Sensitivity of contrast enhanced MRI in multiple sclerosis
Effects of gadolinium dose, magnetization transfer contrast
and delayed imaging

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Summary
Although clinical end points remain the definitive measure of therapeutic efficacy in multiple sclerosis, more sensitive markers of disease activity are required to screen potential disease-modifying agents. The use of gadolinium contrast-media in MRI studies increases both the reliability and sensitivity of detecting active lesions in multiple sclerosis. We studied three potential methods for further improving sensitivity: the use of 0.3 mmol/kg (triple-dose) gadolinium-diethylenetriaminepenta-acetic acid (Gd-DTPA), magnetization transfer (MT) contrast imaging and the introduction of a delay between contrast-medium injection and imaging. Fifty patients were studied (seven with benign, 14 with relapsing–remitting, 10 with secondary progressive, 16 with primary progressive and three with transitional multiple sclerosis). Imaging was performed on two occasions, 24–72 h apart, with triple- and single-dose Gd-DTPA. Pairs of contrast-enhanced T1-weighted studies, with and without MT, were obtained at three different times, i.e. within early (0–20 min), short-delay (20–40 min) and long-delay (40–60 min) time-windows. Nineteen patients did not have the full complement of studies. Seven patients suffered minor self-limiting adverse events possibly related to triple-dose Gd-DTPA. Overall, triple-dose Gd-DTPA resulted in a 75% increase in the number of enhancing lesions detected compared with the single dose (P < 0.002). The use of MT or delay alone did not significantly increase the sensitivity of either single- or triple-dose studies. The combination of MT and short delay increased the number of enhancing lesions detected with single-dose Gd-DTPA by 47% (P < 0.05) and with triple-dose Gd-DTPA by 27% (P < 0.01). Detection was not significantly further improved by a long delay. The most sensitive modality was MT imaging with a long delay following triple-dose Gd-DTPA, resulting in the detection of 126% more enhancing lesions than in standard single-dose imaging (P < 0.05). This applies to all subgroups except for primary progressive multiple sclerosis, in which none of these methods alone or in combination improved the sensitivity. We conclude that for relapsing–remitting and secondary progressive multiple sclerosis, the combination of triple-dose Gd-DTPA and delayed MT imaging more than doubles the sensitivity to contrast-enhancing lesions.

Keywords: multiple sclerosis; magnetic resonance imaging; gadolinium enhancement; magnetization transfer contrast

Abbreviations: Gd-DTPA = gadolinium-diethylenetriaminepenta-acetic acid; MT = magnetization transfer; EDSS = Expanded Disability Status Scale

Introduction
The ability to alter the clinical course or eventual disability in multiple sclerosis is generally agreed to be the definitive outcome measure for assessment of potential new therapies (Miller et al., 1996; Rudick et al., 1996). Nevertheless, because the clinical course is highly variable, markers of disease activity are required that are related to, but more sensitive than, clinical measures. Such techniques would allow more rapid screening of new therapies in exploratory (phase I/II) trials, in addition to acting as supplementary markers of disease activity in definitive (phase III) studies.

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where a clinical end-point is the primary outcome measure. In relapsing–remitting and secondary progressive multiple sclerosis, serial T2-weighted MRI reveals 5–10 times as many new lesions as there are clinical relapses (Willoughby et al., 1989; Thompson et al., 1991). Gadolinium-diethylene-triaminepenta-acetic acid (Gd-DTPA) enhancement, by detecting blood–brain barrier breakdown and inflammation in new and reactivated chronic lesions (Hawkins et al., 1990; Kermode et al., 1990a, b; Katz et al., 1993), further increases the reliability and sensitivity of detecting active lesions (Miller et al., 1993; Miller, 1994). In relapsing–remitting and secondary progressive multiple sclerosis, the presence of such enhancement is more frequent during relapse and correlates well with clinical activity (Gonzalez-Scarano et al., 1987; Thompson et al., 1991, 1992; Smith et al., 1993; Frank et al., 1994). In addition, for patients with relapsing–remitting and secondary progressive multiple sclerosis, short-term serial measurement of the number of Gd-DTPA-enhancing lesions may have a predictive value for long-term clinical outcome (Loseff et al., 1996a, b). In benign multiple sclerosis, where there is relatively little clinical deterioration over time, longitudinal studies using conventional doses of Gd-DTPA have revealed much lower rates of activity than those seen in relapsing–remitting multiple sclerosis (Thompson et al., 1992; Kidd et al., 1994). For patients with primary progressive multiple sclerosis, few new lesions are usually seen on monthly T2-weighted images and there is usually little or no enhancement with conventional doses of Gd-DTPA, despite steady clinical deterioration (Thompson et al., 1991).

Several methods have been proposed to increase the conspicuity of gadolinium-enhancing lesions in a variety of neurological diseases, including multiple sclerosis. These include the use of a higher (0.3 mmol/kg) dose of Gd-DTPA, introduction of a delay between contrast-medium injection and imaging, and the utilization of magnetization transfer (MT) contrast.

