Detection of Active Plaques in Multiple Sclerosis Using 3 and 12 Directional Diffusion-weighted Imaging: Comparison with Gadolinium-enhanced MR Imaging

Rahimi S., Azari A., Ghaemmaghami P., Meftahi G.H., Pirzad Jahromi G.*

ABSTRACT

Background: Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by exacerbations of neurological dysfunction due to inflammatory demyelination. MRI is the most sensitive method to make a diagnosis of multiple sclerosis. Contrast-enhanced T1-weighted imaging (CE T1WI) is used as the gold standard to distinguish active and inactive MS lesions. However, Gadolinium-based contrast agents (GBCAs) have some contraindications. Diffusion-weighted imaging (DWI) can detect diffusion alterations in active inflammatory lesions. The purpose of this study is to investigate whether common DWI (3 directional) and 12 directional DWI used in Diffusion tensor imaging can be an alternative to CE T1WI for demonstrating active (enhanced) MS lesions.

Material and Methods: In this cross sectional study, at two different hospitals, 138 patients who presented with CNS symptoms suggestive of demyelinating disease were examined. CE T1WI using 0.1 mmol/kg gadolinium as well as 3 & 12 directional DWI was done for all patients. To determine the reliability and accuracy of 3 & 12 directional DWI for delineating the enhancement of demyelinating lesions on CET1W, Intraclass correlation coefficient (ICC) and the plot of sensitivity versus specificity is called receiver operating characteristic (ROC) curve and the area under the curve (AUC) were calculated.

Results: 114 patients (82.6%) revealed contrast enhancement in CE T1WI, 117 (84.7%) and 107 (77.5%) patients demonstrated hyperintense lesions on DWI 12 & DWI 3 respectively. The intraclass correlation coefficient (ICC) for DWI 12 was higher than 0.92; however, for DWI 3 was less than 0.64. The DWI 12 data generated a sensitivity and specificity of 94.7% and 62.5%, combined with an AUC of 84%. Besides the sensitivity, specificity and AUC for DWI 3 CE were 86%, 62.5 and 79%, respectively.

Conclusion: Among 2 different DWI sequences, 12 directional DWI images have higher reliability and accuracy. Therefore, despite lower sensitivity compared to CE T1WI, it can be a practical diagnostic sequence in discriminating enhancing lesions from non-enhancing lesions when performing CE-MRI is a concern for the patient. Concerning the cons and pros of CE T1WI and DWI 12, these two sequences can be used in combination in order to reach higher sensitivities, leading to earlier diagnosis and more cost effective treatment.

Keywords
Demyelinating diseases, Diffusion magnetic resonance imaging, Diffusion tensor imaging, Gadolinium, Magnetic resonance imaging, Multiple sclerosis

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*Corresponding author: G. Pirzad Jahromi
Neuroscience Research Centre, Baqiyatallah University of Medical Sciences, Tehran, Iran
E-mail: pirzad_g_24@yahoo.com
Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system (CNS) characterized by exacerbations of neurological dysfunction due to inflammatory demyelination [1, 2]. The standardized criteria used to confirm the diagnosis of MS are known as the McDonald or "Dublin" criteria. The 2010 Revisions to the McDonald Criteria define “dissemination in space (DIS) and time (DIT)” using features of clinical history and MRI [3], with supportive evidence sometimes provided by cerebrospinal fluid oligoclonal bands or elevated IgG index [4]. MRI is the most sensitive method to reveal asymptomatic dissemination of lesions in space and time [5] and has improved prognosis and therefore, treatment of patients with MS. Because of the possibility of earlier diagnosis, which is critical in the treatment of the disease [6, 7].

