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## Sensitivity of Enhanced MR in Multiple Sclerosis: Effects of Contrast Dose and Magnetization Transfer Contrast

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**BACKGROUND AND PURPOSES:** New strategies have been developed to improve the sensitivity of contrast-enhanced MR imaging in quantifying disease activity in patients with multiple sclerosis (MS). The goal of the present study was to evaluate the sensitivity of T1-weighted images after injection of a triple dose of contrast material and application of a magnetization transfer (MT) pulse in the detection of enhancing lesions as compared with the conventional approach.

**METHODS:** Monthly MR images were obtained in 13 patients with relapsing-remitting MS for a period of 3 months. The MR studies were performed on two separate occasions with single- and triple-dose contrast material. In each session, T1- and T2-weighted spin-echo images with and without the MT pulse were obtained before and after contrast administration. All images were evaluated in a blinded fashion and scored in random order and consensually by two readers. The number of total and new enhancing lesions and active images was counted.

**RESULTS:** Eighty-six percent more enhancing lesions and 54% more new enhancing lesions were detected with triple-dose as compared with single-dose non-MT sequences, whereas single-dose MT images depicted 33% more enhancing lesions and 18% more new enhancing lesions than the single-dose non-MT images. Twenty-nine percent more lesions were detected on triple-dose non-MT images than on single-dose MT images. The combination of a triple dose of contrast material and MT did not produce any significant change in detection of enhancing lesions as compared with a triple dose of contrast without MT.

**CONCLUSION:** The use of a triple dose of contrast material is the best approach to maximize the sensitivity of enhanced MR imaging.

MR imaging is a powerful tool to evaluate the natural course of disease and to assess the efficacy of new treatment in patients with multiple sclerosis (MS) (1, 2). In MS, active lesions are considered to be any new lesion seen on serial proton density- or T2-weighted

images (1) and any lesion that enhances after the administration of contrast agent on T1-weighted images (3). Enhancement represents areas with blood-brain barrier (BBB) breakdown associated with inflammatory changes (4) and it is a very sensitive marker of disease activity in MS (1, 3, 5). It also increases the specificity of MR imaging in the diagnosis of MS (4–7) and is partially predictive of the subsequent evolution of the disease (1, 8–10).

Currently, several new strategies have been developed to improve the sensitivity of contrast-enhanced MR imaging in patients with MS (1, 11, 12). Among these, the use of a triple dose of contrast material (11–13) and magnetization transfer (MT) contrast (14–23) are among the most sensitive. Several cross-sectional MR studies have reported an increase in the number of enhancing lesions and active images when one or the other of the two approaches is used. More recently, two cross-sectional studies compared the two approaches and found the use of a triple dose to be more sensitive (14, 24) and reproducible (24),

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while the combined use of triple dose, MT contrast, and delayed scanning maximizes the depiction of enhancing lesions (14). At present, however, there are no longitudinal studies comparing the sensitivity of these techniques (ie, standard dose, standard dose plus MT contrast, triple dose, and triple dose plus MT contrast). A longitudinal evaluation is clearly relevant if these techniques are to be used in the context of clinical trials in MS.

The aim of the present longitudinal study was to evaluate the effects of contrast dose and MT contrast on the sensitivity of enhanced MR imaging.

## Methods

### *Patients*

Thirteen patients (three men and 10 women) with clinically definite MS (25) were entered into the study. All patients had a relapsing-remitting course. Their mean age was 35 years (standard deviation, 5.5), the median duration of the disease was 6 years (range, 2 to 10 years), and the median Expanded Disability Status Scale (EDSS) score was 2.0 (range, 0.0 to 4.0) (26). None of the patients had taken immunosuppressive or immunomodulating medications for at least 12 months prior to entry in the study. In addition, they neither had relapses nor had received steroid treatment during the preceding 3 months. For patients who had a relapse during the study that required steroid treatment, the schedule was intravenous methylprednisolone 1 g per day for 3 days. MR imaging was always scheduled either before the start of steroid treatment or 10 days after the end. No other immunosuppressive or immunomodulating treatment was allowed during the study. Approval from the local ethical committees and written informed consent from all the patients were obtained before the study began.