With regard to the dose of gadolinium chelates used, several groups have shown that a dose higher than 0.1 mmol/kg may be beneficial for improved detection of enhancing lesions in various neurological disorders, including multiple sclerosis (Runge et al., 1991; Yuh et al., 1991; Haustein et al., 1993; Mathews et al., 1994; Wolansky et al., 1994; Filippi et al., 1995, 1996a, b). Although experience is relatively limited, this higher dose of Gd-DTPA does not appear to result in more side effects than standard doses (Haustein et al., 1993). The optimal time for imaging after contrast-medium injection is not clear, although dynamic studies in multiple sclerosis with 0.1–0.2 mmol/kg Gd-DTPA have shown marked lesion heterogeneity with maximal intensity occurring anytime between 4 min and 2 h (Kermode et al., 1990). Studies in primary progressive and benign multiple sclerosis have shown possible small advantages in using a 1 h delay after contrast-medium injection (Filippi et al., 1995, 1996b). The mechanisms whereby higher contrast-medium doses and delayed imaging result in improved detection are likely to rely on increased concentration of gadolinium chelates within the lesion, resulting in an increased rate of T1 relaxation (i.e. a shorter T1 relaxation time) and higher signal on T1-weighted images.

An alternative method for improving enhancing lesion conspicuity relies on decreasing the signal of surrounding brain parenchyma using MT contrast (Balaban and Ceckler., 1992). This technique relies on cross-relaxation between mobile ‘free’ water protons and ‘bound’ protons associated with macromolecules such as proteins and cell membrane constituents (Wolff and Balaban, 1989; Balaban and Ceckler, 1992). By using an off-resonance MT presaturation pulse, it is possible to saturate the broad resonance of the bound proton pool, with consequent exchange of magnetization and reduction in the free water signal. In normal brain, this results in decreased signal intensity of brain parenchyma, especially white matter. Although MT presaturation will also reduce the signal intensity of free water protons adjacent to gadolinium, this reduction is small compared with that in normal tissue (Mehta et al., 1995). Several studies have reported improved conspicuity of gadolinium-enhancing lesions in multiple sclerosis using MT contrast (Tanttu et al., 1992; Finelli et al., 1994; Mehta et al., 1995). To date, however, no investigators have compared or combined triple-dose Gd-DTPA and MT imaging directly in the same multiple sclerosis patients. By combining these methods, the aim of this study was to optimize sensitivity to detection of blood–brain barrier breakdown. Such optimization would be of potent value both for treatment trials, allowing shorter and smaller exploratory (phase I/II) studies and, for clinical practice, where diagnostic accuracy might be improved. Any potential increase in sensitivity may be useful in furthering our understanding of the pathogenesis of multiple sclerosis; this is especially relevant for the primary progressive form of disease, where serial MRI studies of the brain and spinal cord using 0.1 mmol/kg Gd-DTPA have detected little or no blood–brain barrier breakdown despite steady clinical deterioration (Thompson et al., 1991; Kidd et al., 1996).

We have prospectively studied the individual and combined effects of Gd-DTPA dose (0.1 mmol/kg versus 0.3 mmol/kg) and MT contrast on enhancing lesion conspicuity in multiple sclerosis. In addition, we have attempted to determine the optimal time for imaging, following contrast-medium injection for each of these methods.

**Material and methods**

**Subjects**

Fifty patients aged 24–56 years with clinically definite multiple sclerosis (Poser et al., 1983) were recruited from the population of patients attending the out-patient department of the National Hospital for Neurology and Neurosurgery; 14 had relapsing–remitting multiple sclerosis, defined as a history of relapses and remissions either occurring for <10 years or with disability on the Kurtzke Expanded Disability Status Scale (EDSS) (Kurtzke, 1983) >3; seven had benign
multiple sclerosis, as defined by a relapsing–remitting course for >10 years with EDSS ≤ 3; 10 had secondary progressive multiple sclerosis, as defined by an initial relapsing–remitting course followed by a subsequent progressive neurological deterioration for at least 6 months with or without superimposed relapses; 16 patients had primary progressive multiple sclerosis, as defined by a progressive neurological deterioration from onset, without relapse or remission; three patients were classified as having transitional multiple sclerosis, as defined by a single transient episode consistent with demyelination followed by a progressive neurological deterioration, without relapse or remission.

All patients underwent a detailed history and complete neurological examination by one observer (N.C.S.). Patients were classified as above and disability was scored with the EDSS and Kurtzke’s functional score (Kurtzke, 1983). In addition, the classification of all the patients was critically reviewed by an experienced neurologist. Exclusion criteria included pregnancy, breastfeeding, a history of allergy, any previous adverse reaction to contrast media, current asthma, or any history of asthma requiring hospital admission. No patients were admitted to the study within 1 month of a clinical relapse. In addition, no patients had received steroids within the previous month or other immunosuppressive therapy within the previous 6 months.

All patients gave written, informed consent to participate in the study, which had been approved by the joint ethics committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery.

**MRI protocol**

All imaging was carried out with a 1.5 Tesla superconducting system using a standard quadrature headcoil. Patients were imaged with identical protocols on two separate days (24–72 h apart, consecutive where possible). The only difference between these two sessions was the dose of Gd-DTPA used (0.3 mmol/kg on the first day and 0.1 mmol/kg on the second day).

First, T2- and proton-density weighted images of the brain were acquired using a dual fast-spin echo sequence (TR 3020 ms, TEef 19 and 90 ms, 46 contiguous 3 mm axial oblique slices, echo train length 8, 256 × 256-pixel image matrix, 24 × 18 cm² field of view, acquisition time 8 min). The patient was then removed from the imager and an intravenous cannula was inserted. A long line was attached to the cannula and flushed with normal saline. Imaging resumed with a pair of T1-weighted images (spin echo, TR 600 ms, TE 17 ms, 46 contiguous 3 mm axial oblique slices, one excitation, 256 × 256-pixel image matrix, 24 × 18 cm² field of view), acquired separately, with and without MT presaturation. Acquisition time was 8 min 11 s for non-MT and 10 min 18 s for the MT-prepared scans. For presaturation, a Hamming apodized 3-lobe sinc pulse, duration 12 ms and peak amplitude equivalent to a 520°-flip angle, was applied 1 kHz off resonance; this sequence had been optimized in a previous experiment to cause low-signal lesions on T1-weighted images almost to disappear with MT presaturation, without allowing lesions to become hyperintense. Without moving the patient, Gd-DTPA contrast-medium was administered as a bolus, followed by 5 ml normal saline via the long line. Imaging resumed with T1-weighted sequences identical to those attained pre-injection, alternating MT and non-MT acquisitions over 1 h. This resulted in pairs of MT and non-MT studies at three time points [early (first 20 min), short-delay (20–40 min) and long-delay (40–60 min)] for each dose of Gd-DTPA. Contrast-enhanced imaging commenced with or without MT in alternate patients, and this sequence remained constant for both sessions.