Myelin breakdown and formation of white matter lesions is associated with disruption in blood brain barrier (BBB) as the primary trigger of tissue inflammation and edema [8]. The edema results in different signal intensities in different sequences of MRI as well as contrast enhancement (CE) [9]. CE-MRI which is used as a gold standard to distinguish active from inactive lesions in the brain [10]. After gadolinium injection, active plaques (new developing inflammatory lesions) may reveal diffuse or ring enhancement which points out destruction of the blood–brain barrier [11]. However, gadolinium based contrast agents (GBCAs) have contraindications, such as increased risk to develop nephrogenic systemic fibrosis in patients with acute or chronic severe renal insufficiency (glomerular filtration rate below 30 mL/min/1.73 m²) and allergy to GBCAs [12, 13]. Besides, in the 2013, the American College of Radiology states that because it is unclear how GBCAs will affect the fetus, these agents should be administered with caution in pregnant women [12]. In patients with contraindications or relative contraindications to GBCAs, an alternative MRI sequence may be needed for early and accurate diagnosis of MS. Diffusion-weighted imaging (DWI) measures the microscopic random translational motion of water molecules which are affected by microstructures and microdynamic process [14]. Diffusion-weighted imaging (DWI) has been widely used to diagnose acute ischemic infarction and also to detect diffusion alterations in active inflammatory lesions [15]. The diffusion is restricted in MS plaques, and normal appearing white matter (NAWM) is actually affected in these patients. Whether it can substitute for contrast-enhanced T1-weighted imaging (CE T1WI) to differentiate different features of demyelinating disease (e.g., DIT) has yet to be verified. Along this line, Diffusion tensor imaging (DTI) can be used to study the direction and magnitude of water molecule’s motion which is primarily parallel to the direction of fiber tracts in the brain [16], with MR diffusion tensor imaging (DTI), diffusion anisotropy can be quantified, and subtle white matter (WM) changes that are not normally seen on conventional MR imaging can be detected. DTI has been applied in various diseases, such as Alzheimer disease, multiple sclerosis MS, and human immunodeficiency virus (HIV) infections to monitor and assess WM changes [17]. One of the most important factor in DTI acquisition is the number of diffusion-encoding gradient directions (NDGD). As NDGD increases, more DW images are used for the calculation of diffusion tensor, resulting in more accurate diffusion tensor estimation and a higher signal-to-noise ratio (SNR). The main fiber tracts were detected with NDGD of six orientations; however, the use of larger NDGD (≥ 11 orientations) could provide improved tract characteristics at the expense of longer scanning time [17]. While diffusion-encoding gradients in common DWI (3 directional) is applied along three orthogonal directions (such as x, y, z) [18].

The purpose of this study was to investigate the relationship of the signal intensity of demy-
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eliminating lesions on conventional DWI (DWI 3) and 12 direction DWI (DWI 12) which is used in DTI to the status of enhancement on CE T1WI in baseline brain MRI in patients with clinically definite MS (CDMS).

Material and Methods

Study population

In this cross sectional study, from August 2016 to October 2017, patients who presented with CNS symptoms suggestive of demyelinating disease were examined. Patients with final diagnosis of clinically definite MS (CDMS) made by experienced neurologists after two or more clinical attacks of CNS demyelinating events and objective clinical evidence of two or more lesions as defined by the McDonald Criteria. The inclusion criteria also included: (1) age at onset between 17 and 45 years old; (2) CE T1WI and DWI with 3 and 12 directional DWI included in the MRI protocol; (3) no use of disease modifying drugs (e.g. interferon) or steroid before baseline brain MRI examinations to eliminate their effect on contrast enhancement and edema in demyelinating lesions. The patients were asked to confirm their willingness to participate in the trial by signing a written Informed Consent form.

MRI sequences and imaging analysis

The MRI studies were fulfilled on 1.5-T MR scanners (Siemens Avanto). The brain MRI sequences included spin echo (SE) T1-weighted imaging (T1WI), fast spin echo (FSE) T2-weighted imaging (T2WI), and T2-fluid-attenuated inversion recovery (T2-FLAIR) in the axial plane, T2WI in the coronal plane, T1WI and T2-FLAIR in the sagittal plane, and CE T1WI in the axial, coronal, and sagittal planes after injection of 0.1 mmol/kg of Gadolinium-Based Contrast Agents (GBCAs). CE-MRI was performed 5 minutes after gadolinium injection using a T1W image (TR: 430, TE: 8.7, slice thickness: 5 mm). DWIs were acquired with a single-shot echo planar spin-echo sequence in three and twelve orthogonal directions with a b value of 1000 sec/mm2 and a baseline image with a b value of 0 sec/mm2, Noise level: 40, band width: 964 Hz/px, echo spacing: 1.15 ms, TR: 3400, TE: 102) (Imaging settings are shown in Table 1). Apparent diffusion coefficient (ADC) and exponential ADC (eADC) maps were automatically generated. The DWIs were performed prior to administration of GBCAs with an identical slice thickness (5 mm) and position to T1WI, T2WI, and T2-FLAIR. The demyelinating lesions were first labeled by an experienced neuroradiologist on T2WI, T2-FLAIR and CE T1WI. Then the remaining demyelinating lesions were determined as either enhancing or nonenhancing on DWI with 3 and 12 orientations. On DWI, ADC and eADC maps, the signal intensity of the lesions was determined as either hyperintense, isointense or hypointense to the surrounding normal-appearing white matter. CE T1WI (either enhancing or non-enhancing) was taken as a gold standard for diagnosis of MS active lesions, and the signal intensity of each lesion (hyperintense or non) on DWIs was compared to the status of enhancement on CE T1WI.

