Double Inversion Recovery Brain Imaging at 3T: Diagnostic Value in the Detection of Multiple Sclerosis Lesions


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BACKGROUND AND PURPOSE: To prospectively determine the sensitivity in the detection of multiple sclerosis (MS) lesions by using double inversion recovery (DIR), fluid-attenuated inversion recovery (FLAIR), and T2-weighted turbo spin-echo (T2 TSE) MR imaging at 3T.

METHODS: Seventeen patients presenting with a clinically isolated syndrome (CIS) suggestive of MS, 9 patients with definite MS, and 6 healthy control subjects were included. Imaging was performed on a 3T MR system using DIR, FLAIR, and T2 TSE sequences. Lesions were counted and classified according to 5 anatomic regions: infratentorial, periventricular, deep white matter, juxtacortical, and mixed white matter-gray matter. The sensitivity at DIR was compared with the corresponding sensitivity at FLAIR and T2 TSE sequence. The contrast between lesions and normal-appearing gray matter, normal-appearing white matter, and CSF was determined for all sequences.

RESULTS: Because of higher lesion-white matter contrast, the DIR showed a higher number of lesions compared with the FLAIR (7% gain, \( P = 0.04 \)) and the T2 TSE (15% gain, \( P = 0.01 \)). The higher sensitivity was also significant for the infratentorial region compared with the FLAIR (56% gain, \( P = 0.02 \)) and the T2 TSE (44% gain, \( P = 0.02 \)). Compared with the FLAIR, no significant changes of the lesion load measurements were observed in the supratentorial brain: slightly higher numbers of periventricular and mixed gray matter-white matter lesions on the DIR were counterbalanced by a slightly reduced sensitivity regarding juxtacortical lesions.

CONCLUSION: DIR brain imaging at 3T provides the highest sensitivity in the detection of MS lesions especially in the infratentorial region.

Multiple sclerosis (MS) is the most frequent chronic inflammatory demyelinating disease of the central nervous system (CNS), predominantly affecting the white matter but also parts of the gray matter.\(^1-4\) The diagnosis and disease monitoring of MS is mainly based on MR imaging, which allows the establishment of an early diagnosis of MS within diagnostic criteria.\(^5,8\) Furthermore, MR imaging has a substantial prognostic value in patients with clinically isolated syndromes (CIS) suggestive of MS concerning the prediction of the conversion to definite MS as well as long-term disability and brain atrophy.\(^9-13\)

MR imaging in the diagnosis of MS is performed as a multisequence protocol including T2-weighted, fluid-attenuated inversion recovery (FLAIR) and precontrast and postcontrast T1-weighted sequences.\(^14,15\) The pulse sequences show different sensitivities in the detection of inflammatory brain lesions depending on their anatomic location. FLAIR imaging provides the highest sensitivity in the detection of lesions close to the CSF, such as the juxtacortical and the periventricular white matter, but is less sensitive in the posterior fossa.\(^16-18\) T2-weighted conventional spin-echo or turbo spin-echo (T2 TSE) sequences are known to be more sensitive in the detection of infratentorial lesions but have difficulties detecting juxtacortical lesions.\(^13,16-18\) Unfortunately, no pulse sequence is available that provides a combination of a high sensitivity for the detection of supratentorial and infratentorial brain lesions in MS patients.

Several years ago, a double inversion recovery pulse sequence (DIR) was introduced.\(^19\) This sequence provides 2 different inversion pulses, which attenuates the CSF as well as the whole white matter, thus achieving a superior delineation between gray and white matter. So far, this sequence has been evaluated at 1.5T in only a limited number of patients with various disease entities, including vascular, inflammatory, malignant, and degenerative CNS diseases.\(^20,21\)

The aim of our study was to evaluate the diagnostic value of a DIR sequence at high-field MR imaging operating at 3T in the detection of MS lesions by prospectively comparing DIR with FLAIR and T2-weighted pulse sequences.

