pm standard error of the mean), significantly greater than on the conventional postcontrast T1-weighted images with a average contrast-to-noise ratio of 21 ± 2 ($P < .001$). The average contrast-to-noise ratio of the enhancing lesions on the precontrast images was 16 ± 1 and 4 ± 1 for T1-weighted magnetization transfer and T1-weighted sequences, respectively ($P < .001$) (Table). The

addition of magnetization transfer therefore increased contrast-to-noise ratio on both precontrast and postcontrast images. There was an overall decrease in the mean signal intensity of the enhancing lesions of approximately 12% to 16% on magnetization transfer images compared with the conventional T1-weighted images. The increase in the contrast-to-noise ratio was primarily attributable to a large decrease of $34\% \pm 2\%$ in signal intensity of the background (white matter) on magnetization transfer images. Fifty of the 59 contrast-enhancing lesions were seen on both the T1-weighted and T1-weighted magnetization transfer images. However, in 9 lesions contrast enhancement was visible only on postcontrast T1-weighted magnetization transfer images, not on T1-weighted images.

Nonenhancing Lesions

For nonenhancing lesions (Figs 1 and 2), the contrast-to-noise ratios were not significantly different on precontrast and postcontrast images for both the T1-weighted and T1-weighted magnetization transfer sequences. The contrast-to-noise ratio was significantly higher ($P < .0001$) for nonenhancing lesions on the T1-weighted magnetization transfer than on the conventional T1-weighted images. The magnetization transfer effect without gadopentetate dimeglumine was significant. The nonenhancing lesions did not differ from the enhancing lesions in contrast-to-noise ratio on either the conventional or T1-weighted magnetization transfer precontrast images (Table).

High Signal Lesions

There were a total of 14 (nonenhancing, 7; enhancing, 7) lesions that had a high signal intensity (Fig 2) on the precontrast T1-weighted magnetization transfer images, similar to that of enhancing lesions on the postcontrast images. The 7 nonenhancing lesions showed no measurable or visible change on the precontrast and postcontrast images, whereas the 7 enhancing lesions all had an increase in signal/size on the postcontrast images. These areas of high signal varied from punctate to approximately 15 mm in diameter.