<table>
<thead>
<tr>
<th>sequence</th>
<th>CET1W</th>
<th>DWI 12</th>
<th>DWI 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR (ms)</td>
<td>430</td>
<td>3400</td>
<td>3400</td>
</tr>
<tr>
<td>TE (ms)</td>
<td>8.7</td>
<td>109</td>
<td>102</td>
</tr>
<tr>
<td>Matrix size (phase × read out)</td>
<td>256 × 256</td>
<td>192 × 192</td>
<td>192 × 192</td>
</tr>
<tr>
<td>FOV (mm)</td>
<td>230 × 230</td>
<td>230 × 230</td>
<td>230 × 230</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Slices</td>
<td>21</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>NSA</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Band width (Hz/px)</td>
<td>150</td>
<td>964</td>
<td>964</td>
</tr>
<tr>
<td>b-factor (s/mm²)</td>
<td>-</td>
<td>1000</td>
<td>1000</td>
</tr>
<tr>
<td>Diff directions</td>
<td>-</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Scan time</td>
<td>1 min 54 sec</td>
<td>2 min 24 sec</td>
<td>53 sec</td>
</tr>
</tbody>
</table>
**Statistical analysis**

To determine the reliability and accuracy of 12 & 3 directional DWI to delineate the enhancement of demyelinating lesions on CE-T1W, we used two statistical methods:

1. To examine the reliability of the measurements obtained from brain imaging in 138 patients, Intraclass correlation coefficient (ICC) and limits of agreement were calculated to evaluate the reliability of the DWIs in comparison to CETW1. Based on the 95% confident interval of the ICC estimate, values less than 0.5, between 0.5 and 0.75, between 0.75 and 0.9, and greater than 0.90 are indicative of poor, moderate, good, and excellent reliability, respectively (Table 2) [19].

Data were analyzed with SPSS version 23 (IBM Inc., Chicago, Illinois, USA) and MedCalc software version 11.X86 (bvba, Ostend, Belgium). P-values less than 0.05 were considered significant.

### Results

#### Participants

All 138 cases examined were from patients with CDMS. Among the analyzed patients, 102 (74%) were female and 36 (26%) were male. Ranging in age from 17-45 years (mean: 31 years, standard deviation: 7.1). The interval between symptoms onset and baseline brain MRI examinations ranged from 1 to 60 days (mean: 20.4 days, standard deviation: 12.5).

#### Test Results

114 patients (82.6%) showed contrast enhancement in CE T1WI, 117 (84.7%) and 107 (77.5%) patients showed hyperintense lesions in DWI 12 & DWI 3 respectively. The intra-class correlation coefficient (ICC) for DWI 12 was higher than 0.9; however, for DWI 3 was less than 0.7 (Table 4).

In order to confirm the specificity, sensitivity and accuracy of DWI 12 & 3 as potential diagnostic sequences in discriminating enhancing lesions from non-enhancing lesions, versus CE T1WI a further receiver-operator-characteristics (ROC) test was processed. DWI 12 data generated a sensitivity and specificity of 94.7% and 62.5%, combined with an AUC (area under the curve) of 84%. Besides the sensitivity, specificity and AUC for DWI 3 to predict the enhancement of the demyelinating lesions on CE T1WI were 86%, 62.5 and 79%, respectively. Furthermore, the difference between two AUC (DWI 12 & 3) was statistically significant (P=0.04) (Figure 1).

Demyelinating lesions showed four different imaging patterns according to their signal intensity on different MRI sequences. Results are summarized in Table 5.

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**Table 2: The criteria of Intraclass correlation coefficient (ICC).**

<table>
<thead>
<tr>
<th>ICC Value</th>
<th>Reliability</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.9</td>
<td>excellent</td>
</tr>
<tr>
<td>0.75-0.9</td>
<td>good</td>
</tr>
<tr>
<td>0.5-0.75</td>
<td>moderate</td>
</tr>
<tr>
<td>&lt;0.5</td>
<td>poor</td>
</tr>
</tbody>
</table>

**Table 3: The criteria of the area under the curve (AUC).**

<table>
<thead>
<tr>
<th>AUC Value</th>
<th>Accuracy of Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.9</td>
<td>Highly accurate</td>
</tr>
<tr>
<td>0.8-0.9</td>
<td>accurate</td>
</tr>
<tr>
<td>0.7-0.8</td>
<td>Moderately accurate</td>
</tr>
<tr>
<td>0.5-0.7</td>
<td>uninformative</td>
</tr>
</tbody>
</table>
Detection of active MS plaques using multi directional DWI

After the administration of a gadolinium-based contrast agent (GBCAs) the same lesions may appear hyperintense (enhancing) if they are in the acute inflammatory phase and these lesions were considered active owing to contrast enhancement. Due to some GBCAs side effects and limitations, several studies have evaluated active MS plaques using alternative sequences [15, 22, 23]. The main interest of this study was to evaluate the reliability and comparability of 3 & 12 directional DWI compared to CE T1WI in diagnosing enhanced MS lesions.