All patients were initially blinded to Gd-DTPA dose administered for the first session (0.3 mmol/kg) and were all asked an open-ended question regarding any adverse events after imaging and again at the second session 24–72 h later. For the second session (0.1 mmol/kg Gd-DTPA), those patients who had suffered possible adverse events following the triple-dose and were worried about further contrast administration were unblinded before having the single dose. All patients were asked to contact us if they suffered any adverse events following the second session (0.1 mmol/kg).

For all imaging, patients were repositioned using techniques described elsewhere (Gallagher et al., 1997). To minimize artefactual contrast variations on the processed films, transmitter and receiver gains were manually standardized for all the non-MT acquisitions at both sessions, and separately standardized for MT acquisitions. In addition, window levels were manually set separately for MT and non-MT unenhanced images to allow optimal contrast for each type of scan. These window levels remained identical for the comparable pre- and post-injection images at each session.

All images were assessed by one experienced neuroradiologist (C.D.G.) who was blinded to patient identity, all clinical information, Gd-DTPA dose and imaging details (delay and MT). Because MT images resulted in loss of contrast between grey and white matter, an element of unblinding was unavoidable. Unenhanced non-MT T1-weighted images acquired at the second imaging session were assessed for all patients. No patient showed evidence of residual Gd-DTPA enhancement. Unenhanced MT-prepared T1-weighted images were assessed for evidence of high lesion signal that might make assessment of the contrast-enhanced study more difficult. This was observed in only three patients (one each with transitional, relapsing–remitting and secondary progressive multiple sclerosis), and in each case it affected only a single lesion. In five patients (one with relapsing–remitting, three with secondary progressive and one with primary progressive multiple sclerosis) the normal-appearing white matter surrounding lesions (as assessed on the T2-weighted images) appeared as a faint bright rim. This phenomenon was also seen on some comparable non-MT T1-weighted images, although it was less notable. Contrast-enhanced non-MT and MT-prepared T1-weighted images were analysed individually in a random...
order (patients, Gd-DTPA dose and acquisition modality). All contrast-enhanced studies were assessed with the comparable unenhanced MT/non-MT image for evidence of enhancing lesions. Before commencing the analysis, films from 15 patients studied were assessed both by the study rater (C.D.G.) and a separate experienced neuroradiologist (I.F.M.) to standardize the criteria for definition of enhancing lesions and to ensure reliable observer agreement. Strict criteria were applied to the designation of an enhancing lesion: all ‘definite’ enhancing lesions were included, whereas areas of bright signal indistinguishable from flow artefact or Gd-DTPA contrast within vessels, without comparable high signal on T2- or proton density-weighted images, were excluded. None of the high-signal regions noted on unenhanced MT images, described above, appeared to change in signal intensity following contrast medium, and were not found, in retrospect, to be enhanced on any non-MT images.

Statistical analysis
MRI data were analysed using the Wilcoxon matched-pairs signed rank sum test.

Results
Clinical data
Of the 50 patients recruited (Table 1), 19 patients (three with benign, five with relapsing–remitting, five with secondary progressive, and six with primary progressive multiple sclerosis) failed to complete the full protocol. Of these, six were imaged before the MT sequence was available. Two patients did not have a second imaging session with 0.1 mmol/kg Gd-DTPA. In one case this was due to claustrophobia. The other patient developed an urticarial rash and penile swelling after the first session and was excluded from a second. Both adverse events in this patient were mild and settled spontaneously within 2 days, although he went on to develop septicaemia secondary to a urinary tract infection. Part of one patient’s imaging was omitted due to vomiting immediately following injection of 0.3 mmol/kg Gd-DTPA; there were no adverse events after the next day’s dose of 0.1 mmol/kg Gd-DTPA. Causes for the other incomplete studies included discomfort or spasms in three patients, headache associated with flushing and a subjective sensation of facial congestion in one patient (after 0.3 mmol/kg Gd-DTPA), urinary difficulties in three patients (urgency, frequency or incontinence), and practical difficulties in three patients (lack of time or imager failure). One patient with an incomplete study due to imager failure noticed flushing and paraesthesiae following the 0.3 mmol/kg Gd-DTPA. One patient who completed the protocol noticed a dry mouth immediately following contrast-medium injection on both days of the study. Two patients suffered from gastrointestinal upsets a few hours following the first study with 0.3 mmol/kg Gd-DTPA (diarrhoea in one and diarrhea with vomiting in the other); they experienced no adverse events following the lower dose of contrast medium. Overall, seven of the 50 patients (14%) who received the triple dose suffered adverse events possibly related to Gd-DTPA (allergic reaction, flushing with paraesthesiae, flushing and a sensation of facial congestion followed by headache, diarrhea, diarrhea and vomiting, vomiting following contrast-medium injection, or dry mouth immediately following contrast-medium injection).

