Original Article

Efficacy of diffusion-weighted imaging in symptomatic and asymptomatic multiple sclerotic plaques

Farzad Tahmasebi Arashloo[1], Farnaz Fahimi Hanzaei[1], Behnaz Sedighi[2], Ghazaleh Amjad[3], Ladan Younesi[3]

[1]Clinical Research Unit, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, [2]Neurology Research Center, Kerman University of Medical Sciences, Kerman, [3]Shahid Akbar Abadi Clinical Research Development Unit, Iran University of Medical Sciences, Tehran, Iran

Abstract

Introduction: Magnetic resonance imaging (MRI) currently accompanies clinical findings in disease diagnosis, patients' follow-up, assessment of drugs complications, and evaluation of treatment response. Although contrast-enhanced MRI (CE-MRI) is considered as the imaging modality of choice for multiple sclerosis (MS), due to disease chronicity, applying multiple doses of gadolinium-based contrast agents (GBCAs) increases the risk of nephrogenic syndrome in patients with acute (ARF) and chronic renal syndromes (CRF). Moreover, the effect of gadolinium on the fetus is not well-known in pregnant patients. Therefore, this study evaluates the possibility of replacing postcontrast images with physiologically based MRI sequences such as diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC). **Method:** We prospectively evaluated 26 patients with known multiple sclerosis. The patients with MS attacks and the asymptomatic patients who were referred for follow-up were enrolled. Conventional MRI including postcontrast T1W, DWI, and ADC were performed for all patients. The signal intensity (SI) of all enhancing and nonenhancing plaques of more than 10 × 10 mm size were investigated in all sequences and analyzed. **Results:** A total of 83 plaques were detected in T2-FLAIR sequences of which 51 plaques were enhanced (68%) after gadolinium administration. While 42 MS plaques had hypersignal intensity in DWI (56%), 32 plaques had iso- or hyposignal intensities in DWI (44%). No statistically significant values were obtained. **Conclusion:** Although DWI could not replace CE-MRI, using these two modalities together could increase detection of active MS plaques and alter patients' therapy and prognosis.

Keywords: Diffusion weight imaging, magnetic resonance imaging, multiple sclerotic plaques

Introduction

Multiple sclerosis (MS) is the most common inflammatory autoimmune disorder of the central nervous system (CNS) and is the most common cause of nontraumatic neurologic disability in adults.[1] About 2.5 million people worldwide suffer from this disease and high prevalence of this disorder is found in Iran.[1,2] Multifocal demyelination and axonal injury caused by autoimmune inflammatory process is considered as the disease pathophysiology.[3] Tissue inflammation could damage the myelin and the blood–brain barrier.[1] Although clinical findings are yet applied in diagnosing MS, magnetic resonance imaging (MRI) is a promising tool for determining the spatial and temporal distributions of demyelinating plaques in the brain and spinal cord.[4] Moreover, MRI is used for evaluation of treatment response, monitoring of the disease, and assessment of drugs complications.[5] The mandatory conventional MRI sequences used in MS disease assessment are T1 weighted, fluid-attenuated inversion recovery (FLAIR), T2 weighted and pre- and post-single-dose gadolinium T1 weighted imaging.[6]

Address for correspondence: Dr. Ghazaleh Amjad, Shahid Akbar Abadi Clinical Research Development Unit, Iran University of Medical Sciences, Tehran, Iran.
E-mail: amjad.gh@iums.ac.ir

Received: 24-04-2019 **Revised:** 19-06-2019 **Accepted:** 16-07-2019

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_420_19

How to cite this article: Arashloo FT, Hanzaei FF, Sedighi B, Amjad G, Younesi L. Efficacy of diffusion-weighted imaging in symptomatic and asymptomatic multiple sclerotic plaques. J Family Med Prim Care 2019;8:2409-13.