### *MR Imaging*

MR imaging was performed using a 1.5-T superconductive system for all patients every 28 ( $\pm 5$ ) days on four occasions. On each scanning occasion, the MR examination was split into two sessions, separated by an interval of 12 to 24 hours. During the first session, the following imaging studies were obtained: one dual-echo, conventional spin-echo (CSE) sequence with parameters of 2000/30,90/1 (TR/TE/excitations); two noncontrast T1-weighted (560/14/2) CSE images with and without the MT pulse; and two contrast-enhanced T1-weighted images (with the same acquisition parameters as before contrast injection) obtained 5 minutes after the injection of contrast material. During the second session, the following studies were obtained with the same parameters as above: two noncontrast T1-weighted images with and without the MT pulse, and two contrast-enhanced T1-weighted images with and without the MT pulse obtained 5 minutes after the contrast injection. The dose of contrast was randomized so that in the first session the patient received either a single dose (0.1 mmol/kg) or a triple dose (0.3 mmol/kg), with the opposite dose given during the second session. Thus, on each monthly occasion, each patient had four contrast-enhanced T1-weighted images: single-dose images with and without the MT pulse and triple-dose images with and without the MT pulse. The MT pulse used was a 50-millisecond sinc-gaussian pulse, cut off at the third zero crossing, with a duration of 15 milliseconds, amplitude of 620°, power of 15.7  $\mu$ T, bandwidth of 400 Hz, and frequency offset of 2000 Hz. The MT pulse was applied before each excitation pulse (off resonance). To avoid the bias introduced by the time elapsed since injection, the sequences obtained with and without MT were acquired randomly.

For all images, 24 contiguous interleaved axial sections were acquired with a 5-mm section thickness, a 205  $\times$  256 matrix, and a 220-mm field of view. The same acquisition protocol was used throughout the study. For follow-up studies, the image planes were carefully repositioned according to published guidelines (1).

### *Safety Assessment*

At the end of each scanning session, the patients, who were unaware of the contrast dose, were asked about any discomfort or side effects related to contrast administration. This inquiry was repeated by telephone 2 days after the completion of each monthly visit. The questions were posed by the same observers throughout the study. Every 28 ( $\pm 5$ ) days, blood was collected from each patient in a routine manner prior to the MR examination, and the following types of chemical and hematologic analyses were performed: red and white blood cell count, platelet count, hemoglobin level, hematocrit, mean corpuscular volume, blood urea and creatinine, levels of aminotransferase aspartate, aminotransferase alanine,  $\gamma$ -glutamyltransferase, alkaline phosphatase, and total bilirubin and iron levels. Abnormal results were considered to be those falling outside the normal ranges.

### *Image Review*

The enhanced T1-weighted images were assessed to determine the total number of enhancing lesions and the number of new enhancing lesions in a manner described in previously published guidelines (7). The assessment process had three stages.

*Stage 1.*—Each of the four sets of contrast-enhanced T1-weighted images from each patient was viewed in a consensual fashion by two of us, with the films presented in random order. The observers were unaware of the contrast dose, the patient to whom the images belonged, and the time point of the acquisition. Because MT images are easily recognizable, an element of unblinding was unavoidable.

*Stage 2.*—Next, the four sets of images obtained at each time point from each patient were compared to evaluate whether lesions seen on some but not all the images could be seen retrospectively on the others. The observers were still unaware of the contrast dose used, the scanning delay, and the patients' clinical characteristics. Thus, after this stage, each lesion had been reassessed.

*Stage 3.*—For each patient and for the two contrast doses and pre- and post-MT images, the four monthly images were evaluated side-by-side to count the new enhancing lesions. Throughout the entire image evaluation process, the corresponding dual-echo and noncontrast T1-weighted images were used to confirm possible areas of enhancement.

### *Statistical Analysis*

The Wilcoxon signed rank test was used to assess the effect of contrast dose and MT contrast on the measured number of total and new enhancing lesions. The effect of contrast dose and MT contrast on the images with at least one enhancing lesion, and the images with at least one new enhancing lesions were analyzed by using the McNemar test for paired data.

