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MRI detection of hypointense brain lesions in patients with multiple sclerosis: T1 spin-echo vs. gradient-echo

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ABSTRACT

Objective: Compare T1 spin-echo (T1SE) and T1 gradient-echo (T1GE) sequences in detecting hypointense brain lesions in multiple sclerosis (MS).

Background: Chronic hypointense lesions on T1SE MRI scans are a surrogate of severe demyelination and axonal loss in MS. The role of T1GE images in the detection of such lesions has not been clarified.

Design/methods: In 45 patients with MS [Expanded Disability Status Scale (EDSS) score (mean ± SD) 3.5 ± 2.0; 37 relapsing-remitting (RR); 8 secondary progressive (SP)], cerebral T1SE, T1GE, and T2-weighted fluid-attenuated inversion-recovery (FLAIR) images were acquired on a 1.5 T MRI scanner. Images were re-sampled to axial 5 mm slices before directly comparing lesion detectability using Jim (v.7. Xinapse Systems). Statistical methods included Wilcoxon signed rank tests to compare sequences and Spearman correlations to test associations.

Results: Considering the entire cohort, T1GE detected a higher lesion volume (5.90 ± 6.21 vs. 4.17 ± 4.84 ml, p < 0.0001) and higher lesion number (27.82 ± 20.66 vs. 25.20 ± 20.43, p < 0.05) than T1SE. Lesion volume differences persisted when considering RR and SP patients separately (both p < 0.01). A higher lesion number by T1GE was seen only in the RR group (p < 0.05). When comparing correlations between lesion volume and overall neurologic disability (EDSS score), T1SE correlated with EDSS (Spearman r = 0.29, p < 0.05) while T1GE (r = 0.23, p = 0.13) and FLAIR (r = 0.24, p = 0.12) did not.

Conclusion: Our data suggest that hypointense lesions on T1SE and T1GE are not interchangeable in patients with MS. Based on these results, we hypothesize that T1GE shows more sensitivity to lesions at the expense of less pathologic specificity for tissue destruction than T1SE.

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1. Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the CNS, characterized by lesions and atrophy of the brain and spinal cord. MRI techniques have been the key in defining disease pathology and severity [1]. T1-weighted spin-echo (T1SE) images may show chronic hypointense lesions, which are known to represent severe/irreversible demyelination with axonal loss [1–6]. However, T1-weighted gradient-echo (T1GE) sequences also commonly show hypointense lesions in patients with MS [7]. Such images have an increasing role in both research and clinical settings with the growing use of 3 T scanners [1,8,9]. While the underlying pathologic substrate of chronic hypointense MS lesions on T1SE scans has been determined [3], there are no similar studies to date assessing the pathologic specificity of such lesions on T1GE scans. In this study, we compared T1SE and T1GE sequences side-by-side in patients with MS to clarify to what extent hypointense lesions are interchangeable between the two pulse sequences.

2. Methods

2.1. Subjects

Subjects’ demographic and clinical data are summarized in Table 1. We studied 45 consecutive patients with MS, all of which were assessed by a neurologist within one week of MRI for

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disability by the Expanded Disability Status Scale (EDSS) and timed 25-foot walk.

2.2. Image acquisition

All patients underwent brain MRI on the same scanner (1.5 T Gyroscan ACS-NT; Phillips, Best, the Netherlands) using the same acquisition protocol, including 2D T1-weighted spin-echo (T1SE), 3D T1-weighted gradient-echo (T1GE), and 2D T2-weighted fluid-attenuated inversion-recovery (FLAIR). Only non-contrast images were available; the patients did not receive intravenous gadolinium. T1SE images had a voxel size of $0.89 \text{mm} \times 0.89 \text{mm} \times 5 \text{mm}$, TR = 400 ms, TE = 10 ms, 24 gapless axial slices. T1GE had a voxel size of $0.98 \text{mm} \times 0.98 \text{mm} \times 2.5 \text{mm}$, TR = 24 ms, TE = 7 ms, 70 gapless coronal slices. FLAIR images had a voxel size of $0.94 \text{mm} \times 0.94 \text{mm} \times 5 \text{mm}$, TR = 8000 ms, TE = 120 ms, inversion time = $2200 \text{ms}$, 24 gapless axial slices.