Methods

Patients and Healthy Control Subjects

Twenty-six patients were prospectively included in this intraindividual comparative study. Seventeen patients presented with a CIS suggestive of MS (median age, 40 years; range, 19–56 years; mean disease duration, 5 months; range, 0–8 months; median Expanded Disability Status Scale [EDSS], 1; range, 0–4). Nine patients had a relapsing-remitting course of multiple sclerosis (median age, 36 years; range, 23–47 years; mean disease duration, 51 months; range, 3–189 months; median EDSS, 1.5; range, 0–6). Among the patients presenting with CIS, 10 patients presented with unilateral optic neuritis, 3 patients with spinal cord syndromes, 3 patients with brain stem syndromes, and one patient with a polysymptomatic CIS. In addition, 6 healthy control subjects (3 men, 3 women; median age, 28 years) were...
inversion pulse and the 90° excitation pulse. The short inversion time TI2 (325 ms) is according to the guidelines of the Consortium of MS Centers.14

5/0.9/0.9 mm. The scan orientation and repositioning was performed metric and resolution parameters using a measured voxel size of sequences were performed with identical anatomic positions and geo-

Because of the additional second inversion pulse, the first inversion time of the FLAIR sequence has to be prolonged compared with the TI of the FLAIR sequence to provide a sufficient CSF attenuation. The detailed sequence parameters are given in Table 1. All measurements were obtained using the region-of-interest analysis. The regions were placed in the lesions, the NAWM, NAGM, and CSF. The contrast measurements between lesions and the NAWM were performed separately in the infratentorial, periventricular, juxtacortical, and deep white matter regions. Signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) could not be calculated because of the automatic implementation of the constant level appearance (CLEAR) algorithm for signal intensity homogeneity correction of the images obtained by the 8-element SENSE head coil.

Statistical Analysis
The analysis of brain lesions on the different pulse sequences was performed lesion- and patient-wise. The statistical differences in both analyses were assessed using the Wilcoxon test for matched pairs. The relative comparison of the numbers of lesions on DIR versus FLAIR and T2 TSE, respectively, was expressed as percentage gain or a loss in the number of detected brain lesions.

The significances of contrast differences between the 3 sequences were assessed using the Wilcoxon test for matched pairs. All calculations were performed by the SPSS software package (SPSS, Chicago, Ill.). P values $\leq 0.05$ were considered as statistically significant.

Results

Healthy Control Subjects
Besides discrete high-signal-intensity changes caused by CSF effusion effects in the periventricular white matter and in the periaqueductal area, no unspecific white matter or gray matter abnormalities were identified on the T2 TSE, FLAIR, and DIR images.

The DIR images showed slightly more artifacts in the posterior fossa in terms of vascular and flow artifacts than the corresponding FLAIR and T2 TSE images. Both readers found that those artifacts did not impair the diagnostic quality compared with the FLAIR and T2 TSE images. The attenuation of the CSF was sufficient and similar on the FLAIR and DIR images.

Patients with CIS and MS
The detailed results of the lesion load analysis are given in Table 2. In our patients with suspected or definite MS, 201 lesions could be identified with T2 TSE, 216 lesions with FLAIR, and 232 lesions with DIR. This higher overall detection rate at DIR was significant compared with both T2 TSE ($P = 0.01$) and FLAIR ($P = 0.04$) MR imaging. Considering the different anatomic regions, the higher detection rate of the DIR imaging was significant for the detection of infratentorial lesions compared with the T2 TSE ($P = 0.02$) and FLAIR ($P =

Table 1: MRI sequence parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DIR</th>
<th>FLAIR</th>
<th>T2 TSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of view (mm)</td>
<td>230</td>
<td>230</td>
<td>230</td>
</tr>
<tr>
<td>Matrix</td>
<td>256</td>
<td>256</td>
<td>256</td>
</tr>
<tr>
<td>Section thickness (mm)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Measured voxel size (mm)</td>
<td>0.90/0.90/5</td>
<td>0.90/0.90/5</td>
<td>0.90/0.90/5</td>
</tr>
<tr>
<td>SENSE factor</td>
<td>1.5</td>
<td>1.6</td>
<td>1.6</td>
</tr>
<tr>
<td>Turbo factor</td>
<td>13</td>
<td>38</td>
<td>16</td>
</tr>
<tr>
<td>Repetition time (ms)</td>
<td>11000</td>
<td>12000</td>
<td>4100</td>
</tr>
<tr>
<td>Echo time (ms)</td>
<td>29</td>
<td>140</td>
<td>100</td>
</tr>
<tr>
<td>Inversion time (ms)</td>
<td>3400/325*</td>
<td>2950</td>
<td></td>
</tr>
<tr>
<td>Number of signals averaged</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bandwidth/pixel (Hz)</td>
<td>277.9</td>
<td>287</td>
<td>184.3</td>
</tr>
<tr>
<td>Acquisition time (minutes:seconds)</td>
<td>3:18</td>
<td>4:00</td>
<td>2:19</td>
</tr>
</tbody>
</table>

Note:—DIR indicates double inversion recovery; FLAIR, fluid-attenuated inversion recovery; T2 TSE, T2-weighted turbo spin-echo; SENSE sensitivity encoding.