Hyperintense lesions in T2 weighted and FLAIR sequences are nonspecific and may be caused by edema, gliosis, and demyelination, Wallerian degeneration, or axonal loss. Although active inflammatory activity could increase blood–brain barrier permeability, postcontrast T1-weighted images are too delicate instrument to detect this type of CNS damage.[7] However, active perivascular inflammation could be recognized by contrast enhancement in demyelinating lesions.[8] Since, MR imaging is more sensitive than clinical findings in distinguishing early MS plaques, clinicians are inclined to monitor subclinical disease activity for treatment choices by this modality.[9] Owing to disease chronicity, applying multiple doses of Gadolinium-based contrast agents (GBCAs) in disease follow-up increases the risk of nephrogenic syndrome in patients with acute (ARF) and chronic renal syndromes (CRF). Moreover, the impact of this contrast is not fully understood in pregnant patients.[8,10] Therefore, in this study, we assess the role of physiologically based techniques such as diffusion weighted images (DWI) in combination with apparent diffusion coefficient (ADC) in detecting MS plaques. The goal of this study is to study the possibility of replacement of these sequences instead of postcontrast images.

Method and Patients

Patients

We evaluated prospectively 26 patients with known multiple sclerosis and fulfilled McDonald Criteria 2010[11] from April 2017 to May 2018. Diagnosis was performed by an expert neurologist with 10 years of experience in treating MS. The patients with MS attacks and also the asymptomatic patients who were referred for follow-up were enrolled in the study.

Image evaluation

Conventional MRI with and without contrast, DWI, and ADC were performed for all patients in the university imaging center. All images were made by a 1.5 T MRI scanner (Siemens MAGNETOM Avanto, Germany).

Conventional MRI were done using a phased array head coil.

Axial, coronal, and sagittal multiecho T2-weighted spin echo were performed as per the following conditions: TR = 4320 *ms*, TE = 103 *ms*, slice thickness = 6 mm, flip angle = 150°, FOV = 220 × 185 mm^2, image matrix = 224 × 320, pixel size = 0.8 × 0.7 mm^2.

The FLAIR sequence was carried out with TR = 4500 ms and TE = 87 ms.

Axial, coronal, and sagittal pre- and postcontrast spin-echo T1-weighted images (TE/TR = 8.1/400, slice thickness = 6 mm, flip angle = 90°, FOV = 230 × 195 mm^2, image matrix = 218 × 320, pixel size: 0.7 × 0.8 mm^2) were also obtained.

The postcontrast images were obtained 15 minutes after administration of 10 cc Dotarem (Gadoterate Meglumine) and 0.5 mmol/mL in the antecubital region of patients.

MR diffusion imaging

Axial multi b-value DWI using EPI method with TE/TR = 102/3400, slice thickness = 5 mm, flip angle = 90°, FOV = 230 × 230 mm^2, image matrix = 192 × 192, pixel size = 1.2 × 1.2 mm, b-value = 0, 500, 1000 s/mm^2 were performed before contrast administration.

Postprocessing of ADC maps for b-value = 500 and 1000 were achieved with MATLAB 7.14 (Math Works Inc).

Image evaluation

All MRI images were evaluated by an expert neuroradiologist with 5 years of experience in treating MS disease. T2 weighted and FLAIR sequences were primarily assessed for MS plaques and the plaques were counted and registered. The postcontrast images were appraised for MS plaques enhancement. The signal intensity of all plaques which showed contrast enhancement after gadolinium (Gd) administration were measured in T2, FLAIR, pre and postcontrast T1 weighted images, DWI, and ADC using rectangular regions of interest (ROIs). Nonenhancing plaques which had high signal intensity in T2-FLAIR sequences and were more than 10 × 10 mm in size were included in the study and their signal intensities were assessed similar to that of enhanced plaques.

Statistical analysis

Descriptive variables were calculated and stated as mean ± SD and frequencies. For comparison of SI between T1, T2, and contrast enhanced T1, we used repeated-measure ANOVA test. Before implementing this test, we assessed the normality of continuous variables by Kolmogorov–Smirnov test. Pairwise comparisons between groups were done considering Bonferroni correction. In addition, comparison of continuous variables between enhanced and nonenhanced plaques was done by *t*-test after checking normality of data. The diagnostic performance of continuous variables in differentiating enhanced and nonenhanced plaques were evaluated by receiver operating characteristic (ROC) curves. Considering cross-tabulation of hyperintensity in DWI versus enhanced plaques, the diagnostic indices of DWI hyperintensity in diagnosis of enhancing plaques were also calculated. *P* values lower than 0.05 were considered as statistically significant.