2.3. MRI analysis

Lesions on each of the FLAIR, T1SE, and T1GE images were first marked by a trained observer (SD). These were verified by a senior observer (ST). All three images were reviewed concurrently. The trained observer then measured whole brain lesion volumes from all three images by a semi-automated edge-finding tool using Jim (v.7, Xinapse Systems, West Bergholt, UK; www.xinapse.com), as previously described [10]. It was not possible for the raters to be blinded to the type of T1-weighted MRI sequence because T1SE and T1GE images had distinct differences in their tissue contrast. A hypointensity on T1SE or T1GE images was only classified as a lesion if it also showed at least partial hyperintensity on FLAIR images, a requirement that was applied to avoid the inclusion of benign cysts or enlarged perivascular spaces as MS lesions. In addition, whole brain lesion number was measured for T1SE and T1GE images.

Given the differences in native orientation and resolution between the T1SE and T1GE images, the latter were re-sampled to match T1SE images (and approximate the FLAIR images) in orientation and voxel size using Jim. The primary analysis in all subjects was performed using native T1SE, re-sampled T1GE, and native FLAIR images.

To assess whether image resampling alone would have any effect on the diagnostic yield, we performed a sub-study of 10 randomly chosen T1SE scans. The two image sets were matched on voxel size and axial orientation. The Pearson correlation between total cerebral lesion volume obtained from native vs. re-sampled was an $r = 0.99$, indicating very high agreement; therefore, we present the full cohort data obtained from the native T1SE images. Sample images are shown in Fig. 1.

### Table 1

Demographics and clinical data.

<table>
<thead>
<tr>
<th>Patients with MS ($n$)</th>
<th>$n = 45$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>$42.3 \pm 8.3$ (23–59)</td>
</tr>
<tr>
<td>Men</td>
<td>$n = 12$ (27%)</td>
</tr>
<tr>
<td>Disease category</td>
<td>Relapsing-remitting: $n = 37$ (82%)</td>
</tr>
<tr>
<td></td>
<td>Secondary progressive: $n = 8$ (18%)</td>
</tr>
<tr>
<td>Disease duration</td>
<td>$11.0 \pm 7.8$ (1–38)</td>
</tr>
<tr>
<td>EDSS score</td>
<td>$3.5 \pm 2.0$ (1–8)</td>
</tr>
<tr>
<td>T25FW</td>
<td>$13.3 \pm 29.5$ (4–170)</td>
</tr>
</tbody>
</table>

Key: mean ± standard deviation (range); MS, multiple sclerosis; disease duration (years), years since first symptoms; EDSS, Expanded Disability Status Scale; T25FW(s), timed 25 foot walk.

### 2.4. Statistical analysis

T1SE and T1GE derived lesion volumes and lesion numbers were compared in all patients and between patient subgroups with Wilcoxon tests. Spearman or Pearson correlations were used to assess MRI vs. clinical and MRI vs. MRI relationships. A $p < 0.05$ was considered significant.

### 3. Results

#### 3.1. T1SE vs. T1GE derived lesion volumes and lesion numbers

Considering the entire cohort, a high correlation was seen between T1SE and T1GE when comparing both lesion volume (Spearman $r = 0.98$, $p < 0.0001$) and lesion number ($r = 0.94$, $p < 0.0001$) as depicted in Fig. 2.

Significant differences were seen when comparing T1SE derived lesion measures to T1GE (Table 2, Figs. 1–3). When considering all subjects, T1GE detected a higher lesion volume than T1SE [($\text{mean} \pm \text{SD}$) 5.90 ± 6.21 vs. 4.17 ± 4.84 ml, $p < 0.0001$]. When assessing the RR and SP patient subgroups separately, the significant lesion volume differences persisted. In the RR subgroup, T1GE derived lesion volumes were significantly higher than T1SE measures (4.87 ± 5.05 vs. 3.22 ± 3.49, $p < 0.0001$). The same was observed in the SP patient subgroup (10.64 ± 8.94 vs. 8.52 ± 7.65, $p = 0.008$).

Similarly, when considering the entire cohort, T1GE derived lesion numbers were significantly higher than T1SE (27.82 ± 20.66 vs. 25.20 ± 20.43, $p = 0.02$). These lesion number differences were also observed in the RR patient subgroup (24.95 ± 18.98 vs. 21.73 ± 17.79, $p = 0.01$). However, the difference did not persist in the SP patient subgroup; T1GE and T1SE derived measures were not significantly different (41.13 ± 24.14 vs. 41.25 ± 25.25, $p = 0.98$).

