Detectability of multiple sclerosis lesions with 3 T MRI: A comparison of proton density-weighted and FLAIR sequences

Détection des lésions de sclérose en plaques en IRM 3 T : comparaison entre les séquences FLAIR et densité de protons

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KEYWORDS
FLAIR;
Proton density;
3 T;
Multiple sclerosis

Summary
Objective: Due to the high signal intensity of cerebrospinal fluid (CSF), proton density-weighted (PD-w) images with long repeat times (TR) may be less able to detect periventricular lesions in patients with multiple sclerosis (MS). However, we have found good detectability of MS lesions with PD-w using long TR at 3 Tesla (3 T). For this reason, the aim of this study was to prospectively investigate the detectability of MS lesions at 3 T in PD-w compared with fluid-attenuated inversion recovery (FLAIR) sequences.

Patients and methods: A total of 11 MS patients were examined by a 3 T magnetic resonance (MR) scanner, and their MS lesions were prospectively analyzed on PD-w and FLAIR images by two evaluators; detectability was rated by a three-point scoring system. The Wilcoxon signed-rank test was used for comparisons, and the level of significance was P < 0.05.

Results: Significantly more lesions were detectable on PD-w images (P < 0.001 for both evaluators). In particular, PD-w was superior to FLAIR for the detection of periventricular (P = 0.001 and P = 0.013 for each evaluator respectively) and infratentorial (P < 0.001 for both evaluators) lesions.

Conclusion: This was the first study to compare FLAIR and PD-w with long TR at 3 T; it revealed that PD-w is superior for detecting infratentorial and even periventricular MS lesions, despite the higher signal intensity of CSF. This might be due to the high spin density of MS lesions, thus distinguishing them from the surrounding brain tissue. For this reason, double-echo T2-weighted sequences at 3 T are recommended to improve the detectability of MS lesions.

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Introduction

Magnetic resonance imaging (MRI) plays a key role in the internationally standardized diagnostic criteria of multiple sclerosis (MS) [1,2]. It is a basic tool in the diagnosis of MS, and has improved its diagnostic sensitivity and specificity. Classically, MRI criteria are based on the hyperintense lesions seen on T2-weighted (T2-w) images, contrast enhancement and follow-up [3,4].

Before fluid-attenuated inversion recovery (FLAIR) sequences were introduced into clinical use, proton density-weighted (PD-w) sequences with repetition times (TR) of around 2000 ms were also part of MS protocols. These sequences yielded good contrast between cerebrospinal fluid (CSF) and lesions due to additional T1 effects. Comparative studies using lower field-strength scanners (1.0 T and 1.5 T) found that the FLAIR sequence was highly sensitive in detecting MS lesions, whereas the PD-w was superior for detecting infratentorial lesions [5–8]. Thus, FLAIR is widely accepted in clinical protocols and has replaced the double spin-echo sequence, which yields both T2-w and PD-w images.

Over the past few decades, higher field strengths (3 T) have been introduced into the clinical routine and provided an improved detectability of MS lesions [for a review: Lunde Larsen et al. [9]]. Recent higher-field-strength studies have mainly investigated non-conventional, more sophisticated and specialized sequences to improve sensitivity of lesion detection [10–14]. However, sequences have varied among the investigators and between different MR tomographs. Furthermore, some of these sequences were not suitable as a standard diagnostic procedure because of long acquisition times.

Using standard sequences as a clinical routine, Wattjes et al. [15] found greater sensitivity with FLAIR images for detecting MS lesions at 3 T compared with T2-w images. However, T2-w images were superior in the infratentorial fossa, and no reference was made to PD-w sequences. Indeed, higher field strengths might be disadvantageous for lesion detection in conventional PD-w sequences because of the reduced influence of spin density due to increased T1 effects.

However, when dealing with MS patients, PD-w images with long TR in a 3-T scanner have revealed good contrast between MS lesions and normal brain tissue not only infratentorially, but also in supratentorial periventricular areas. This led us to compare the sensitivity of conventional FLAIR and PD-w images in detecting MS lesions at 3 T.

Methods

Patients

MRI examinations were prospectively performed in 11 consecutive MS patients (10 women; median age: 38 years) admitted to our hospital for routine diagnostic and therapeutic procedures. All patients had been diagnosed with MS according to the McDonald criteria [nine patients had relapsing remitting MS (RRMS), and two had secondary progressive MS (SPMS)], but durations of disease and treatment regimes differed among them.

Table 1. Acquisition parameters for the fluid-attenuated inversion recovery (FLAIR), proton density-weighted (PD-w) and T2-weighted (T2-w) double-echo sequences.