In this study it is revealed that the reliability of DWI 12 was excellent and provided higher reliability than DWI 3 (ICC= 0.93, ICC = 0.64, respectively). Tiny enhancement can be evaluated better on CE T1WI & DWI 12 compared to common DWI (DWI 3). 84.7% patients showed hyperintense lesions in 12 directional DWI however 77.5% cases presented hyperintense lesions in 3 directional DWI. It means that DWI 12 could detect more enhanced lesions than DWI 3. DWI 12 & 3 compared with the CE T1WI assay as a reference and DWI 12 has a good comparability with the CE T1WI (ROC AUC > 0.8); DWI 3 has only satisfactory comparability (ROC AUC > 0.7). Moreover, the difference between two AUC (DWI 12 & 3) was statistically significant and therefore DWI 3 may not replace the CE T1WI as “gold standard” test. Similarly, in

<table>
<thead>
<tr>
<th>sequence</th>
<th>Intraclass Correlation</th>
<th>95% Confidence Interval</th>
<th>F Test with True Value 0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower Bound</td>
<td>Upper Bound</td>
</tr>
<tr>
<td>DWI 12</td>
<td>0.929</td>
<td>0.903</td>
<td>0.949</td>
</tr>
<tr>
<td>DWI 3</td>
<td>0.643</td>
<td>0.533</td>
<td>0.731</td>
</tr>
</tbody>
</table>

Table 4: Results of ICC Calculation in SPSS for DWI 12 & 3.

Discussion

For many years, conventional MRI (including T2- weighted, FLAIR, pre- and post-contrast T1-weighted scans) plays an important role in early diagnosis of MS and monitoring its response to current treatments and upcoming experimental agents [21]. On T2-weighted and FLAIR images, lesions appear hyperintense compared with the background, whereas on T1- weighted images (T1 WI), MS lesions are often isointense to the normal white matter but can be hypointense if chronic tissue injury or severe inflammatory edema occurs. After the administration of a gadolinium-based contrast agent (GBCAs) the same lesions may appear hyperintense (enhancing) if they are in the acute inflammatory phase and these lesions were considered active owing to contrast enhancement. Due to some GBCAs side effects and limitations, several studies have evaluated active MS plaques using alternative sequences [15, 22, 23]. The main interest of this study was to evaluate the reliability and comparability of 3 & 12 directional DWI compared to CE T1WI in diagnosing enhanced MS lesions.

In this study it is revealed that the reliability of DWI 12 was excellent and provided higher reliability than DWI 3 (ICC= 0.93, ICC = 0.64, respectively). Tiny enhancement can be evaluated better on CE T1WI & DWI 12 compared to common DWI (DWI 3). 84.7% patients showed hyperintense lesions in 12 directional DWI however 77.5% cases presented hyperintense lesions in 3 directional DWI. It means that DWI 12 could detect more enhanced lesions than DWI 3. DWI 12 & 3 compared with the CE T1WI assay as a reference and DWI 12 has a good comparability with the CE T1WI (ROC AUC > 0.8); DWI 3 has only satisfactory comparability (ROC AUC > 0.7). Moreover, the difference between two AUC (DWI 12 & 3) was statistically significant and therefore DWI 3 may not replace the CE T1WI as “gold standard” test. Similarly, in
2014, Lo et al. Concluded that although CE-MRI cannot be replaced by common DWI for demonstration of dissemination in time which is necessary in MS diagnosis [15]. While DWI 12 validated with good accuracy (AUC > 0.8). As a result, despite the fact that DWI 12 takes more time, it is more reliable and accurate.