* The long inversion time TI1 (3400 ms) is defined as the interval between the first 180° inversion pulse and the 90° excitation pulse. The short inversion time TI2 (325 ms) is defined as the interval between the second 180° inversion pulse and the 90° excitation pulse.
The DIR detected 56% more infratentorial lesions compared with the FLAIR and 44% compared with the T2 TSE sequence. Regarding the supratentorial brain, higher detection rates were observed using DIR imaging compared with the T2 TSE imaging. This was statistically significant for the periventricular white matter ($P = 0.03$). The relative gain of detected lesions when using DIR imaging compared with T2 TSE imaging was 66% regarding the periventricular region, 10% regarding the juxtacortical region, and 50% regarding the mixed white matter-gray matter region. Compared with FLAIR imaging, DIR imaging showed a similar sensitivity in the detection of supratentorial MS lesions (Fig 2). FLAIR imaging depicted slightly more lesions in the juxtacortical white matter (relative gain of 6%) and deep white matter (relative gain of 3%), whereas DIR imaging identified slightly more lesions in the mixed white matter-gray matter (relative gain of 17%) and periventricular white matter (relative gain of 5%). None of these minor differences in the lesion load measurement reached statistical significance in the patient-wise analysis. Figure 3 gives examples of the higher detection rate of mixed white matter-gray matter lesions on the DIR images.

**Image Contrast Measurements**

The areas of the region of interest had a mean size of 65 mm$^2$ (SD, 23 mm$^2$; range, 34–107 mm$^2$) for the NAGM, 100 mm$^2$ (SD, 37 mm$^2$; range, 48–178 mm$^2$) for the CSF, 101 mm$^2$ (SD, 37 mm$^2$; range, 36–161 mm$^2$) for the NAWM, and 74 mm$^2$ (SD, 39 mm$^2$; range, 24–190 mm$^2$) for the lesions. The results of the contrast measurements of DIR, FLAIR, and T2 TSE imaging are listed in Table 3.

The contrast between lesions and the NAWM was higher on the DIR images compared with the corresponding T2 TSE and FLAIR sequences in every anatomic region (DIR compared with the T2 TSE and FLAIR sequences regarding the juxtacortical, periventricular, and deep white matter region, $P = 0.03$; DIR compared with the T2 TSE and FLAIR sequences regarding the infratentorial brain, $P = 0.03$). The

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**Table 2: Analysis of the lesion load measurement and relative comparisons of the DIR versus the FLAIR and T2-weighted TSE sequences**

<table>
<thead>
<tr>
<th>Region</th>
<th>DIR**</th>
<th>FLAIR*</th>
<th>T2TSE*</th>
<th>Relative Comparison (%)†</th>
<th>DIR/FLAIR</th>
<th>P Value‡</th>
<th>DIR/T2 TSE</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infratentorial</td>
<td>39</td>
<td>25</td>
<td>27</td>
<td></td>
<td>56</td>
<td>0.02</td>
<td>44</td>
<td>0.02</td>
</tr>
<tr>
<td>Periventricular</td>
<td>85</td>
<td>81</td>
<td>76</td>
<td></td>
<td>5</td>
<td>0.16</td>
<td>44</td>
<td>0.03</td>
</tr>
<tr>
<td>Juxtacortical</td>
<td>54</td>
<td>57</td>
<td>49</td>
<td></td>
<td>−6</td>
<td>0.08</td>
<td>10</td>
<td>0.18</td>
</tr>
<tr>
<td>Mixed WM-GM</td>
<td>21</td>
<td>18</td>
<td>14</td>
<td></td>
<td>17</td>
<td>0.32</td>
<td>50</td>
<td>0.06</td>
</tr>
<tr>
<td>Deep WM</td>
<td>35</td>
<td>36</td>
<td>35</td>
<td></td>
<td>−3</td>
<td>0.32</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>232</td>
<td>216</td>
<td>201</td>
<td></td>
<td>7</td>
<td>0.04</td>
<td>15</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Note:—GM indicates gray matter; WM, white matter; DIR, double inversion recovery; FLAIR, fluid-attenuated inversion recovery; T2 TSE, T2-weighted turbo spin-echo.