Only one of the 48 patients (2%) who received the single dose suffered an adverse event possibly related to Gd-DTPA, namely a dry mouth immediately following contrast-medium injection.

<table>
<thead>
<tr>
<th>MRI data</th>
</tr>
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<tbody>
<tr>
<td>Figure 1 allows a comparison of all imaging protocols in the 31 patients who completed the full study (four with benign, nine with relapsing–remitting, five with secondary progressive, 10 with primary progressive and three with transitional multiple sclerosis). To assess the individual and combined effects of MT, delayed imaging and Gd-DTPA contrast-medium dose, data from all the patients entered into the study is presented.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effects of Gd-DTPA contrast-medium dose</th>
</tr>
</thead>
</table>
| Early contrast-enhanced T1-weighted non-MT images were assessed in all multiple sclerosis subgroups to evaluate the effect of 0.3 mmol/kg (triple-dose) versus 0.1 mmol/kg (single-dose) Gd-DTPA (Table 2). The use of the triple dose in 48 patients studied (seven with benign, 13 with relapsing–remitting, nine with secondary progressive, 16 with primary progressive and three with transitional multiple sclerosis) resulted in an overall 75% increase in the number of enhancing lesions detected (132 with the single dose versus 231 with

Table 1 Clinical data

<table>
<thead>
<tr>
<th>Multiple sclerosis type</th>
<th>Patients</th>
<th>Age in years mean (range)</th>
<th>Mean disease duration (years)</th>
<th>EDSS (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>7 (1 : 6)</td>
<td>43 (37–50)</td>
<td>18</td>
<td>2.5</td>
</tr>
<tr>
<td>Relapsing–remitting</td>
<td>14 (3 : 11)</td>
<td>34 (24–51)</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>10 (4 : 6)</td>
<td>39 (26–50)</td>
<td>12</td>
<td>7.5</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>16 (12 : 4)</td>
<td>44 (27–56)</td>
<td>9</td>
<td>7.5</td>
</tr>
<tr>
<td>Transitional</td>
<td>3 (1 : 2)</td>
<td>42 (35–50)</td>
<td>17</td>
<td>8</td>
</tr>
</tbody>
</table>

EDSS = Expanded Disability Status Scale; M = male; F = female.
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Effects of delayed imaging

Short delay (imaging at 20–40 min). The effect of a short delay for both single and triple doses of Gd-DTPA contrast-medium was assessed in 44 patients who had all such studies (six with benign, 12 with relapsing–remitting, nine with secondary progressive, 14 with primary progressive and three with transitional multiple sclerosis). With early single-dose imaging a total of 131 enhancing lesions was detected within 14 active studies. With a short delay in imaging, 165 enhancing lesions were detected within 15 active studies (one patient each with benign, relapsing–remitting and secondary progressive multiple sclerosis were active only with delayed imaging; one patient each with benign and primary progressive multiple sclerosis were active only with early imaging). In the same patients, early triple-dose imaging showed 225 enhancing lesions within 15 active studies. Further addition of a short delay to triple-dose imaging showed 243 enhancing lesions within 18 active studies (one patient each with relapsing–remitting, secondary progressive and transitional multiple sclerosis were active only with delayed imaging). The overall trend for short-delay imaging to increase the number of enhancing lesions detected was not statistically significant for either single-dose or triple-dose studies.

Long delay (imaging at 40–60 min). The effect of long delay for both single and triple doses of Gd-DTPA contrast-medium was assessed in 35 patients who had all such studies (five with benign, nine with relapsing–remitting, seven with secondary progressive, 11 with primary progressive and three with transitional multiple sclerosis). With early single-dose imaging, 88 enhancing lesions were detected within eight active studies. With a long delay in imaging, 113 enhancing lesions were detected within eight active studies (one patient with benign multiple sclerosis was active only with delayed imaging and one with primary progressive multiple sclerosis showed a single enhancing lesion noted only with early imaging). In the same patients, early triple-dose imaging showed 132 enhancing lesions within nine active studies; with long-delay triple-dose imaging

<table>
<thead>
<tr>
<th>Multiple sclerosis type</th>
<th>Patients (n)</th>
<th>Total number of enhancing lesions (and patients with active scans)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>with a Gd-DTPA dose of 0.1 mmol/kg</td>
<td>0.3 mmol/kg</td>
</tr>
<tr>
<td>Benign</td>
<td>7</td>
<td>1 (1)</td>
<td>11 (4)</td>
</tr>
<tr>
<td>Relapsing–remitting</td>
<td>13</td>
<td>46 (7)</td>
<td>86 (7)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>9</td>
<td>83 (5)</td>
<td>133 (5)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>16</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Transitional</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>48</td>
<td>132 (15)</td>
<td>231 (17)</td>
</tr>
</tbody>
</table>

*Wilcoxon matched-pairs signed rank sum test.
this increased to 190 enhancing lesions and an additional three active studies. The overall trend for long-delay imaging to increase the number of enhancing lesions detected was not statistically significant for either single-dose or triple-dose studies.

**Short versus long delay.** There were no significant differences between short-delay and long-delay imaging for either single-dose [88 (early) versus 119 (short delay) versus 113 (long delay) enhancing lesions in 35 patients] or triple-dose studies [145 (early) versus 170 (short delay) versus 186 (long delay) enhancing lesions in 38 patients].