Results

Twenty-six patients, 5 males (19.2%) and 21 females (80.8%), were enrolled in this study [mean age: 33.3 ± 8.2, range: 17-50]. A total of 83 plaques were detected in T2-FLAIR sequences of which most of them were in supratentorial (92.78%) and six plaques were observed in infratentorial (7.22%) regions. In addition, we assessed the details of 51 enhancing plaques (68%) and 24 nonenhancing plaques which had more than 10 × 10 mm

size in this study (32%). Eight plaques had missing data in at least one obtained MRI sequences.

The means of MS plaques' signal intensity in different sequences are shown in Table 1.

Forty-two MS plaques had hypersignal intensity in DWI (56%) and 32 plaques had iso- or hyposignal intensities in DWI (44%). Among the 51 enhancing plaques, 33 plaques had hypersignal intensity in DWI (64.7%) but 18 lesions had iso- or hyposignal intensities (35.3%). The details of DWI signal intensity in enhancing and nonenhancing plaques and sensitivity, specificity, accuracy, PPV, NPV, LR of positive test and LR of negative test of DWI signal intensity in enhancing plaques are displayed in Tables 2 and 3, respectively.

The number of enhancing and nonenhancing plaques evaluated by T1, T2 signal intensities, ADC, and DWI were listed in Table 4.

The efficacy of DWI and ADC numbers in enhancing and nonenhancing MS plaques was evaluated by ROC analysis [Figure 1]. The index of this analysis is AUC (area under the curve). The details of mentioned criteria are noted in Table 5.

Discussion

Random movement of water molecules from one location to other locations is considered as diffusion and it is the basic concept of diffusion weighted imaging (DWI). Diffusion in pure water is an example of random movement or Brownian motion in which water molecules move freely in all directions (isotropic diffusion). In contrast, in the brain tissues, mostly in white matter tracts which are covered by myelin, the mobility of water molecules is restricted in a directed pathway. Hence, this kind of diffusion is entitled as "anisotropic diffusion."

Restricted diffusion is due to reduction of water molecules mobility in extracellular space or in white matter tracts. In demyelinating diseases such as multiple sclerosis (MS), myelin and blood–brain barrier damages conduce to inflammatory cell infiltration and reduction of anisotropic diffusion of water molecules.[12]

In very acute MS lesions, demyelination or extracellular edema causes expansion of extracellular space and increase the apparent diffusion coefficient (ADC). But the inflammatory cytokines get discharged as mitochondrial dysfunction is responsible for cytotoxic edema and decrease of ADC in acute MS plaques.[13]

So, the main purpose of this study was to evaluate the reliability of DWI and ADC to detect MS plaques although contrast enhanced (CE) MRI is generally considered as the imaging modality of choice. In this study, we evaluated both acute symptomatic patients and asymptomatic patients who were

Table 1: The means of signal intensity of MS plaques in different sequences

	n	Min	Max	Mean	Std. Deviation
DWI	75	77.00	222.00	124.6933	24.17446
ADC	75	639.00	1423.00	951.7867	194.75801
T1SI	73	226.00	729.00	365.8082	95.35936
T2SI	73	131.00	437.00	269.7260	79.71150
Contrast T1SI	75	161.00	567.00	323.9733	97.18942

DWI: Diffusion Weighted Imaging, ADC: Apparent Diffusion Coefficient

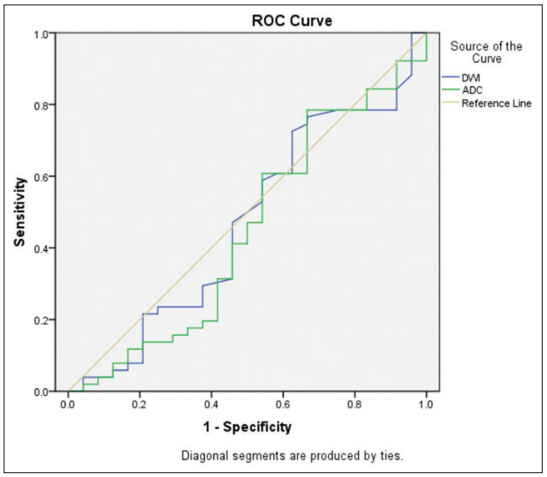

Figure 1: ROC curve for determining the efficacy of DWI and ADC number in enhancing and nonenhancing MS plaques. ROC: Receiver Operating Characteristic, DWI: Diffusion Weighted Imaging, ADC: Apparent Diffusion Coefficient

