

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

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## ABSTRACT

**Background:** Multiple Sclerosis (MS), distinguished by aggravating the function of central nervous system because of inflammatory demyelination. The most sensitive method for MS diagnosis is Magnetic resonance imaging (MRI). To distinguish inactive and active MS lesions, contrast-enhanced T1-weighted imaging (CE T1WI) is being used as a gold standard. There are some contraindications in gadolinium based contrast agents (GBCAs) usage. Moreover, diffusion-weighted imaging (DWI) can discover diffusion changes involved inflammatory lesions.

**Objective:** The current research aims at investigating if typical DWI (3 directional) and 12 directional DWI could be a substitute for CE T1WI in order to show active lesions of MS.

**Material and Methods:** In this cross-sectional study, 138 patients with CNS symptoms were examined. For all patients, along with CE T1WI, 3 & 12 directional DWI were performed. Intraclass correlation coefficient (ICC), receiver operating characteristic (ROC), the sensitivity versus specificity plot and the area under the curve (AUC) were calculated.

**Results:** There was a contrast enhancement in CE T1WI for 114 patients (82.6%); in addition, hyper-intense lesions on DWI 3 and DWI 12 were shown in 107 (77.5%) and 117 patients (84.7%) in order. Sensitivity, specificity and AUC were 94.7%, 62.5% and 84% for DWI 12. Moreover, the results were 86%, 62.5 and 79% for the sensitivity, specificity and AUC for DWI 3 respectively.

**Conclusion:** In spite of lower sensitivity of 12 directional DWI compared to CE T1WI, it could be used as a diagnostic sequence in differentiating enhanced lesions from non-enhanced ones when CE-MRI is a worry.

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## Keywords

Demyelinating Diseases; Magnetic Resonance Imaging; Diffusion Tensor Imaging; Gadolinium; Multiple Sclerosis

## Introduction

Multiple Sclerosis (MS) has been known as chronic diseases in central nervous system (CNS) characterized by exacerbations of neurological dysfunction because of inflammatory demyelination [1, 2]. The McDonald or “Dublin” standards are the criteria, which are used for confirming the MS diagnosis. Using features of clinical history and MRI, 2010 revisions to the McDonald standards

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define “dissemination in space (DIS) and time (DIT)” [3]. Moreover, supportive evidence is occasionally provided by cerebrospinal fluid oligoclonal bands or elevated IgG index [4] in time and space. Nevertheless, MRI is the best method to detect asymptomatic spread of lesions [5] and causes prognosis and MS treatment to be improved since the early diagnosis leads into diseases treatment [6, 7].

Formation of white matter lesions and myelin breakdown leads into disruption in blood brain barrier (BBB) as edema and the primary trigger of tissue inflammation [8]. The edema causes various signal intensities in contrast enhancement and various sequences of MRI (CE) [9]. CE-MRI applied as a gold criterion for differentiating inactive from active lesions in the brain [10]. After injecting gadolinium, active plaques with new developing inflammatory lesions might reveal ring or diffuse or enhancement showing devastation the blood–brain obstacle [11]. Although gadolinium based contrast agents (GBCAs) contains contraindications, including incremental risk to advance nephrogenic systemic fibrosis in patients suffering from allergy to GBCAs and chronic or acute serious renal deficiency (glomerular filtration rate below 30 mL/min/1.73 m<sup>2</sup>) [12, 13]. Furthermore, in 2013, it was announced by the American College of Radiology that these agents ought to be controlled cautiously in pregnant women since it is not clear how GBCAs will have an effect on the fetus [12]. A preference MRI sequence might be necessary for accurate as well as early MS diagnosis for patients with relative contraindications or contraindications to GBCAs. The microscopic random translational motion of water molecules, which are affected with microstructures besides microdynamic process can be measured by diffusion-weighted imaging (DWI) [14]. In active inflammatory lesions, diffusion-weighted imaging (DWI) is extremely utilized for diagnosis of acute ischemic infarction as well as detection of diffusion changes [15]. Since normal appearing

white matter (NAWM) actually has an effect on MS patients, the diffusion is restricted in MS plaques. DWI could be used as a preference for contrast-enhanced T1-weighted imaging (CE T1WI) to distinguish various aspects of demyelinating disease. In order to study the magnitude and direction of water molecule’s motion paralleled to the direction of fiber tracts in the brain, diffusion tensor imaging (DTI) can be used [16]. Diffusion anisotropy can be quantified using MR diffusion tensor imaging (DTI); in addition, the unclear changes of white matter (WM) usually seen on conventional MR imaging can be found. DTI has been used in different diseases, including multiple sclerosis MS, Alzheimer disease, and human immunodeficiency virus (HIV) infections to check and investigate the changes of WM [17]. The number of diffusion-encoding gradient directions (NDGD) is one of the most crucial factors in DTI acquisition. Due to an increase in NDGD, more DW images are used to compute diffusion tensor, resulting in an estimation of more precise diffusion tensor as well as a higher signal-to-noise ratio (SNR). However, NDGD of six orientations detected the basic fiber tracts, and characteristics of improved tract could be provided by larger NDGD ( $\geq 11$  orientations) at longer scanning time [17]. Besides, diffusion-encoding gradients are applied along three orthogonal directions such as  $x, y, z$  in common DWI (3 directional) [18].