## Results

A total of 208 contrast-enhanced images were obtained and analyzed (52 for each of the four MR techniques). No enhancing lesions were seen on the noncontrast T1-weighted images at the beginning of each second scanning session. Tables 1 and 2 give the total number of enhancing lesions and the number of

**TABLE 1: Total and mean number of enhancing lesions per month per patient detected by the four different MR techniques**

	Single Dose	Triple Dose	% Difference	P Value*
Contrast				
Total	112	208	+86	<.005
Mean (range)	2.15 (0–11)	4.00 (0–18)		
Contrast + MT				
Total	149	205	+37	<.01
Mean (range)	2.87 (0–16)	3.94 (0–19)		
% Difference	+33	–1		
P value*	<.01	NS		

\* Statistical analysis by Wilcoxon signed rank test.

**TABLE 2: Total and mean number of new enhancing lesions per month per patient detected by the four different MR techniques**

	Single Dose	Triple Dose	% Difference	P Value*
Contrast				
Total	72	111	+54	<.01
Mean (range)	1.85 (0–10)	2.85 (0–13)		
Contrast + MT				
Total	85	109	+28	<.05
Mean (range)	2.18 (0–14)	2.79 (0–14)		
% Difference	+18	–2		
P value*	NS	NS		

\* Statistical analysis by Wilcoxon signed rank test.

new enhancing lesions as well as the average number of lesions per month per patient seen on the single-dose and triple-dose images obtained with and without the application of an MT pulse.

Significant increases of 86% ( $P < .005$ ) and 54% ( $P < .01$ ) in the number of total and new enhancing lesions were observed when comparing non-MT single- and triple-dose images, and increases of 37% ( $P < .01$ ) and 28% ( $P < .05$ ) were found when comparing MT single-dose images with non-MT triple-dose images. The application of the MT pulse significantly increased the sensitivity of single-dose images in the detection of the total number of enhancing lesions ( $P < .01$ ) (Figs 1–3). An 18% increase was also observed for the number of new enhancing lesions, but this increase was not statistically significant. Application of the MT pulse after injection of the triple dose of contrast did not change the sensitivity of the technique (Figs 2 and 3).

No statistical differences were observed in the number of active images in comparisons of the techniques (Table 3). Eighty percent of lesions considered enhancing on the contrast-enhanced MT T1-weighted images were seen as hyperintense lesions on the non-contrast MT T1-weighted images. No patient reported discomfort or side effects over the entire duration of the study. No permanent or significant changes in the blood test parameters tested were found during the follow-up period.

## Discussion

Our study shows that the use of a triple dose of contrast material and the application of an MT pulse to single-dose T1-weighted sequences significantly increase the sensitivity of enhanced MR imaging in detecting active lesions in patients with MS. This may have implications in the design of MR-monitored clinical trials, as it may result in a considerable reduction in the number of MR images needed to obtain adequate statistical power. The increased MR imaging sensitivity may also improve our understanding of disease evolution and the strength of the correlation between clinical and MR measures.

There is general agreement as to the value of enhanced MR imaging for monitoring short-term MS evolution, either natural or modified by treatment (1, 2). In such a context, optimization of image timing, sequences, and contrast dose is essential (1, 3, 6). Several recent cross-sectional studies have documented that the use of a triple dose of contrast material markedly increases the detection of enhancing lesions in patients with MS (11–14). Our longitudinal study confirms this effect and its magnitude, thus suggesting that the higher sensitivity of triple-dose contrast may be due to the detection of lesions that would never be detected on serial single-dose images.

Our study also showed that MT single-dose sequences are more sensitive than non-MT single-dose sequences. This approach was, however, less sensitive than non-MT triple-dose sequences. A previous study (24) also showed that interrater variability in reporting enhancing lesions is much higher when MT images are used. This may be because variable numbers of lesions that are hyperintense on contrast-enhanced MT images are already hyperintense on noncontrast MT images (19, 24), as shown in the present study. A cross-comparison of noncontrast and contrast-enhanced MT images to count the number of enhancing lesions seems to be mandatory. Clearly, a lower sensitivity coupled with a lower reproducibility may result in the need to obtain a greater number of images to show the effects of treatment. Nevertheless, one must also consider the increased costs of MR-monitored trials when serial triple-dose images are used.