#### 3.2. RR vs. SP patient subgroups

As shown in Table 2, when comparing RR and SP patient groups, SP patients had a significantly higher T1SE lesion volume ($p = 0.04$) and lesion number ($p = 0.03$) than RR patients; however, this was not seen on T1GE scans (both $p > 0.05$). The aforementioned differences were not robust in that RR and SP patients were not significantly different in terms of their T1GE and T1SE method disparities (volume and number both $p > 0.35$).

#### 3.3. Correlation between MRI and neurologic function

Among all MRI lesion measures, only T1SE lesion volume showed significant correlations with clinical status (Table 3). T1SE

### Table 2

Hypointense lesion volume and number: T1SE vs. T1GE.

<table>
<thead>
<tr>
<th>FLAIR</th>
<th>2D T1 spin-echo</th>
<th>3D T1 gradient-echo</th>
<th>$p$ (T1SE vs. T1GE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesion vol. (ml)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>12.9 ± 13.2</td>
<td>4.2 ± 4.8</td>
<td>5.9 ± 6.2</td>
</tr>
<tr>
<td>RR</td>
<td>10.7 ± 10.0</td>
<td>3.2 ± 3.5</td>
<td>4.9 ± 5.1</td>
</tr>
<tr>
<td>SP</td>
<td>23.1 ± 20.7</td>
<td>8.5 ± 7.7</td>
<td>10.6 ± 8.9</td>
</tr>
<tr>
<td>$p$ (RR vs. SP)</td>
<td>0.11</td>
<td>0.04</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Lesion number</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>–</td>
<td>25.2 ± 20.4</td>
<td>27.8 ± 20.7</td>
</tr>
<tr>
<td>RR</td>
<td>–</td>
<td>21.7 ± 17.8</td>
<td>25.0 ± 19.0</td>
</tr>
<tr>
<td>SP</td>
<td>–</td>
<td>41.3 ± 25.3</td>
<td>41.1 ± 24.1</td>
</tr>
<tr>
<td>$p$ (RR vs. SP)</td>
<td>–</td>
<td>0.03</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Key: data are mean ± standard deviation; total cerebral hypointense lesion volume and number are shown; FLAIR, fluid-attenuated inversion-recovery; RR, relapsing-remitting MS; SP, secondary progressive MS; FLAIR lesion number was not assessed; vol., volume. * $p < 0.05$.
**Fig. 1.** MRI scans from a patient showing the higher sensitivity of T1GE vs. T1SE in detecting a multiple sclerosis (MS) white matter lesion. This is a 45 year-old woman with relapsing-remitting MS of 11 years disease duration and mild physical disability (Expanded Disability Status Scale score=2.5; Timed 25 foot walk=5.7 s). The white arrows show a lesion detected by FLAIR and T1GE but not T1SE. The patient’s whole brain lesion volume was: FLAIR = 15.9 ml, T1SE = 4.1 ml, T1GE = 4.8 ml. Note: FLAIR, fluid-attenuated inversion-recovery; T1SE, T1 spin-echo; T1GE, T1 gradient-echo. Resampled T1SE and T1GE images are shown.

**Fig. 2.** Cerebral hypointense lesion volume and number in 45 patients with multiple sclerosis: T1SE vs. T1GE. A high correlation was seen between T1SE and T1GE when comparing both total cerebral volume and number of lesions. Note: T1SE, T1 spin-echo; T1GE, T1 gradient-echo; vol., total cerebral volume (ml); num, total cerebral number of lesions; small circles indicate individual subjects; large circles represent means.