Table 2: DWI signal intensity in enhancing and nonenhancing plaques

			DWI Signal		Total
			Hyper	Iso or Hypo	
T1Contrast enhancing	Enhancing plaque	Count	33	18	51
		% within T1 Cont	64.7%	35.3%	100.0%
		% within DWI Sig	78.6%	54.5%	68.0%
	Nonenhancing plaque	Count	9	15	24
		% within T1 Cont	37.5%	62.5%	100.0%
		% within DWI Sig	21.4%	45.5%	32.0%
Total		Count	42	33	75
		% within T1 Cont	56.0%	44.0%	100.0%
		% within DWI Sig	100.0%	100.0%	100.0%

DWI: Diffusion Weighted Imaging

referred for follow-up. The study showed that DWI and ADC could not replace CE-MRI in detecting active MS plaques and the achieved mean of DWI and ADC levels of enhancing and nonenhancing plaques were almost similar. On ROC analysis, the AUC of DWI and ADC also demonstrated unprofitable levels and we could not find any appropriate cutoff point for these two criteria to detect active plaques.

In 2014, Lo *et al.* assessed 22 patients with acute MS attack who had 384 plaques. They declared that DWI could be used as the screening method owing to its high sensitivity where the use of gadolinium is a concern but according to many false positive lesions, it could not be replaced CE-MRI.[14]

In 2016, Davoodi *et al.* detected borderline *P* value and showed that although CE-MRI is more efficient than DWI, this effectiveness is not so substantial.[15]

Table 3: Sensitivity, specificity, accuracy, PPV, NPV, LR of positive test and LR of negative test of DWI signal intensity in enhancing plaques

Index	Estimate	Lower 95% CI	Upper 95% CI
Sensitivity	0.69	0.54	0.81
Specificity	0.67	0.46	0.83
Accuracy	0.68	0.56	0.78
Predictive value of positive test	0.79	0.63	0.90
Predictive value of negative test	0.55	0.36	0.72
Likelihood ratio of positive test	2.1	1.2	3.6
Likelihood ratio of negative test	2.1	1.3	3.5
Cohen's Kappa	0.34	0.12	0.55

PPV: Positive Predictive Value, NPV: Negative Predictive Value, LR: Likelihood Ratio, DWI: Diffusion Weighted Imaging

Table 4: T1, T2 signal intensities, ADC, and DWI number of enhancing and nonenhancing plaques

T1 Cont		*n*	Mean	Std. Deviation	*P*
DWI	Enhancing plaque	51	123.3725	21.47646	0.494
	Nonenhancing plaque	24	127.500	29.41901	
ADC	Enhancing plaque	51	937.3137	183.77633	0.352
	Nonenhancing plaque	24	982.541	217.17554	
T1 SI	Enhancing plaque	49	364.1429	106.41017	0.833
	Nonenhancing plaque	24	369.2083	69.40804	
T1 SI	Enhancing plaque	49	264.5102	80.66704	0.428
	Nonenhancing plaque	24	280.3750	78.32031	

ADC: Apparent Diffusion Coefficient, DWI: Diffusion Weighted Imaging

Lo *et al.* illustrated that all enhancing lesions have abnormal hyperintensity on DWI with 100% sensitivity and 100% NPV but many false positive high signal lesions in DWI were not enhanced on CE-MRI.[13] In our study, we found 18 nonhyperintense plaques on DWI in our 51 enhancing lesions (69% sensitivity, 67% specificity, 55% NPV, 79% PPV). However, similar to Lo *et al.* study, we found multiple high-signal plaques without contrast enhancement.

In line with the study by Davoodi *et al.*, in three of our patients, we found nine plaques (37%) with restricted diffusion in DWI but without contrast enhancement in CE-MRI,[14] which is a remarkable finding. The mentioned lesions were typical of MS plaques and, since the patients did not have any risk factors of ischemic lesions, they should not have been considered as false positive lesions. Our findings were consistent with those of previous studies that diffusion weighted imaging along with CE-MRI would increase positive cases.[14,15]

The limitations of our study are as follows: (1) We decided to exclude asymptomatic plaques smaller than 10 × 10 mm because the spatial resolution and signal-to-noise ratio of DWI were moderately suboptimal in comparison with SE/FSE imaging. (2) We did not enroll spinal cord plaques because DWI could not be regularly performed in our institution. (3) We evaluated asymptomatic patients and the acute symptomatic patients together. The DWI sequence is mostly appropriate for acute plaques. The previous studies demonstrated that if MRI is achieved within the first 30 days after symptom onset, DWI more often could strengthen the CE-MRI abilities. (4) In addition, our case population is fairly small.