**Effects of MT imaging**
The individual effect of MT imaging was assessed at the early time (0–20 min post contrast) for both single- and triple-dose studies in 42 patients (six with benign, 10 with relapsing–remitting, seven with secondary progressive, 16 with primary progressive and three with transitional multiple sclerosis) (see Fig. 2). With conventional single-dose non-MT imaging, a total of 90 enhancing lesions was detected within 10 active studies. With single-dose MT imaging 119 enhancing lesions were detected within 12 active studies (one patient each with benign, relapsing–remitting and primary progressive multiple sclerosis were active only with MT imaging; one patient with primary progressive multiple sclerosis showed a single enhancing lesion only with non-MT imaging). In the same patients, triple-dose non-MT imaging showed 156 enhancing lesions within 12 active studies. With triple-dose MT imaging 169 enhancing lesions were detected within 15 active studies (one patient each with relapsing–remitting, secondary progressive, primary progressive and transitional multiple sclerosis were active only with MT imaging; one patient with benign multiple sclerosis showed a single enhancing lesion only with non-MT imaging). The overall trend for MT imaging to increase the number of enhancing lesions detected was not statistically significant for either single-dose or triple-dose studies.

Within this patient group, the effect of MT imaging was variable. With single-dose studies, MT imaging increased detection of enhancing lesions in seven patients and decreased detection in three others; for three patients where enhancement was noted, there was no difference. With triple-dose studies, MT imaging increased detection of enhancing lesions in eight patients and decreased detection in three others; for four patients where enhancement was noted, there was no difference.

**Comparison of MT and triple-dose Gd-DTPA**
The effect of early single-dose MT imaging was compared with early triple-dose non-MT imaging in 43 patients studied (six with benign, 11 with relapsing–remitting, seven with secondary progressive, 16 with primary progressive and three with transitional multiple sclerosis). The number of enhancing lesions detected with triple-dose non-MT imaging was significantly higher than with single-dose MT imaging (160 versus 119; \( P < 0.05 \), Wilcoxon matched-pairs signed rank sum test). Whilst the overall number of active studies was also higher with the triple dose (13 versus 12), two studies were active only with single-dose MT imaging (one patient each with relapsing–remitting and primary progressive multiple sclerosis).

**Effects of combining MT and delayed imaging**
The combination of MT with short-delay imaging was assessed for 40 patients in single-dose (Table 3) and 41 patients in triple-dose studies (Table 4). Compared with early non-MT imaging, significantly more enhancing lesions were detected with this combined approach \( (P < 0.05 \) for single-dose studies and \( P < 0.01 \) for triple-dose studies, Wilcoxon matched-pairs signed rank sum test). For the single dose there was no difference in the overall number of active studies, although one patient with primary progressive multiple sclerosis showed activity only on the early, non-MT images. For the triple dose, the combination of MT and short delays resulted in three additional active studies (from 10 to 13).

At both doses of contrast medium, there were no significant differences between short and long delay for detecting enhancing lesions [130 (short delay) versus 126 (long delay) enhancing lesions in 34 patients in the single-dose studies, and 186 (short delay) versus 194 (long delay) enhancing lesions in 35 patients in the triple-dose studies].

For individual benign, relapsing–remitting and secondary progressive subgroups, MT imaging with either short or long delay increased the overall number of enhancing lesions detected for both single- and triple-dose studies, although these increases were not statistically significant.

**Comparison of delayed MT (single-dose) and early non-MT imaging (triple-dose Gd-DTPA)**
The effects of combined MT and short-delay imaging (the most sensitive of the single-dose studies) were compared with those of early non-MT imaging following the triple dose in 40 patients (five with benign, 10 with relapsing–remitting, seven with secondary progressive, 15 with primary progressive and three with transitional multiple sclerosis). The number of enhancing lesions detected with short-delay MT imaging following single-dose Gd-DTPA was 132 (with 10 active studies), compared with 154 enhancing lesions detected (and a single additional active study) with early non-MT triple-dose studies. These differences were not statistically significant.

**Effects of combining MT, triple-dose Gd-DTPA and delayed imaging**
The combination of triple-dose Gd-DTPA, MT contrast and long delay was compared with conventional, early single-
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Table 3  Effect of MT imaging (short-delay) 20–40 min after single-dose Gd-DTPA

<table>
<thead>
<tr>
<th>Multiple sclerosis type</th>
<th>Patients (n)</th>
<th>Total number of enhancing lesions (and patients with active scans) with 0.1 mmol/kg Gd-DTPA</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-MT, early</td>
<td>MT, short-delay</td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Relapsing–remitting</td>
<td>10</td>
<td>24 (4)</td>
<td>30 (4)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>7</td>
<td>64 (4)</td>
<td>100 (4)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>15</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Transitional</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>90 (10)</td>
<td>132 (10)</td>
</tr>
</tbody>
</table>

*Wilcoxon matched-pairs signed rank sum test (NS = not significant).

Table 4  Effect of MT imaging (short-delay) 20–40 min after triple-dose Gd-DTPA

<table>
<thead>
<tr>
<th>Multiple sclerosis type</th>
<th>Patients (n)</th>
<th>Total number of enhancing lesions (and patients with active scans) with 0.3 mmol/kg Gd-DTPA</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Non-MT, early</td>
<td>MT, short-delay</td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
<td>2 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Relapsing–remitting</td>
<td>11</td>
<td>44 (4)</td>
<td>55 (5)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>8</td>
<td>107 (4)</td>
<td>130 (5)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>14</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Transitional</td>
<td>3</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>154 (11)</td>
<td>196 (14)</td>
</tr>
</tbody>
</table>

*Wilcoxon matched-pairs signed rank sum test (NS = not significant).

dose, non-MT imaging in 35 patients studied (five with benign, nine with relapsing–remitting, five with secondary progressive, 13 with primary progressive and three with transitional multiple sclerosis). The use of such a combination resulted in an overall 126% increase in the number of enhancing lesions detected, the greatest of any approach studied (90 with early single-dose non-MT imaging versus 196 with long-delay triple-dose MT imaging; \( P < 0.05 \), Wilcoxon matched-pairs signed rank sum test). For these 35 patients, the number of active studies increased from eight to 10 with this combined approach (two patients with benign, one each with relapsing–remitting and transitional multiple sclerosis were active only with the triple dose, MT and long delay; one patient each with primary progressive and secondary progressive multiple sclerosis were active only with early, non-MT, single-dose studies).