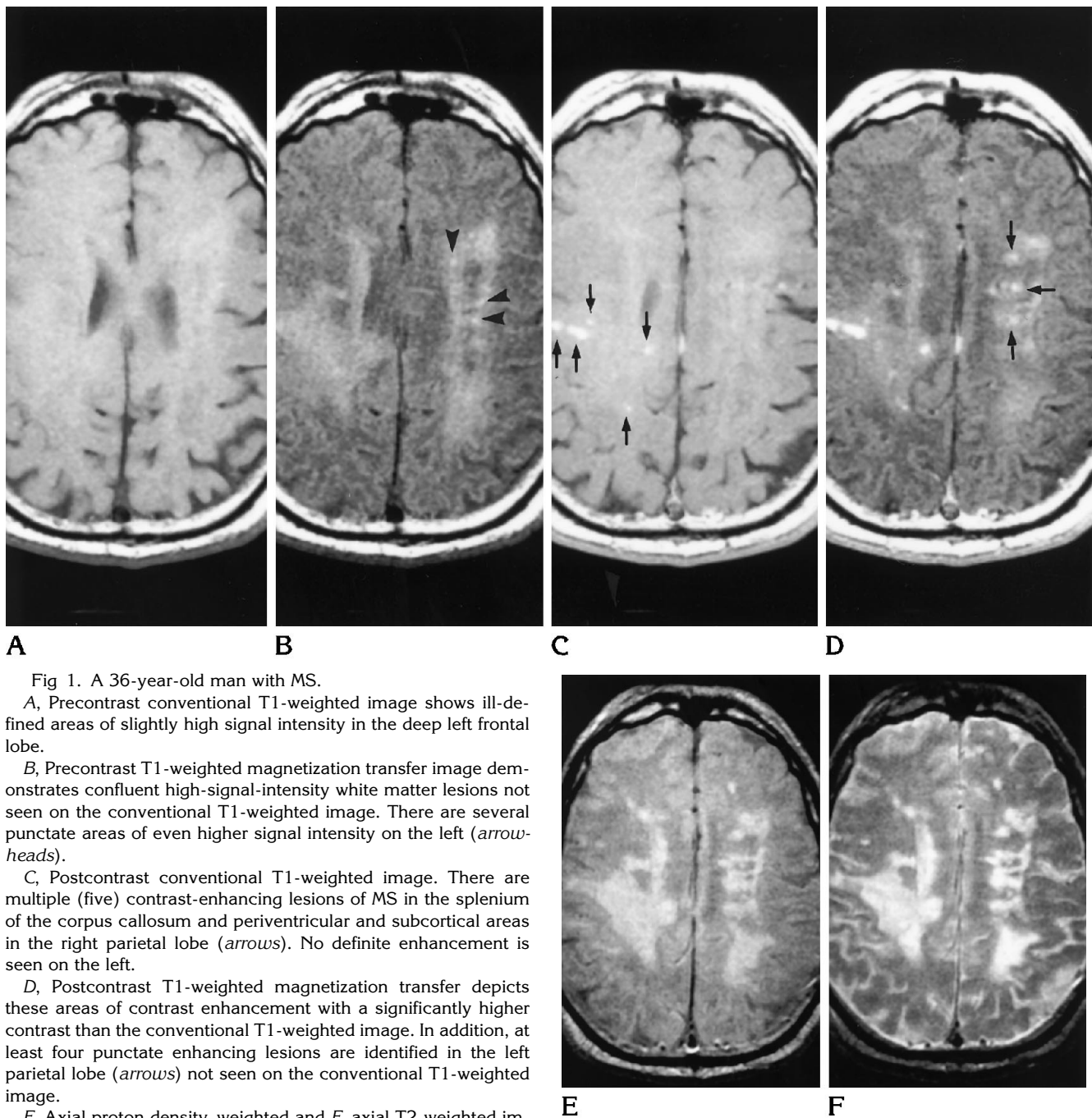


Fig 1. A 36-year-old man with MS.

A, Precontrast conventional T1-weighted image shows ill-defined areas of slightly high signal intensity in the deep left frontal lobe.

B, Precontrast T1-weighted magnetization transfer image demonstrates confluent high-signal-intensity white matter lesions not seen on the conventional T1-weighted image. There are several punctate areas of even higher signal intensity on the left (*arrowheads*).

C, Postcontrast conventional T1-weighted image. There are multiple (five) contrast-enhancing lesions of MS in the splenium of the corpus callosum and periventricular and subcortical areas in the right parietal lobe (*arrows*). No definite enhancement is seen on the left.

D, Postcontrast T1-weighted magnetization transfer depicts these areas of contrast enhancement with a significantly higher contrast than the conventional T1-weighted image. In addition, at least four punctate enhancing lesions are identified in the left parietal lobe (*arrows*) not seen on the conventional T1-weighted image.

E, Axial proton density-weighted and F, axial T2-weighted images both demonstrate the enhancing and the nonenhancing lesions. The extensive white matter changes on the T2-weighted images are depicted on T1-weighted magnetization transfer images.