Conclusion

Our study showed that although DWI could not replace CE-MRI to distinguish active MS plaques, it could increase detection of lesions in combination with contrast imaging. More studies with expansive cases are required to evaluate DWI capabilities in demyelinating diseases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Table 5: The AUC for determining the efficacy of DWI and ADC number in enhancing and nonenhancing MS plaques

Area Under the Curve						
Test Result Variable (s)		Area	Std.Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
Dimension0	DWI	0.468	0.074	0.658	0.323	0.614
	ADC	0.448	0.075	0.467	0.300	0.596

AUC: Area Under the Curve, DWI: Diffusion Weighted Imaging, ADC: Apparent Diffusion Coefficient

References

1. Hygino da Cruz LC Jr, Batista RR, Domingues RC, Barkhof F. Diffusion magnetic resonance imaging in multiple sclerosis. Neuroimaging Clin N Am 2011;21:71-88.
2. Izadi S, Nikseresht A, Sharifian M, Sahraian MA, Hamidian Jahromi A, Aghighi M, *et al.* Significant increase in the prevalence of multiple sclerosis in Iran in 2011. Iran J Med Sci 2014;39:152-3.
3. Dutta R, Trapp BD. Relapsing and progressive forms of multiple sclerosis: Insights from pathology. Curr Opin Neurol 2014;27:271-8.
4. Zare Mehrjardi M, Darabi M, Bagheri SM, Kamali K, Bijan B. The role of ultrasound (US) and magnetic resonance imaging (MRI) in penile fracture mapping for modified surgical repair. Int Urol Nephrol 2017;49:937-45.
5. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: A meta-analysis of randomized trials. Lancet Neurol 2013;12:669-76.
6. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, *et al.* MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 2016;15:292-303.
7. Zivadinov R1, Sepcić J. Use of magnetic resonance imaging in the diagnosis and prognosis of multiple sclerosis. Lijec Vjesn 2006;128:295-308.
8. Thomsen HS, Morcos SK, Almén T, Bellin MF, Bertolotto M, Bongartz G, *et al.* Nephrogenic systemic fibrosis and gadolinium-based contrast media: Updated ESUR contrast medium safety committee guidelines. Eur Radiol 2013;23:307-18.
9. Simon JH, Bermel RA, Rudick RA. Simple MRI metrics contribute to optimal care of the patient with multiple sclerosis. Am J Neuroradiol 2014;35:831-2.
10. ACR manual on contrast media. (Version 9, 2013 [Internet] Reston, VA: American College of Radiology, ACR Committee on Drugs and Contrast Media; c2013). [cited 2013 March 21]. Available from: http://www.acr.org/~/media/ACR/Documents/PDF/QualitySafety/Resources/Contrast%20Manual/2013_Contrast_Media.pdf.
11. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al.* Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
12. Rueda-Lopes FC, Hygino da Cruz LJ, Doring TM, Gasparetto EL. Diffusion-weighted imaging and demyelinating diseases: New aspects of an old advanced sequence. AJR Am J Roentgenol 2014;202:W34-42.
13. Rosso C, Remy P, Creange A, Brugieres P, Cesaro P, Hosseini H. Diffusion-weighted MR imaging characteristics of an acute strokelike form of multiple sclerosis. AJNR Am J Neuroradiol 2006;27:1006-8.
14. Lo CP, Kao HW, Chen SY, Chu CM, Hsu CC, Chen YC, *et al.* Comparison of diffusion-weighted imaging and contrast-enhanced T1-weighted imaging on a single baseline MRI for demonstrating dissemination in time in multiple sclerosis. BMC Neurol 2014;14:100.
15. Davoodi Y, Foroughipour M, Torabi R, Layegh P, Matin N, Shoeibi A. Diffusion weighted imaging in acute attacks of multiple sclerosis. Iran J Radiol 2016;13:e21740.