* Data are numbers of detected lesions.
† Data are relative differences in the numbers of detected lesions expressed as percentages of lesion numbers identified with DIR imaging compared with the corresponding FLAIR and T2 TSE imaging.
‡ $P$ value was obtained from the patient-wise analysis by Wilcoxon analysis for matched pairs indicating that more or fewer patients showed higher lesion load measurement with DIR imaging in comparison with the corresponding FLAIR or T2 TSE imaging.
contrast between the lesion and the CSF was also superior using DIR imaging compared with T2 TSE and FLAIR imaging ($P = 0.05$ compared with both T2 TSE and FLAIR imaging). Regarding the contrast between lesions and the NAGM, FLAIR, and T2 TSE imaging showed slightly higher contrast values that did not reach statistical significance (FLAIR compared with DIR, $P = 0.72$; T2 TSE compared with DIR, $P = 0.29$).

**Discussion**

Despite new emerging MR techniques in the diagnostic work-up of patients with suspected or definite MS, including MR spectroscopy and diffusion tensor imaging, the diagnosis of MS is still based mainly on conventional multi-sequence MR imaging protocols. Over the past few years, inversion recovery pulse sequences, such as FLAIR sequences, have increasingly been incorporated into imaging protocols and guidelines for the detection of inflammatory brain lesions. Because of the attenuation of the CSF, FLAIR imaging is highly sensitive in the detection of supratentorial brain lesions, especially in the juxtacortical and periventricular white matter. A more recently established double inversion pulse technique by using a combination of 2 inversion pulses provides a sufficient attenuation of both CSF and the NAWM. Two major studies focused on the diagnostic value of this type of sequence concerning different applica-
parallel imaging protocols. In addition, high-field MR imaging provides an almost linear increase of the signal intensity values in faster imaging techniques, including contrast-to-noise ratio, and they enable us to invest these higher field strengths up to 1.5T. Higher magnetic field strengths are providing an almost linear increase of the sensitivity in the detection of inflammatory brain lesions compared with lower magnetic field strengths up to 1.5T, leading to diagnostic relevance in terms of diagnostic imaging criteria. The experiences of DIR brain imaging in the past are limited to magnetic field strengths up to 1.5T. Higher magnetic field strengths are providing an almost linear increase of the signal-to-noise ratio, and they enable us to invest these higher signal intensity values in faster imaging techniques, including parallel imaging protocols. In addition, high-field MR imaging in patients with MS provides a significantly higher sensitivity in the detection of inflammatory brain lesions compared with lower magnetic field strengths up to 1.5T, leading to diagnostic relevance in terms of diagnostic imaging criteria. Therefore, 3T MR imaging is a promising method to achieve DIR imaging with an acceptable acquisition time in combination with a high sensitivity in the detection of MS lesions.

In this study, we introduced a DIR pulse sequence at 3T, which allows a sufficient attenuation of the CSF and the NAWM. This achieved an improved contrast ratio and delineation between gray and white matter compared with the corresponding T2 TSE and FLAIR imaging. Regarding the detection of MS lesions, DIR imaging provides higher contrast ratios between lesions and the NAWM in all anatomic locations compared with FLAIR and T2 TSE imaging. This resulted in a high sensitivity in the detection of supratentorial brain lesions that was similar to the “gold standard” of FLAIR imaging. However, DIR at 3T showed a slightly lower sensitivity in the detection of lesions in the juxtacortical white matter that was counterbalanced by a higher lesion load measurement concerning the mixed white matter-gray matter lesions, similar to results at 1.5T. Concerning white matter-gray matter lesions, this higher sensitivity at 3T is not as strongly developed compared with the results at 1.5T using a 3D DIR sequence. However, this finding is quite interesting because the contrast between lesions and the NAGM of the DIR is almost similar to the contrast at the FLAIR and T2 TSE sequences. The major reason for these different detection rates in the juxtacortical white matter and the mixed white matter-gray matter lesions is the sharp delineation between gray and white matter on the DIR, which allows a very stringent differentiation between purely juxtacortical lesions and lesions already touching the cortical area. Therefore, some of the lesions initially identified as juxtacortical lesions on the FLAIR and T2 TSE have to be categorized as mixed white matter-gray matter lesions on the DIR, leading to lower numbers of juxtacortical and higher numbers of mixed white matter-gray matter lesions. In addition, in concordance with the results at 1.5T, the contrast measurements between lesions and the NAGM show a relatively high variation. At the time of the zero crossing of the CSF and NAWM magnetization on the DIR, the magnetization of the NAGM is also decreased (in absolute terms), leading to a signal intensity attenuation in the magnitude images and, therefore, in some cases, to a better lesion conspicuity within the NAGM. Since recently performed histopathologic studies revealed that intracortical lesions are frequently observed in MS patients, the detection of those intracortical lesions is becoming increasingly important and is therefore of diagnostic and prognostic interest.