The higher sensitivity of the triple dose versus the MT single-dose technique may be due to the depiction of a greater number of lesions with less intense BBB damage on triple-dose images, owing to the higher transmembrane gradient of the contrast material, which is not reached when the other technique is used. Although the detection of lesions with different degrees of BBB damage may result in a better and more complete understanding of MS evolution, it might be questioned whether the suppression of such lesions due to the effects of treatment may significantly affect the subsequent evolution of the disease.

The use of an MT pulse after the injection of a triple dose of contrast agent does not further increase the sensitivity of enhanced MR imaging. On the contrary, when we applied the MT pulse, three small periventricular lesions were no longer seen. This



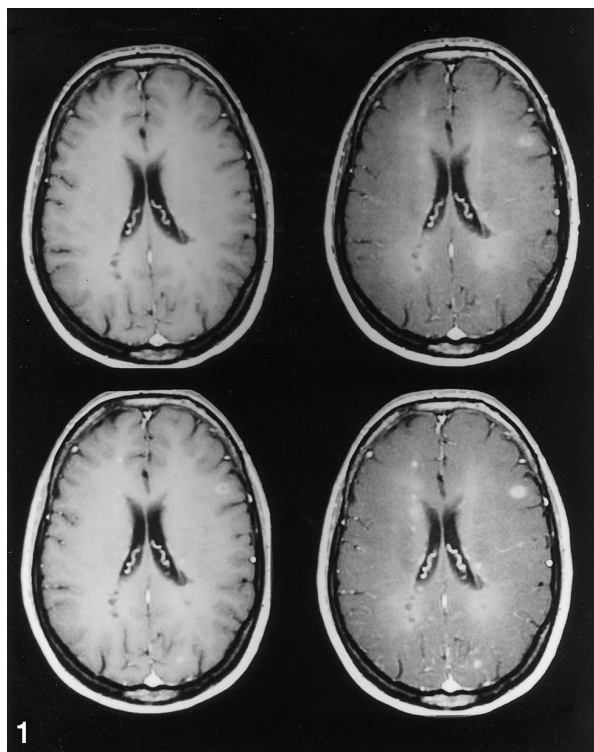


FIG 1. Enhanced axial MR images of the brain obtained without (left column) and with (right column) an MT pulse, after a single (upper row) and triple (lower row) dose of contrast material. Two enhancing lesions are present on the MT single-dose image (upper right) and one more lesion, located at the level of the left occipital white matter, is seen on triple-dose image. On the triple-dose MT images, enhancing lesions are well depicted with two additional punctate enhancements shown in the right paraventricular white matter.

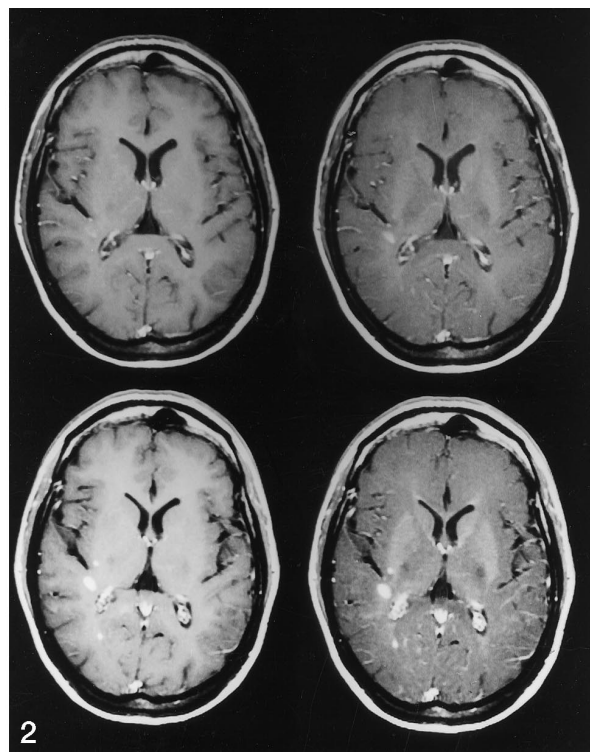


FIG 2. Enhanced axial MR images of the brain obtained without (left column) and with (right column) an MT pulse, after a single (upper row) and triple (lower row) dose of contrast material. A paratrigonal enhancing lesion is seen better on the single-dose MT images; two more lesions are present on the triple-dose images, more evident when the MT pulse is applied.