**Fig. 3.** MRI scans from a patient showing the higher sensitivity of T1GE vs. T1SE in detecting juxtacortical/cortical multiple sclerosis (MS) lesions. The upper panel shows the native images. The lower panel shows zoomed and cropped images to illustrate the key findings. This is a 45 year-old woman with relapsing-remitting MS of 13 years disease duration and mild physical disability (Expanded Disability Status Scale score = 1.5; Timed 25 foot walk = 6.0 s). The white arrows show lesions detected by FLAIR and T1GE but not T1SE. The patient’s whole brain lesion volume was: FLAIR = 38.3 ml, T1SE = 12.5 ml, T1GE = 16.2 ml. Note: FLAIR, fluid-attenuated inversion-recovery; T1SE, T1 spin-echo; T1GE, T1 gradient-echo. Resampled T1SE and T1GE images are shown.
correlated significantly with EDSS score \( (r = 0.299, p < 0.05) \), while T1GE \( (r = 0.231, p = 0.127) \) and FLAIR \( (r = 0.237, p = 0.116) \) did not. In addition to EDSS score, correlations between lesion volume and disease duration and timed 25-foot walk were compared; however, no significant associations were found (Table 3).

4. Discussion

The purpose of this study was to clarify the role of a T1GE sequence in MS cerebral hypointense lesion detection by direct comparison to a conventional T1SE sequence. The results indicate, from several perspectives, that T1GE images show more sensitivity than T1SE. This included the detection of both a significantly higher lesion number and total cerebral lesion volume than T1SE. Furthermore, the increased sensitivity to a higher lesion volume was broadly present in the cohort, continuing to persist when separately considering the RR and SP patient subgroups. However, the significant increase in lesion number detection by T1GE vs. T1SE scans was not seen in the SP subgroup. This comparison may have been under-powered due to the small sample size in the SP group. Alternatively, this may relate to the change in biologic dynamics as patients progress from the RR to SP phase of the disease. As disability increases, patients are known to experience a plateauing of adaptive immunity-related new inflammatory events and are thus less likely to form new lesions [11,12]. However, the lesion load may continue to slowly increase due to innate immunity-mediated chronic inflammation and Wallerian degeneration [12]. The T1GE and T1SE images were obtained on the same scanner at the same time and were matched on voxel size/resolution. Thus the higher sensitivity is likely intrinsic to the T1GE pulse sequence owing to technical factors such as improved tissue contrast [13].

We also assessed the validity of the two sequences, defined as the relationships between MRI findings and clinical status. The findings of this study suggest that T1GE images show a closer relationship to disease severity than T1SE. This higher validity of T1SE was seen in several ways. First, when comparing RR to SP patients, a significantly higher lesion volume was shown in SP patients on T1SE but not T1GE images. Second, when comparing MRI findings to the level of neurologic function, only T1SE-defined lesion load showed a significant (albeit weak-to-moderate) correlation with EDSS score, a relationship that has been shown by several previous studies [1–3,5,14]. Thus, we hypothesize that the lesions shown on T1GE are less specific for destructive irreversible changes (e.g. severe demyelination, axonal loss) than T1SE. Such lesions on T1GE images may instead represent a wide range of pathologic features, some of which are mild and potentially reversible (e.g. inflammation, edema, gliosis, partial demyelination). Such non-specificity would be analogous to what has been reported within T2 hyperintense MS lesions, which also show weaker relationships to clinical status than T1SE-defined hypointense lesions [2,4,15].

Our study suggests that T1GE and T1SE derived lesion measures are not interchangeable. The T1SE sequence appears to be less sensitive but more specific in detecting focal lesions with severe tissue damage compared to the T1GE sequence. Nonetheless, our study does not discount the continuing important role of T1GE images in MS research. Such images provide a range of benefits compared to conventional SE sequences such as the improved detectability of cortical lesions and the improved suitability of these images for fine structure definition and morphometric segmentations [7,13,16–20].

There are limitations of our study worthy of comment. We performed this study with low resolution images on a 1.5 T scanner at one time point, with a limited sample size. Given the small size of the SPMS subgroup, the RR vs. SP comparisons should be viewed as pilot data representing preliminary results. In addition, a possible bias was present due to the inability to blind the observers to image type. Furthermore, the native resolution differences between the T1SE and T1GE images may have introduced inherent partial volume averaging differences despite the resampling of the data sets. Future studies should longitudinally assess any differences at higher field strength (e.g. 3T) platforms with 3D high resolution data sets. In addition, it would be interesting to extend our results by performing histological analysis in order to verify whether T1GE images do in fact show less pathologic specificity for destructive lesions than T1GE images.

Conflict of interest

None of the other authors or institutions has a conflict of interest.

Support and disclosures

None.

References