This purpose of this study is to assess the signal-intensity relationship of demyelinating lesions on conventional DWI (DWI 3) and 12 direction DWI (DWI 12) used in DTI for enhancement status on CE T1WI in baseline brain MRI in patients, who have clinically definite MS (CDMS).

## Material and Methods

### Study population

In this cross-sectional study, firstly, patients with CNS symptoms similar to demyelinating

illness were examined from August 2016 to October 2017. Secondly, experienced neurologists diagnosed patients with clinically definite MS (CDMS) after some clinical invasion of CNS demyelinating events as well as impartial clinical evidence of some lesions, which were described based on the McDonald standards that they can be as follows: 1) age should be at beginning of 17 until 45 years old. 2) CE T1WI and DWI are with 3 and 12 directional DWI in the protocol of MRI. 3) There is not any using disease adapting drugs or examinations of steroid pre-baseline brain MRI for removing their impact on edema and contrast improvement in demyelinating lesions. It was asked from the patients to confirm that are willing for participating in this study and to sign a written informed consent form.

### MRI sequences and imaging analysis

The MRI researches were carried out completely on 1.5-T MR scanners (Siemens Avanto). The brain MRI succession consisted of spin echo (SE) T1-weighted imaging (T1WI), T2-fluid-attenuated inversion recovery (T2-FLAIR) in the axial plane, fast spin echo (FSE) T2-weighted imaging (T2WI), T1WI and T2-FLAIR in the sagittal plane, T2WI in the coronal plane, besides CE T1WI in the axial, sagittal as well as coronal planes post-injecting 0.1 mmol/kg of gadolinium-based contrast agents (GBCAs). 5 min after injecting gadolinium, CE-MRI was done via a T1W image (TR: 430, TE: 8.7, slice thickness: 5 mm). DWIs were obtained from one echo planar spin-echo succession at three and twelve orthogonal path, associated with a b value of 1000 sec/mm<sup>2</sup> as well as a baseline image with a b value of 0 sec/mm<sup>2</sup>, band width: 964 Hz/px, noise level: 40, echo spacing: 1.15 ms, TE: 102 and TR: 3400). In Table 1, image setting is demonstrated. Exponential ADC (eADC) maps and apparent diffusion coefficient (ADC) were automatically made. Before administrating GBCAs with a thickness of similar slice (5 mm) in addition to position to T1WI, T2WI,

and T2-FLAIR, DWIs were done. Firstly, the demyelinating lesions were labeled using a neuroradiologist, who had enough experience to work on T2WI, T2-FLAIR and CE T1WI. Secondly, the rest demyelinating lesions were established as either improving or nonimproving on DWI with 3 as well as 12 orientations. On ADC, eADC as well as DWI maps, the lesions signal intensity was established as either isointense, hyperintense or hypointense into the surrounding white matter with normal appearance. CE T1WI, which is either improving or nonimproving, was as a gold criteria for diagnosing MS active lesions. Furthermore, the signal intensity of each lesion, which is hyperintense or none, on DWIs was compared with the enhancement status on CE T1WI.

### Statistical analysis

Two statistical methods were used for determining the accuracy as well as reliability of 12 & 3 directional DWI and to describe the improvement of demyelinating lesions on CET1W, including intraclass correlation coefficient (ICC), and limits of agreement were calculated to evaluate the reliability of measurements, obtained from brain imaging 138

**Table 1:** Scan parameters used to obtain images.

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

patients, and the DWIs compared to CETWI. According to the 95% certain interval in the ICC estimation, values, which are lower than 0.5, between 0.5 and 0.75 and 0.75 and 0.9, in addition to more than 0.90 are indicative of poor, mild, good, as well as great reliability, respectively (Table 2) [19].

The sensitivity vs specificity was termed receiver operating characteristic (ROC) curve as well as the area under the curve (AUC) with 95% confidence intervals (95% CI) was mentioned as an efficient measure of accuracy with significant interpretations. The criteria of AUC are shown in Table 3 [20].

The analysis of data were done using SPSS version 23 (IBM Inc., Chicago, Illinois, USA) and MedCalc software version 11.X86 (bvba, Ostend, Belgium). P-values less than 0.05 had a significant difference.