<table>
<thead>
<tr>
<th></th>
<th>FLAIR</th>
<th>PD-w/T2-w</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix size</td>
<td>320 x 256</td>
<td>320 x 256</td>
</tr>
<tr>
<td>Field of view (mm)</td>
<td>220 x 176</td>
<td>220 x 176</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>131</td>
<td>12/104</td>
</tr>
<tr>
<td>Repeat time (ms)</td>
<td>6140</td>
<td>4260</td>
</tr>
<tr>
<td>Inversion time (ms)</td>
<td>2146</td>
<td>—</td>
</tr>
<tr>
<td>Flip angle (')</td>
<td>130</td>
<td>150</td>
</tr>
<tr>
<td>Bandwidth (Hz/pixels)</td>
<td>446</td>
<td>186</td>
</tr>
<tr>
<td>Acceleration factora</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Number of averages</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Echo train length</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Orientation</td>
<td>Axial</td>
<td>Axial</td>
</tr>
<tr>
<td>Slice number</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Slice gap (mm)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Acquisition time (min s)</td>
<td>5.09</td>
<td>3.56</td>
</tr>
</tbody>
</table>

a Parallel imaging.

Magnetic resonance imaging (MRI)

Patients were examined on a Magnetom Verio 3 T Scanner (Siemens, Erlangen, Germany) using an eight-channel head coil. The protocol included an axial double-echo T2-w sequence, axial FLAIR and axial T1-weighted (T1-w) images before and after administration of contrast agent (gadobutrol), as well as sagittal T2-w and coronal contrast-enhanced T1-w images. All axial sequences were performed using the same spatial coordinates and orientation. The acquisition parameters used in our MS protocol are presented in Table 1.

Image analyses

Analyses were performed on the FLAIR and PD-w images by two independent neuroradiologists, one of whom was more experienced in the evaluation of MS lesions. While the first evaluator (‘evaluator 1’, an experienced junior neuroradiologist) began evaluation of lesions on PD-w, the second (‘evaluator 2’, a senior neuroradiologist) started the analyses on FLAIR. Only lesions more than 3 mm in diameter were included in the analysis. Hyperintense lesions were classified by location as infratentorial lesions, periventricular lesions, subcortical lesions, white-matter (WM) lesions and cortical lesions. Also, the lesions were additionally graded by recognizability as: firstly, the evaluator was sure it was a lesion, and not a partial-volume effect, artifact or perivascular space; secondly, the evaluator was not entirely sure it was a lesion; and thirdly, the lesion was only detectable in one sequence (missed in the other sequence).

Statistical analysis

A non-parametric paired test (Wilcoxon’s signed-rank test) was used to test the null hypothesis that the PD-w sequence...
with long TR was inferior to FLAIR for detecting MS lesions at 3T. As the first step, all lesions detected on FLAIR and PD-w images by both evaluators were compared. In the second step, the lesion detection rate of each evaluator comparing FLAIR and PD-w at each location was analyzed separately. A lesion was ranked as 'better defined' in one sequence compared with the other when it had a better grade of recognizability (see above), and as 'equally defined' when it had the same grade. The PD-w and T2-w images were not compared.

### Results

Evaluator 1, who started with the PD-w sequences, found 352 hyperintense lesions (mean: 32 per patient; range: 11–73), whereas evaluator 2, who started the analyses with FLAIR, found 277 lesions (mean: 25 per patient; range: 11–55). Evaluator 1 detected 261 equivalent lesions on both PD-w and FLAIR sequences, 21 of which were rated as better defined on FLAIR while 70 were considered better defined on PD-w. The null hypothesis was rejected (Z = –5.398 for evaluator 1, Z = –5.728 for evaluator 2; *P* < 0.001 for both). Evaluator 2 detected 227 equivalent lesions on both PD-w and FLAIR sequences; five lesions were rated as better defined on FLAIR, and 45 were considered better defined on PD-w (Table 2). Also, the global detection rate on PD-w sequences was significantly better for both evaluators. According to location, PD-w images were clearly more reliable for detecting infratentorial and periventricular lesions. Infratentorial lesions were detected at a higher rate on PD-w compared with FLAIR sequences for both evaluators (*P* < 0.001), and periventricular lesions were also significantly better detected by PD-w sequences by both evaluators. In addition, evaluator 1 detected significantly more WM lesions on PD-w than on FLAIR after first analyzing the PD-w sequence (Tables 3 and 4). The results were different for evaluator 2, who first analyzed FLAIR; in this case, the detection rate with PD-w was not better than with FLAIR (*P* < 0.1). Furthermore, the detection of cortical and subcortical lesions was not inferior on PD-w sequences compared with FLAIR.

### Discussion

Regarding supratentorial lesions, previous reports [5–7] have shown comparable detection rates when comparing PD-w and FLAIR at 1.0 T and 1.5 T. Before FLAIR was introduced, PD-w sequences with shorter TR (between 2000 and 3000 ms) were used in addition to T2-w spin-echo (SE) sequences. The shorter TR sequences yielded a T1 effect whereby CSF was hypointense in relation to the brain parenchyma. As MS lesions have higher water content [16] and spin density, the detectability of the parenchymal changes may have been reduced. In contrast, FLAIR suppresses liquid signals (for example, CSF) whereas MS lesions maintain their hyperintense signals. This increases the contrast between the lesion and CSF or brain tissue, with better visibility of intraparenchymal changes.

To date, many studies have compared the detectability of MS at 1.5 T and 3 T [17,18], including PD-w, and found

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**Table 2** Total number of detected lesions for each evaluator.