In contrast to almost similar detection rates in the supratentorial brain, DIR identified significantly more inflammatory lesions in the infratentorial brain even compared with the T2 TSE sequence, which is still the diagnostic “gold standard” in the infratentorial region at higher magnetic field strengths. Because a higher infratentorial lesion load is important for the prediction of long-term disability in patients with the first clinical event suggestive of MS, this result has major prognostic relevance. A better detection of infratentorial pathologies on DIR has already been observed at 1.5T, leading to the conclusion that this has primarily not been influenced by the higher field strength in our study. However, the relatively short echo time of 29 ms pronounces a more proton density-weighted effect of our DIR sequence. This might be partially responsible for the impressive high detection rate and lesion contrast in the infratentorial brain region.

Although artifacts in the posterior fossa, such as vascular and flow artifacts, were slightly pronounced on DIR imaging, the higher sensitivity in the detection of infratentorial lesions was not influenced by a possible misinterpretation of artifacts for lesions. Because infratentorial lesions could not be identified on DIR imaging in the healthy control subjects, a misinterpretation of artifacts for infratentorial lesions was not influenced by a possible misinterpretation for MS, this result has major prognostic relevance. A better detection of infratentorial pathologies on DIR has already been observed at 1.5T, leading to the conclusion that this has primarily not been influenced by the higher field strength in our study. However, the relatively short echo time of 29 ms pronounces a more proton density-weighted effect of our DIR sequence. This might be partially responsible for the impressive high detection rate and lesion contrast in the infratentorial brain region.

**Table 3: Contrast measurements of the DIR, FLAIR, and T2 TSE sequences**

<table>
<thead>
<tr>
<th>Lesion/NAWM</th>
<th>DIR</th>
<th>FLAIR</th>
<th>T2 TSE</th>
<th>DIR vs FLAIR †</th>
<th>DIR vs T2 TSE †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infratentorial</td>
<td>0.460 ± 0.125</td>
<td>0.137 ± 0.060</td>
<td>0.181 ± 0.067</td>
<td>3.36</td>
<td>2.54</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0.788 ± 0.098</td>
<td>0.253 ± 0.070</td>
<td>0.341 ± 0.085</td>
<td>3.11</td>
<td>2.31</td>
</tr>
<tr>
<td>Deep WM</td>
<td>0.720 ± 0.066</td>
<td>0.217 ± 0.047</td>
<td>0.298 ± 0.070</td>
<td>3.32</td>
<td>2.42</td>
</tr>
<tr>
<td>Juxtacortical</td>
<td>0.772 ± 0.110</td>
<td>0.253 ± 0.045</td>
<td>0.335 ± 0.047</td>
<td>3.05</td>
<td>2.30</td>
</tr>
<tr>
<td>Lesion/NAGM</td>
<td>0.190 ± 0.097</td>
<td>0.198 ± 0.064</td>
<td>0.213 ± 0.076</td>
<td>0.96</td>
<td>0.89</td>
</tr>
<tr>
<td>Lesion/CSF</td>
<td>0.832 ± 0.103</td>
<td>0.653 ± 0.243</td>
<td>0.201 ± 0.101</td>
<td>1.27</td>
<td>4.14</td>
</tr>
</tbody>
</table>

Note:—NAWM indicates normal-appearing white matter; WM, white matter; NAGM, normal-appearing grey matter; DIR, double inversion recovery; FLAIR, fluid-attenuated inversion recovery; T2 TSE, T2-weighted turbo spin-echo.

† Data are the contrast values of the DIR sequence in relative comparison with the corresponding contrast value of the FLAIR and T2 TSE sequence.

* Data are presented as means ± SD.
Conclusion
High-field MR imaging at 3T allows the establishment of a fast and accurate DIR imaging protocol. In patients with suspected or definite MS, DIR brain imaging at 3T provides the highest overall sensitivity in the detection of MS lesions compared with the standard pulse sequences of FLAIR and T2-weighted TSE. This higher sensitivity is especially obvious in the infratentorial region and is therefore of major prognostic relevance.

Acknowledgments
We thank Hanno Schimikowski for the help establishing the figures and Renate Blömer for the technical assistance. We also thank Jeroen J. G. Geurts, PhD, for providing his expertise in grey matter pathology and DIR imaging in multiple sclerosis.

References