Discussion

An important pathologic feature of an active MS plaque is the presence of perivenous inflammatory changes associated with local blood-brain barrier breakdown. Previous studies have used gadopentetate dimeglumine as evidence of the disruption of normal blood-brain barrier

and hence active lesions (1, 2, 17, 18). These lesions may or may not be clinically symptomatic. The observation of perivenous inflammation in chronic reactivated lesions of MS suggests that vascular events and demyelination may occur independently. Studies also indicate that demyelination does not always follow the

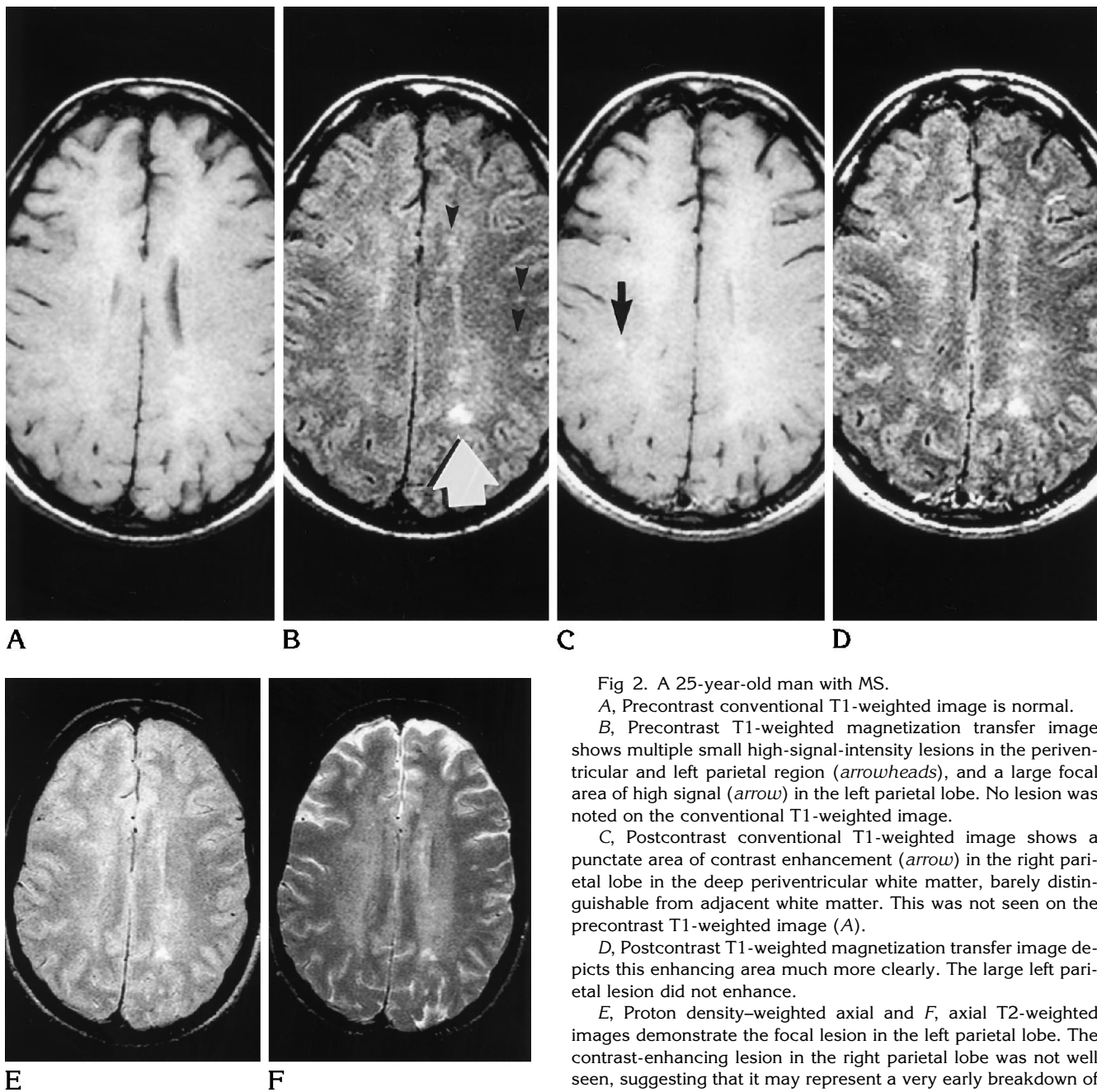


Fig 2. A 25-year-old man with MS.