The combination of triple-dose Gd-DTPA, MT contrast and short delay detected 118% more enhancing lesions than early non-MT single-dose studies (\( P < 0.002 \), Wilcoxon matched-pairs signed rank sum test) (Table 5). For these 39 patients, the number of active studies increased from 10 to 14 (two patients with benign, and one each with relapsing–remitting, secondary progressive and transitional multiple sclerosis were active only with triple-dose Gd-DTPA, MT and short delay; one patient with primary progressive multiple sclerosis was active only with early single-dose, non-MT imaging).

In benign, relapsing–remitting, secondary progressive and transitional multiple sclerosis, delayed MT imaging following triple-dose Gd-DTPA detected more enhancing lesions than early non-MT imaging with the single dose. With long delays, this increase was not statistically significant for any multiple sclerosis subgroup. For short delays, however, increases were significant for both relapsing–remitting (\( P < 0.05 \), Wilcoxon matched-pairs signed rank sum test) and secondary progressive multiple sclerosis subgroups (\( P < 0.05 \), Wilcoxon matched-pairs signed rank sum test).

Discussion

We have demonstrated that triple-dose (0.3 mmol/kg) Gd-DTPA, MT contrast and delayed imaging all affect the number of enhancing lesions detected in multiple sclerosis. The most sensitive combination, MT contrast imaging between 40 and 60 min after administration of triple-dose Gd-DTPA, resulted in a 126% increase in the overall number of enhancing lesions detected over non-MT, early, single-dose imaging (the conventional approach in current use); a shorter delay of 20–40 min resulted in a marginally smaller increase (118%).

While the advantage of combining these techniques is clear, some MRI units normally participating in treatment trials may have difficulties using all three methods, because of financial, time or software limitations. In addition, the post-
marketing surveillance of triple-dose Gd-DTPA is extremely limited compared with that of single-dose administration. We attempted to assess individual effects of each technique. In isolation, only triple-dose Gd-DTPA resulted in significantly increased enhancing lesion detection (75% more than with the single dose). Delayed or MT imaging alone did not result in significant improvements at either single- or triple-dose Gd-DTPA, although it is possible they might have, had we looked at a larger number of patients. The combination of a short delay and MT did significantly increase the number of enhancing lesions detected, by 47% for the single dose and 27% for the triple dose. The number of enhancing lesions detected was not significantly further increased by a long delay, although there was a trend towards this with the triple dose.

Previous groups have suggested that, in multiple sclerosis, the use of MT with single-dose Gd-DTPA may result in an improvement in contrast comparable to that given by triple-dose Gd-DTPA, thereby avoiding the higher cost of the latter and the possibility of more side effects at this higher dose (Finelli et al., 1994). However, in our study, non-MT imaging with a triple dose significantly increased the number of enhancing lesions detected, by 34%, when compared with MT imaging following single-dose Gd-DTPA.

We have observed more adverse events, possibly attributable to Gd-DTPA, using the triple dose: seven (14%) with the triple dose in 50 patients versus one (2%) with the single dose in 48 patients. All these were relatively minor and self-limiting, and it is possible that some were incidental and unrelated to injection of contrast medium. Some of these reactions (i.e. urticaria, vomiting, flushing, paraesthesiae and headache) are well described with Gd-DTPA (Niendorf et al., 1993). The frequency of 2% of possible/probable side effects associated with 0.1 mmol/kg is comparable with that in other studies (Niendorf et al., 1993). A review of studies investigating the safety of 0.1 mmol/kg concluded that the overall frequency of adverse events is in the order of 1% and comparable to that of intravenous physiological saline (Niendorf et al., 1993). In a randomized trial of 199 patients comparing 0.1 mmol/kg and 0.3 mmol/kg Gd-DTPA, a much higher frequency of adverse events with 0.1 mmol/kg was observed (6%), equal to that associated with 0.3 mmol/kg Gd-DTPA (Haustein et al., 1993). In that trial, there was no blinding and assessment of adverse events was carried out only immediately following imaging. In our study, all subjects were initially blinded to dose for the first day (0.3 mmol/kg) and were all assessed for possible adverse events, not only after imaging but also at the second session 24–72 h later. In addition, all patients were asked to contact us if they suffered any adverse events following the second session.