## Results

### Participants

138 patients studied were chosen from individuals with CDMS. 102 (74%) and 36 (26%) patients analyzed were female and male, respectively, from ranging 17-45 years old with

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

>0.9	excellent
0.75-0.9	good
0.5-0.75	moderate
<0.5	poor

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

AUC value	Accuracy of test
>0.9	Highly accurate
0.8-0.9	accurate
0.7-0.8	Moderately accurate
0.5-0.7	uninformative

mean: 31 years and standard deviation: 7.1. There was a range of the interval between the beginning of symptoms and examinations of baseline brain in MRI from 1 to 60 days with mean: 20.4 days and standard deviation: 12.5.

### Test Results

Contrast enhancements were shown in CE T1WI for 114 patients (82.6%); in addition, hyperintense lesions were shown in DWI 12 & DWI3 for 117 (84.7%) and 107 (77.5%) individuals, respectively. For DWI 12, ICC was more than 0.9; nevertheless, it was less than 0.7 for DWI 3 (Table 4).

To confirm the sensitivity, accuracy and specificity of DWI 12 & 3 as potential diagnostic sequences to discriminate improving lesions from non-improving lesions versus CE T1WI, a more receiver-operator-characteristics (ROC) test was conducted. DWI 12 data made a specificity and sensitivity of 62.5% and 94.7%, combined with an AUC (area under the curve) of 84%. In addition, the specificity, sensitivity and AUC for DWI 3 for predicting the improvement of the demyelinating lesions on CE T1WI were 62.5, 86% and 79%, respectively. Moreover, there was the statistically significant difference between two AUC (DWI 12 & 3) (P=0.04) (Figure 1).

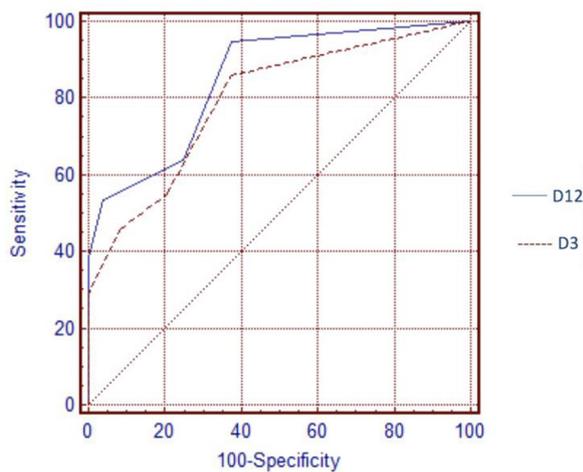
Based on signal intensity on various MRI sequences, demyelinating lesions illustrated four various imaging patterns. Results obtained are shown in Table 5.

### Discussion

Ordinary MRI, consisting of FLAIR, T2-weighted, pre- as well as post-contrast T1-weighted scans has had a vital effect on MS early diagnosis and investigating to upcoming experimental agents as well as treatment [21]. However, lesions are hyper-intense on T2-weighted as well as FLAIR images in comparison with the background, on T1-weighted images (T1 WI), MS lesions have been usually isointense to the white matter; in addition, when tissue injury, which is chronic, or

**Table 4:** Results of intraclass correlation coefficient (ICC) calculation for diffusion-weighted imaging (DWI 12 & 3).

Sequence	Intraclass Correlation	Intraclass Correlation Coefficient		F Test with True Value 0	
		95% Confidence Interval		Value	df1
		Lower Bound	Upper Bound		
DWI 12	0.929	0.903	0.949	27.320	137
DWI 3	0.643	0.533	0.731	4.595	137



**Figure 1:** Difference between two area under the curve (AUC) diffusion-weighted imaging (DWI 12 & 3).

severe inflammatory edema happens, it can be hypointense. After administrating a gadolinium-based contrast agent (GBCAs), if same lesions have been in the acute inflammatory phase and considered active due to contrast

enhancement, they may appear hyperintense. Because of some GBCAs limitations and side effects, active MS plaques were evaluated by some studies with alternative sequences [15, 22, 23]. Mainly, this study aims at investigating the comparability as well as reliability of 3 & 12 directional DWIs in comparison with CE T1WI in diagnosing enhanced MS lesions.

It is shown that the reliability of DWI 12 was the best and made higher reliability compared to DWI 3 (ICC= 0.93, ICC = 0.64, respectively). Small enhancement can be investigated better on CE T1WI & DWI 12 in comparison with common DWI (DWI 3). However, 77.5% cases showed hyperintense lesions in 3 directional DWI, and 84.7% of patients presented hyperintense lesions in 12 directional DWI. Thus, DWI 12 was able to detect more enhanced lesions compared to DWI 3. DWIs 12 & 3 in comparison with the CE T1WI are assayed as a reference; in addition, DWI 12 has a noticeable comparability with the CE T1WI (ROC AUC > 0.8) and DWI 3 has only suitable comparability (ROC AUC > 0.7).