A, Precontrast conventional T1-weighted image is normal.

B, Precontrast T1-weighted magnetization transfer image shows multiple small high-signal-intensity lesions in the periventricular and left parietal region (*arrowheads*), and a large focal area of high signal (*arrow*) in the left parietal lobe. No lesion was noted on the conventional T1-weighted image.

C, Postcontrast conventional T1-weighted image shows a punctate area of contrast enhancement (*arrow*) in the right parietal lobe in the deep periventricular white matter, barely distinguishable from adjacent white matter. This was not seen on the precontrast T1-weighted image (A).

D, Postcontrast T1-weighted magnetization transfer image depicts this enhancing area much more clearly. The large left parietal lesion did not enhance.

E, Proton density-weighted axial and F, axial T2-weighted images demonstrate the focal lesion in the left parietal lobe. The contrast-enhancing lesion in the right parietal lobe was not well seen, suggesting that it may represent a very early breakdown of the blood-brain barrier. The sections are very comparable given the sulcal pattern; this was not a sampling error.

breakdown of the blood-brain barrier (19, 20). The temporal sequence of the inflammatory processes and demyelination still is a topic of considerable interest. Nevertheless, the presence of contrast enhancement in an MS plaque is currently taken as a sign of disease activity, and therefore its detection is important in assessing acute disease burden. If contrast enhancement is to be used as a measure of acute inflammatory change and thus of potentially re-

versible disease, then an accurate measure of it will be necessary to assess treatment protocols. The use of gadopentetate dimeglumine in combination with magnetization transfer on T1-weighted images increases the contrast-to-noise ratios of enhancing lesions, improving their detectability and providing a more accurate measure of inflammatory disease burden. Magnetization transfer saturation can be achieved by using either an on-resonance or an

Contrast-to-noise ratio of MS lesions without and with magnetization transfer

	T1-Weighted Precontrast	T1-Weighted Postcontrast	T1-Weighted Magnetization Transfer Precontrast	T1-Weighted Magnetization Transfer Postcontrast
Nonenhancing	0.6 \pm 1.6	0.3 \pm 2.0	14.0 \pm 2.0	15.0 \pm 1.0
Enhancing	4.0 \pm 1.0	16.0 \pm 1.0	21.0 \pm 2.0	32.0 \pm 2.0

off-resonance pulse. The main advantages of the on-resonance saturation pulse is that it is shorter, and therefore more sections can be obtained within a given time. Also, it is insensitive to B_0 inhomogeneities, and the power deposition is less (15).

The aim of our study was twofold: (a) to determine whether contrast-to-noise ratio measure of lesion detection was improved by the combined use of gadopentetate dimeglumine and magnetization transfer; and (b) to compare signal intensities of enhancing and nonenhancing lesions on precontrast T1-weighted magnetization transfer images. The results show that contrast-enhancing MS lesions had a significantly higher contrast-to-noise ratio on postcontrast T1-weighted magnetization transfer images than on conventional T1-weighted images. In addition, magnetization transfer alone, as seen on the precontrast T1-weighted magnetization transfer images, increases the contrast measures of MS plaques and also shows lesions not seen on the conventional T1-weighted image. Lesion visibility was similar to that on the T2-weighted images. Thus the magnetization transfer technique itself contributes to the increased contrast of MS plaques in addition to the gadopentetate dimeglumine itself; this differs from the results with contrast-to-noise ratio tumors, infections, and infarctions (21). By definition, the nonenhancing lesions of MS did not have a measurable or visible increase in contrast-to-noise ratio after gadopentetate dimeglumine administration. The signal intensity of nonenhancing lesions often was greater than the intensity of the caudate nucleus, our internal standard to detect contrast enhancement (21). Therefore, no normal brain structure could be consistently used as an internal standard to determine contrast enhancement of MS lesions. The clinical importance of this finding is that in MS patients, precontrast T1-weighted magnetization transfer images need to be made to detect abnormal areas of contrast enhancement on T1-weighted magnetization transfer images.