Table 5 Comparison of triple-dose, short-delay MT imaging with conventional single-dose, early non-MT imaging

<table>
<thead>
<tr>
<th>Multiple sclerosis type</th>
<th>Patients (n)</th>
<th>Total number of enhancing lesions (and patients with active scans) with</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.1 mmol/kg Gd-DTPA, non-MT, early</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>5</td>
<td>0</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Relapsing–remitting</td>
<td>10</td>
<td>24 (4)</td>
<td>55 (5)</td>
</tr>
<tr>
<td>Secondary progressive</td>
<td>7</td>
<td>64 (4)</td>
<td>130 (5)</td>
</tr>
<tr>
<td>Primary progressive</td>
<td>14</td>
<td>2 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Transitional</td>
<td>3</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
<td>90 (10)</td>
<td>196 (14)</td>
</tr>
</tbody>
</table>

*Wilcoxon matched-pairs signed rank sum test (NS = not significant).
(0.1 mmol/kg). Without the late assessment at the second imaging session we would have missed three possible adverse events following the triple dose. Previous authors have suggested that a history of allergy may predispose patients to a higher risk of adverse events following Gd-DTPA administration (Niendorf et al., 1993). In addition, information from post-marketing surveillance revealed one death from anaphylactic shock in a patient with asthma (Niendorf et al., 1993). Whilst previous reports suggest that adverse events are not dose-related (Haustein et al., 1993; Niendorf et al., 1993), caution should be maintained regarding those patients at potential risk (e.g. allergies, asthma) until more data are available. In this study, it is possible that the use of bolus Gd-DTPA rather than an infusion contributed to the increased frequency of adverse events noted with the higher contrast dose. In multiple sclerosis, where the time to reach maximal enhancement is relatively long compared with many other pathologies, the use of an infusion over a few minutes might not be too detrimental to the sensitivity. Further studies into tolerance of triple-dose Gd-DTPA would be useful, and these might address such issues. If triple-dose Gd-DTPA is to be used for serial assessment in treatment trials, then any potential increase in power of the study should be weighed against a potential for increased side-effects that may reduce patient compliance and cause premature withdrawal.

In the present study, the MT sequence was designed to allow lesions to become less hypointense or disappear, compared with standard T1-weighted images. The MT presaturation pulse for this sequence resulted in a 16.8% mean reduction in signal intensity for normal white matter, as determined in a separate study of three healthy subjects. Other studies using more powerful MT presaturation pulses, where signal intensity of normal-appearing white matter has been reduced by 35–37%, have reported frequent high signal from multiple sclerosis lesions prior to administration of gadolinium contrast medium (Finelli et al., 1994; Mehta et al., 1995). In order to define enhancing lesions in this situation, signal to noise evaluation before and after contrast medium is desirable, but may be time consuming. Where less powerful MT sequences are used, as in our study, this situation does not arise, and straightforward comparison of images before and after contrast medium should suffice. This approach may also confer an advantage for acquisition, allowing a greater number of thinner slices without exceeding radiofrequency deposition limits. Whichever approach is used, we feel that acquisition of a pre-injection MT-prepared T1-weighted image is essential for analysis of MT-prepared contrast-enhanced images; imaging parameters before and after injection should be identical, with no changes in transmitter or receiver gain, and, for visual assessment of enhancing lesions, window levels should remain constant. All these factors were carefully controlled in our study.

Within the context of treatment trials, it is important to consider the disease subgroups of multiple sclerosis. Whilst the overall detection of enhancing lesions was significantly improved using a combination of triple-dose Gd-DTPA and delayed MT imaging, up to 126% over standard single-dose imaging, this effect differed between subgroups. Compared with standard early non-MT imaging following single-dose Gd-DTPA, the combination of a short delay, MT and triple-dose Gd-DTPA significantly increased detection of enhancing lesions in patients with relapsing–remitting and secondary progressive multiple sclerosis. In 22 patients with relapsing–remitting and secondary progressive multiple sclerosis, we noted that the triple dose alone resulted in a 70% increased yield in enhancing lesions over single-dose Gd-DTPA, which is comparable to the results of a previous study, where a 66% increase was observed (Filippi et al., 1996a). In our study, many more enhancing lesions were seen in patients with relapsing–remitting and secondary progressive multiple sclerosis than in those with benign disease, regardless of imaging modality or dose of Gd-DTPA. This is in keeping with previous studies using delayed imaging and triple dose Gd-DTPA (Filippi et al., 1996a, b).

However, in the 16 patients with primary progressive multiple sclerosis, little enhancement was seen with any approach (no more than two enhancing lesions were noted for any particular combination). These findings are discordant with a recent study comparing the combined effects of delay and triple-dose Gd-DTPA with single-dose MRI in 10 patients with primary progressive disease, in which four enhancing lesions (two active studies) were seen with single-dose Gd-DTPA, 13 enhancing lesions (five active studies) with early triple-dose Gd-DTPA and 14 enhancing lesions (six active studies) 1 h after triple-dose Gd-DTPA (Filippi et al., 1995). The reasons for this discrepancy are not clear. It is unlikely that different imaging parameters contribute; the main difference was our use of 3 mm rather than 5 mm slices, but this might be expected to increase rather than decrease detection, as has been shown with three-dimensional T1-weighted gradient echo sequences in multiple sclerosis (Filippi et al., 1996c). With small studies, there is a possibility of selection bias, although we have studied 16 patients with a negative result. There were differences in clinical parameters between the two studies, our subjects having a longer disease duration (9 versus 6.5 years) and being relatively more disabled (median EDSS 7.5 versus 4.6). In addition, the diagnosis of primary progressive multiple sclerosis is historical, and therefore it is difficult to be absolutely certain about the absence of transient neurological episodes before onset of the progressive course.