**Table 5:** Imaging Patterns of Demyelinating Lesions on Different Magnetic resonance imaging (MRI) Sequences.

Lesion type	MRI sequence				
	T2-FLAIR	CE T1WI	DWI	ADC	eADC
Type I	hyperintense	hyperintense	hyperintense	hypointense	hyperintense
Type II	hyperintense	no enhancement	hyperintense	hyperintense	hypointense
Type III	hyperintense	no enhancement	hypointense	hyperintense	hypointense
Type IV	hyperintense	hyperintense	isointense	isointense	isointense

Moreover, a statistically significant difference has been between two AUC (DWI 12 & 3). Therefore, DWI 3 might not be replaced with the CE T1WI as “gold standard” test. In 2014, based on the study carried out by Lo et al., however, CE-MRI cannot be replaced with common DWI to demonstrate dissemination in time, which is vital in MS diagnosis [15], DWI 12 was validated with good accuracy (AUC>0.8). Therefore, although more time is necessary for DWI 12, it is more accurate and reliable.

The contrast shown using DWI (diverse CE T1WI) depended on the water molecular motion. On DWIs, many false positive type II lesions were not improved on CE T1WI due to two probable causes as follows: initially, the hyperintensity owing to water diffusion changes in the lesions lasts longer and has been also more sensitive, which might continue for several months compared to lesion improvement owing to transient BBB disruption, which last 4–6 weeks [24–26]. Secondly, the high signal intensity of a few lesions on DWI might be ascribed to the effect of “T2 shine-through”. The intensity of signal on DWI is affected with diffusivity of water as well as the intrinsic T2 properties of the tissue, which were examined. The incremental water amount in demyelinating lesions might lead into prolonging T2 relaxation time as well as high signal on T2WI, in addition to hyperintensity on DWI [24]. Echo-planar spin echo T2WI ( $b = 0 \text{ sec/mm}^2$ ) could be utilized to catch an eADC map from DWI images to eliminate the T2 shine-through effect. Based on the results, two MRI sequences, including T1WI and DWI 12, may be used in combination to obtain higher sensitivity; however, every method can individually show the lesions in 80 - 90% of the patients. Therefore, the final decision regarding using DWI 12 in combination with CE-MRI is clinically important.

Based on results this study and unlike study carried out by Lo et al., most of improving lesions include unusual hyperintensity on

DWI. Besides, type IV lesion improving on CE T1WI as well as nonhyperintense on DWI was detected, which is much more prevalent on DWI 3 (86% sensitivity) than DWI 12 (94% sensitivity). Since the spatial resolution besides signal-to-noise ratio of DWI were comparatively suboptimal especially on DWI 3 versus CE T1WI, these small-enhanced lesions (type IV) may not be obviously identified on DWIs; thus, lesions larger than 3mm were studied by Lo et al, [15].

In This study, there were four various imaging patterns of demyelinating lesions as follows: lesions showed improvement on CE T1WI and hyperintensity on DWI (hypointensity on the ADC & hyperintensity on the eADC), implying BBB damage as well as active perivascular inflammation. In the few cases such as early inflammation stage, active lesions might show limited diffusion along with cytotoxic edema, which imitate the radiological features of serious stroke (decreased ADC). The decreased ADC signal might continue from one to two weeks to change into normal or increased signal [25, 27, 28]. CE T1WI can be useful for differentiating early stage of demyelination from serious ischemic infarction since active demyelinating lesions are occasionally enhanced despite of acute ischemic infarcts [28]. Type II lesions did not show any enhancement and hyperintensity on CE T1WI and DWI II, respectively (hyperintensity on the ADC & hypointensity on eADC). There was any enhancement on the CE T1WI due to the BBB recovery. Although the constant hyperintensity on DWI might have a suggestion of remaining extracellular edema with incremental diffusion, the T2 shine-through effect and prolongation of T2 relaxation time. Type III lesions reveal the lack of improvement on CE T1WI. Besides, hypointensity on DWI (hyperintensity on ADC & hypointensity on eADC) might be owing to axonal loss as well as gliosis with expanding the extracellular space. They might result from “T1 black holes” on MRI as chronic lesions, showing se-

rious tissue destruction [25, 29-31].

## Conclusion

It was found that 12 directional DWI images have higher accuracy and reliability between 2 various DWI sequences. Thus, in spite of lower specificity in comparison with CE T1WI, it could be a useful diagnostic succession to discriminate improving lesions from non-enhancing lesions as performance of CE-MRI is vital for patients. Regarding the advantages as well as disadvantages of CE T1WI and DWI 12, there are two successions, which were used in combining for reaching higher sensitivities, resulting in earlier diagnosis as well as more cost-beneficial treatment.

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## Conflict of Interest

None

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