The MS lesions in this study did not include

end-stage, cystic plaques with very low signal on T1-weighted images. They are not difficult to detect, and the use of magnetization transfer might actually decrease the contrast-to-noise ratio of these lesions, although they still would be easily detected. Magnetization transfer adds information about subtle, nearly isointense lesions on T1-weighted images and contrast enhancement in plaques.

One interesting imaging finding in this study was the presence of high-signal-intensity lesions on the precontrast T1-weighted magnetization transfer images (Fig 2). This high signal throughout the lesion was not apparent on the conventional T1-weighted image and often was of the same magnitude as contrast enhancement but was seen on the precontrast T1-weighted magnetization transfer images. A peripheral rim of hyperintensity on T1-weighted images has been described by Nesbit et al (22). In their study, all four lesions with peripheral rims of hyperintensity showed marked to moderate infiltration with lipid-laden macrophages. Other theories include the presence of free radicals (23). The hyperintensity on T1-weighted magnetization transfer images in our study was present throughout the plaque, not a rim of hyperintensity. This high signal is felt to represent lipid signal. This may be the imaging correlate of the spatially localized proton spectroscopy-identifiable lipid. These areas may represent active demyelination and possible reversible brain damage. Their assessment would be important in assessing treatment protocols and the natural course of MS.

To understand the possible source of this increased signal, a brief review of the structure of the myelin and the effect of magnetization transfer saturation on different chemical states is useful. White matter is composed of myelin sheaths, microglial cells, axons, and capillaries (24). The structure of myelin is represented by a fluid mosaic, which consists of a lipid bilayer with embedded macromolecular proteins (25). The major lipids in myelin are cholesterol and glycerophospholipids. They do not result in a

high signal lipid peak on MR images or spectroscopy in intact myelin. In MS, the most specific and characteristic change is demyelination. With myelin breakdown, there is a moderate increase in the concentration of free lipids and lysosomal enzymes in the macromolecular environment of these lesions (26). Fat (lipid) signal is poorly suppressed by magnetization transfer, as has been noted in several studies in which calculated magnetization transfer ratios were fewer than 5% (9). These hydrophobic lipids, containing medium- and long-chain triglycerides, have T2 values similar to many other biological tissues and do not have any significant direct interaction with free water; therefore they are not considered macromolecules similar to those saturated by the magnetization transfer pulse. The degradation of the myelin in the demyelinating diseases would result in increased concentration of lipids, which would be unaffected by the magnetization transfer saturation (27–30). Thus they would appear of higher signal intensity than the suppressed signal of white matter on magnetization transfer images.

Lipid as the cause of this high signal is further supported by the results of MR spectroscopy. MR proton spectroscopy performed in 14 patients with clinically definite MS has shown prominent resonances in the 0.5 to 2.0 ppm region, which were presumed to originate from lipids and other breakdown products of myelin. These findings also were detected in nonenhancing plaques (7 of 21) (31). In spectroscopic studies, there has been no magnetization transfer between H(r) and fat; therefore, the lipids would not be expected to lose signal with magnetization transfer (32). It is therefore reasonable to conclude that the increased signal seen on the precontrast T1-weighted magnetization transfer images in enhancing and nonenhancing plaques may represent lipid-breakdown products of myelin and is the imaging equivalent of the lipid signal seen with MR spectroscopy.

This imaging finding does pose an interesting question with regard to the definition of disease activity. The presence of lipid suggests active demyelination, which apparently can occur in the absence of contrast enhancement, a presumed marker for active inflammation. Therefore, contrast enhancement may be an incomplete indicator of disease activity if that concept

is to encompass active tissue damage caused by demyelination.

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