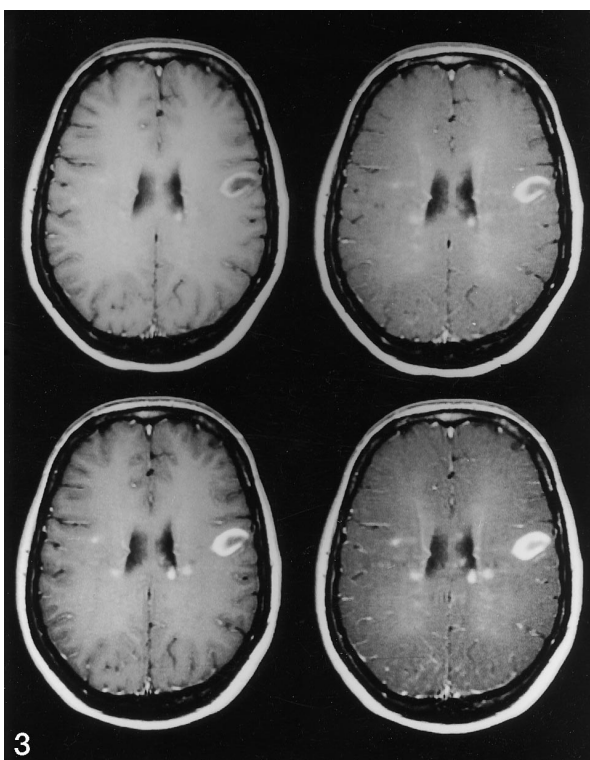


FIG 3. Enhanced axial MR images of the brain obtained without (left column) and with (right column) an MT pulse, after single (upper row) and triple (lower row) doses of contrast material. On the MT single-dose image, two more enhancing lesions are present than on the non-MT single-dose image. One more lesion is seen when a triple dose is used, with or without MT, as compared with the MT single-dose images.

might have been caused by the increased signal intensity of the periventricular white matter on the MT images, which may mask small lesions. This observation, on the one hand, suggests that the triple-dose technique depicts the vast majority of lesions with BBB disruption and, on the other hand, confirms the difficulties already encountered with MT-related artifacts.

Our data are discordant with the findings of Silver

et al (14), who reported an 8% (nonsignificant) increase in lesion enhancement when triple-dose MT sequences were applied. However, it is notable that the MT sequence of Silver and coworkers was performed at three different delay times after contrast injection, ranging from 20 to 60 minutes. In our study, the MT pulse sequence was done within 5 minutes of contrast injection, which might explain the lack of

**TABLE 3: Number of active scans detected by the four different MR techniques**

	Single Dose	Triple Dose	P Value*
Contrast	32	37	NS
Contrast + MT	36	37	NS
P value*	NS	NS	

\* Statistical analysis by McNemar test.

increase in enhancing lesions. Moreover, the same authors (14) reported that the use of a triple dose caused more adverse events than the single dose (14% versus 4%). However, the results of our study, in which all patients were blinded to the dose of contrast used and were closely controlled for each possible adverse event, indicate the safety of this approach.

## Conclusion

Triple-dose contrast is the most sensitive MR technique for detecting enhancing lesions in patients with MS. The application of an MT pulse to T1-weighted sequences after the injection of a single dose of contrast also results in a higher detection rate of enhancing lesions. Larger and longer longitudinal studies are needed to ascertain what impact the additional lesions detected have on disease evolution and to establish the relative gains in statistical power that can be achieved by one or the other of the two techniques.

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