The contrast presented by DWI (unlike CE T1WI) relies on the molecular motion of water. Many false positive type II lesions on DWIs were not enhanced on CE T1WI. There are two possible reasons. Firstly, the hyperintensity due to alterations of water diffusion in the lesions is more sensitive and lasts longer (may persist several months) than lesion enhancement due to transient BBB disruption (which usually lasts 4–6 weeks) [24-26]. Secondly, the high signal intensity of some lesions on DWI may be attributed to the “T2 shine-through” effect. The signal intensity on DWI is influenced by water diffusivity and the intrinsic T2 properties of the tissue being examined. The increased water content in demyelinating lesions may cause prolongation of T2 relaxation time and high signal on T2WI and thus, hyperintensity on DWI [24]. To remove the T2 shine-through effect, echo-planar spin echo T2WI (b = 0 sec/mm²) can be used to obtain an eADC map from DWI images. These results revealed that these two MRI sequences (CE T1WI & DWI 12) could be used in combination, to reach higher sensitivity, although each method can individually demonstrate the lesions in 80 - 90% of the patients. It seems that the final decision about using DWI 12 in combination with CE-MRI is a matter of clinical importance.

Our study reveals that unlike Lo et al. Results, not all of enhancing lesions but most of them have abnormal hyperintensity on DWI and type IV lesion (enhancing on CE T1WI and nonhyperintense on DWI) is found. This type of lesion (type IV) is much more prevalent on DWI 3 (86% sensitivity) compared to DWI 12 (94% sensitivity). As aforementioned this tiny enhanced lesions (type IV) may not be clearly identified on DWIs because the spatial resolution and signal-to-noise ratio of DWI were relatively suboptimal particularly on DWI 3 versus CE T1WI. For this reason, Lo et al. examined lesions larger than 3mm [15].

In our study there were four different imaging patterns of demyelinating lesions. Type I lesions revealed enhancement on CE T1WI and hyperintensity on DWI (hypointensity on the ADC & hyperintensity on the eADC) that implies active perivascular inflammation and BBB damage. In the rare cases like early stage of inflammation, active lesions may reveal restricted diffusion with cytotoxic edema imitating the radiological features of acute stroke (reduced ADC). The reduced ADC signal may last one to two weeks to revert to normal or increased signal [25, 27, 28]. CE T1WI can be helpful to differentiate this early stage of

<table>
<thead>
<tr>
<th>Lesion type</th>
<th>T2-FLAIR</th>
<th>CE T1WI</th>
<th>DWI</th>
<th>ADC</th>
<th>eADC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I</td>
<td>hyperintense</td>
<td>hyperintense</td>
<td>hyperintense</td>
<td>hypointense</td>
<td>hyperintense</td>
</tr>
<tr>
<td>Type II</td>
<td>hyperintense</td>
<td>no enhancement</td>
<td>hyperintense</td>
<td>hyperintense</td>
<td>hypointense</td>
</tr>
<tr>
<td>Type III</td>
<td>hyperintense</td>
<td>no enhancement</td>
<td>hypointense</td>
<td>hyperintense</td>
<td>hypointense</td>
</tr>
<tr>
<td>Type IV</td>
<td>hyperintense</td>
<td>hyperintense</td>
<td>isointense</td>
<td>isointense</td>
<td>isointense</td>
</tr>
</tbody>
</table>

Table 5: Imaging Patterns of Demyelinating Lesions on Different MRI Sequences.
Detection of active MS plaques using multi directional DWI
demyelination from acute ischemic infarction because active demyelinating lesions usually enhance while acute ischemic infarcts do not do it [28]. Type II lesions revealed no enhancement on CE T1WI and hyperintensity on DWI II (hyperintensity on the ADC & hypointensity on eADC). No enhancement on the CE T1WI is probably due to recovery of the BBB. However, the persistent hyperintensity on DWI may suggest residual extracellular edema with increased diffusion, prolongation of T2 relaxation time, and the T2 shine-through effect. Type III lesions show lack of enhancement on CE T1WI and hypointensity on DWI (hyperintensity on ADC & hypointensity on eADC) may be due to axonal loss and gliosis with widening of the extracellular space. They may even result form “T1 black holes” on MRI as chronic lesions, indicating severe tissue destruction [25, 29-31]. The fourth type was already discussed.

Conclusion
Among 2 different DWI sequences, we found that 12 directional DWI images have higher reliability and accuracy. Therefore, despite lower specificity compared to CE T1WI, it can be a practical diagnostic sequence in discriminating enhancing lesions from non-enhancing lesions when performing CE-MRI is a concern for the patient. concerning the cons and pros of CE T1WI and DWI 12, these two sequence can be used in Combination in order to reach higher sensitivities, leading to earlier diagnosis and more cost effective treatment.

Conflict of Interest
None Declared

References
17. Ni, H., et al., Effects of number of diffusion gradi-