<table>
<thead>
<tr>
<th></th>
<th>Evaluator 1</th>
<th>Evaluator 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Better defined on FLAIR</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Better defined on PD-w</td>
<td>70</td>
<td>45</td>
</tr>
<tr>
<td>Equally defined (FLAIR and PD-w)</td>
<td>261</td>
<td>227</td>
</tr>
<tr>
<td>Total number of detected lesions</td>
<td>352</td>
<td>277</td>
</tr>
</tbody>
</table>

FLAIR: fluid-attenuated inversion recovery; PD-w: proton density-weighted.

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**Table 3** Number of detected lesions at each location as analyzed by the two study evaluators.

<table>
<thead>
<tr>
<th>Evaluator</th>
<th>Infratentorial</th>
<th>Periventricular</th>
<th>Subcortical</th>
<th>White matter</th>
<th>Cortical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Better defined on FLAIR</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Better defined on PD-w</td>
<td>25</td>
<td>23</td>
<td>11</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Equally defined</td>
<td>4</td>
<td>6</td>
<td>58</td>
<td>62</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>29</td>
<td>69</td>
<td>72</td>
<td>62</td>
</tr>
</tbody>
</table>

FLAIR: fluid-attenuated inversion recovery; PD-w: proton density-weighted.

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**Table 4** Results of the Wilcoxon signed-rank test of the null hypothesis* for detecting multiple sclerosis (MS) lesions in the various brain regions by the two study evaluators.

<table>
<thead>
<tr>
<th>Evaluator</th>
<th>Infratentorial</th>
<th>Periventricular</th>
<th>Subcortical</th>
<th>White matter</th>
<th>Cortical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><em>P</em></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>0.001</td>
<td>0.013</td>
<td>0.157</td>
</tr>
</tbody>
</table>

*a* Inferiority of proton density-weighted versus fluid-attenuated inversion recovery (FLAIR) sequences.
Figure 1  Transverse fluid-attenuated inversion recovery (FLAIR) (a) and proton density-weighted (PD-w) (b) images show good detectability of periventricular multiple sclerosis lesions (arrows) on PD-w images; on FLAIR, closely adjoining lesions appear as a diffuse hyperintensity (especially on the right) or may even be missed completely.

higher detectability of MS lesions with higher field strengths. However, no study has investigated PD-w versus FLAIR for supratentorial lesions at 3 T.

Higher field strengths generally lead to longer T1 spin-lattice relaxation times. To minimize T1 effects, the present study used PD-w with long TR (4260 ms). In such sequences, CSF is hyperintense compared with cerebral parenchyma. In fact, PD-w proved to be superior, not inferior, for the detection of periventricular MS lesions (Fig. 1). It appears that the good detectability of the lesions may be attributed to their high signal intensity as well as the high contrast between the lesions and periventricular brain tissue. Notably, PD-w images also revealed good discrimination of anatomical structures, particularly by defining and differentiating between lesions and perivascular spaces. This finding is remarkable, considering that FLAIR is so widely accepted and regarded as superior for the evaluation of supratentorial lesions. However, it should be noted that our study did not evaluate FLAIR images after contrast administration. Kataoka et al. [19] have suggested that early contrast-enhanced imaging with FLAIR may be helpful for the further detection of MS plaques, especially periventricular and juxta-cortical lesions.

According to our present results, the detection of supratentorial WM lesions apparently depends on which sequence the evaluator rated first. The evaluator who started with PD-w detected more WM lesions than the evaluator who analyzed FLAIR first. This suggests that more attention is paid to analysis of the initial sequence, and also that FLAIR is the less sensitive sequence, all the more so as the evaluator who started with PD-w was less experienced than the other evaluator. This also raises the question of whether FLAIR presents closely adjoining lesions as a single lesion, thereby offering an explanation as to why fewer lesions were detected by evaluator 2.

In the posterior fossa, the PD-w sequence at 3 T and long TR clearly yielded a better detection rate for MS lesions (Fig. 2). This finding is in line with previous reports comparing PD-w and FLAIR at 1.5 T [5–7]. Compared with FLAIR, PD-w is less prone to pulsatile inflow CSF artifacts in the posterior fossa. The detection of infratentorial MS lesions is crucial for confirming the diagnosis of MS according to the Barkhof criteria, as their presence implies an increased risk of disability [20,21].

Finally, the number of cortical lesions found in this study was small (17 in total), making a reliable statement about these lesions impossible. A further limitation of our present study was the use of only one scanner; this means that the consistency of our findings remains to be confirmed by other 3-T scanners.
MS lesions in proton density MR-images at 3T

Figure 2  Transverse FLAIR (a), PD-w (b) and T2-weighted (c) images show that, in the posterior fossa, PD-w clearly offers better detectability of multiple sclerosis lesions at 3T. This finding is in line with previously reported data comparing PD-w and FLAIR sequences at 1.5T. Lesions (arrows) may be missed on FLAIR images.

Conclusion

FLAIR should not replace PD-w sequences at 3T in MR protocols for MS patients. Instead, PD-w and T2-w double-echo sequences with long TR should be performed in addition to FLAIR. A further advantage is that these double-echo sequences do not prolong overall scan time.
Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References