Our findings in the primary progressive group raise the possibility that the pathological substrate of the slow progression in disability may be independent of blood–brain barrier disruption. Pathological studies have, however, shown inflammatory activity in patients with primary progressive multiple sclerosis, albeit less intense than in those with secondary progressive disease (Revesz et al., 1994). In relapsing–remitting and secondary progressive multiple sclerosis, the presence of gadolinium enhancement within lesions has been correlated with evidence of inflammation...
and active demyelination, as demonstrated by pathological examination of tissue obtained from post-mortem or stereotaxic biopsy (Nesbit et al., 1991; Katz et al., 1993; Rodriguez et al., 1993). It appears that, in primary progressive multiple sclerosis, the milder inflammatory changes are generally not associated with evident changes in blood–brain barrier permeability to gadolinium based contrast media. Studies of the blood–brain barrier using CSF markers nevertheless suggest that some disruption is commonly present (McLean et al., 1993), but do not differentiate between focal or diffuse changes in blood–brain barrier disruption. Whereas focal changes might result in visible enhancing lesions (contrasting with surrounding non-inflammatory tissue), diffuse disruption might be expected to cause subtle widespread intensity changes not apparent on visual evaluation. This might be studied using coregistration and subtraction methods on images before and after contrast medium. Such analysis will be the subject of a future report.

The study results have direct relevance to the use of gadolinium-enhanced MRI as an indicator of therapeutic efficacy in treatment trials. Whilst we have shown that the number of enhancing lesions detected may be significantly increased in relapsing–remitting and secondary progressive subgroups using the above methods, this has not been paralleled by such noticeable increases in the number of active studies. Indeed, some active studies with standard techniques were designated inactive with potentially more sensitive techniques. It is possible that minor amounts of patient movement during the study might have influenced the detection of small enhancing lesions. This may also reflect potential difficulties in interpreting areas of high signal, and in differentiating contrast enhancement from artefact. Such difficulties were highlighted by the results from the reported patient with primary progressive multiple sclerosis who showed activity with conventional early non-MT single-dose imaging alone. Retrospective analysis confirmed a small focal area of high signal in the left hemisphere on these images (with an underlying area of $T_2$/proton-density weighted hyperintensity), whilst subsequent images from the completed series confirmed this as a likely false positive result, with more obvious flow artefact arising from the third ventricle in this same region. Whilst imaging with triple-dose Gd-DTPA would always be expected to increase visible enhancement compared with the single dose (Tofts, 1996), techniques such as MT and delayed imaging might be expected to have different effects upon different lesions. This is especially likely with delayed imaging, where the time for optimal enhancement will depend on lesion size and the degree of blood–brain barrier deficit (Tofts, 1996). In a study of patients with relapsing–remitting and secondary progressive multiple sclerosis, it has been shown that delayed imaging 1 h following Gd-DTPA administration significantly increases the number of enhancing lesions detected that are over 10 mm$^2$, whilst smaller lesions may be better detected if imaging immediately follows Gd-DTPA administration (Filippi et al., 1996a).

When considering ‘activity’ (i.e. the presence of at least one enhancing lesion), it is likely that delayed imaging will have different effects for different lesions; this would account for the variable effect of delay on activity noted in this study, where certain patients were designated active only on early images. In this study, MT imaging appeared to result in an overall trend towards increased detection of enhancing lesions, although individual patients responded differently. Whilst the individual effect of MT imaging might be expected to differ according to the amount of tissue disruption both within the enhancing lesion and surrounding tissue, the lesion conspicuity should theoretically always be comparable or improved. In this study, MT imaging appeared to show fewer enhancing lesions than non-MT imaging in a minority of patients. Whilst differing degrees of flow artefact between the different imaging techniques might possibly account for this, it is more likely that small differences in imaging time following contrast-medium injection are responsible. The study was designed to minimize such effects, in that corresponding MT and non-MT images were acquired within 10 min of each other for each timepoint, and patients were alternated with respect to whether the post-contrast imaging sequence commenced with MT or non-MT imaging. Such differences in time of acquisition might account for individual patient variability, whilst the overall effect of MT in the whole group should be minimally affected due to the number of patients studied.

For any potential imaging technique to confer an advantage over existing methods, it should not only be more sensitive but should also have comparable or improved reliability. Previous authors have shown comparable inter-rater reproducibility for assessment of single-dose, triple-dose and 1 h delayed triple-dose images (Filippi et al., 1996d). The reliability of MT imaging and combined MT, delayed triple-dose imaging is currently being evaluated and will be the subject of a future report.

Another key question that remains to be answered is whether serial studies with triple-dose contrast medium would detect more lesions overall than those seen with serial single-dose imaging. Possible explanations for the increased sensitivity with cross-sectional evaluation include that (i) more new enhancing lesions are seen, or (ii) the same number of enhancing lesions are seen but they enhance for longer, i.e. on serial studies there will be more persistently enhancing lesions. Serial studies are required to resolve this.

The findings in this and other studies indicate that triple-dose Gd-DTPA, MT contrast and delayed imaging probably all increase the sensitivity of contrast-enhanced MRI studies in relapsing–remitting and secondary progressive multiple sclerosis, although the gain is greatest from the use of the triple dose. In contrast, in primary progressive multiple sclerosis, such methods are unlikely to be useful. Further studies are required to evaluate the reproducibility and longitudinal sensitivity of such combinations; the choice of optimal technique will require consideration of multiple
Acknowledgements

We wish to thank all those who volunteered for imaging and Miss K. Birnie, Miss A. Fletcher, Miss H. Gallagher, Miss B. Gunn, Miss L. Hughes, Miss P. Robinson and Miss S. Webb who carried this out. The NMR Research Unit is supported by a generous grant from the Multiple Sclerosis Society of Great Britain and Northern Ireland.

References


Miller DH, Albert PS, Barkhof F, Francis G, Frank JA, Hodgkinson factors including cost, safety, sensitivity, reproducibility and clinical predictive value.


Received October 24, 1996. Revised January 3, 1997. Accepted February 8, 1997