Original Article

Comparison of Apparent Diffusion Coefficient Value Measurement and Contrast-Enhanced T1-Weighted Imaging in Detecting Active Demyelinating Lesions in Multiple Sclerosis

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Objective: To find a difference in apparent diffusion coefficient (ADC) values of non-enhancing and enhancing lesions in patients with multiple sclerosis (MS) and to find a cutoff ADC value to predict the enhancement of the MS lesion.

Materials and Methods: A retrospective review of magnetic resonance imaging (MRI) of the brain in MS patients between January 2015 and December 2019 was done. The MS plaques in the images were mapped in fluid attenuation inversion recovery (FLAIR) and post-contrast T1-weighted imaging sequences (T1WI). The lesions were categorized into enhancing and non-enhancing lesions based on the presence of enhancement on post-contrast T1WI. The ADC value of each lesion was measured using circular regions of interest (ROI) placed in the enhancing portion. The difference in mean ADC values between the two groups was assessed.

Results: There were 22 patients with 194 MS lesions. The mean ADC values of the enhancing lesions at $0.891\pm0.164\times10^{-3}$ mm^2/s were significantly lower than those of the non-enhancing lesions at $1.303\pm0.280\times10^{-3}$ mm^2/s ($p<0.001$). A cutoff ADC value of 1.117×10^{-3} mm^2/s was used to distinguish between the enhancing and the non-enhancing lesions. The best results were obtained with a sensitivity of 93.9%, specificity of 71.4%, positive predictive value (PPV) of 40.3%, negative predictive value (NPV) of 98.3%, and accuracy of 75.3%.

Conclusion: ADC value measurement can be used to predict the enhancement of the MS plaque, which may be helpful as a screening tool for active demyelinating plaque in MS patients.

Keywords: Multiple sclerosis; Active demyelinating lesion; Active MS; Contrast-enhanced T1-weighted imaging; ADC value

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Multiple sclerosis (MS) is the most frequent primary demyelinating pathology in the central nervous system, affecting approximately 350,000 people in the USA and 2.5 million worldwide[1]. In Thailand, the estimated prevalence rate was about two per 100,000 population[2]. Although a diagnosis of MS is based on clinical findings, magnetic resonance imaging (MRI) also provides supportive data to facilitate the diagnosis of MS, according to the McDonald criteria. Aside from the diagnosis, the major use of MRI in patients with MS is a routine follow-up tool for assessing treatment response[3]. Serial MRI with gadolinium (Gd)-enhanced contrast every three to twelve months has been recognized as sensitive imaging for evaluating active MS lesions due to the enhancement of the active MS lesion on contrast-enhanced T1-weighted imaging (T1WI)[4].

Although gadolinium-based contrast agents (GBCAs) have long been considered safe when administered at recommended doses, reports and studies confirm the deposition of GBCAs in human tissues, including the brain[5-7]. Since the onset of MS ranges between 20 to 40 years of age, patients with MS can be exposed to the GBCAs multiple times, which may increase the deposition of GBCAs in their bodies.

Previous studies have compared fluid-attenuated inversion recovery imaging (FLAIR) with Gd-enhanced sequence[8]. However, in the authors'

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institute, the standard protocol for brain MRI does not include the precontrast FLAIR sequence.

Diffusion-weighted imaging (DWI) is a method of signal contrast generation based on the molecular motion of water within the tissue[9], which is included in every MRI of the brain in the present study institute. It can be used in several circumstances, such as evaluating acute stroke and the cellularity of the tumor[10]. In diffusion MRI, a diffusion coefficient called apparent diffusion coefficient (ADC) value can be calculated. The present study aimed to compare the ADC values between the enhancing and the non-enhancing MS lesions and find the cutoff ADC value that could be used to predict the enhancement of MS lesions.

Materials and Methods

Study setting

The local Ethics committee approved the present study(COA MURA2020/432). The informed consent was waived.

Patient selection

A retrospective study was conducted on all patients diagnosed with multiple sclerosis who underwent pretreatment MRI of the brain between January 2015 and December 2019. The patients with no available imaging and demographic data or inadequate imaging study were excluded. All of the medical records of the selected patients were reviewed for demographic and clinical data.

MRI technique

MRI examinations were acquired on 1.5-T (Signa; GE Medical Systems, Milwaukee, Wisconsin, USA and Ingenia, Philips Healthcare, Best, the Netherlands) and 3-T scanners (Ingenia, Philips Healthcare, Best, the Netherlands) using a 15-channel receiver head coil.

On the 3-T scanner, the following sequences were acquired: axial 3D TSE T1-weighted image (TR/TE 662/10; flip angle, 70°) with and without Gd-DTPA; axial TSE T2-weighted image (TR/TE, 4,158/86; flip angle, 90°); axial FLAIR FS+Gd (TR/TE, 4,800/326); axial SWI (TR/TE, 31/10; section thickness, 2.0 mm; flip angle, 17°) or coronal T2*-weighted GRE (TR/TE, 1,044/16; flip angle, 18°). DWI was performed using a single-shot echoplanar imaging pulse sequence (TR/TE, 3,000/90 ms). Diffusion-sensitizing gradients were applied sequentially along the three orthogonal planes, and images were obtained at b values of 0 and 1,000 s/mm².

On the 1.5-T scanner (Signa; GE Medical Systems, Milwaukee, Wisconsin, USA), the following sequences were acquired: axial TSE T1-weighted image (TR/TE 400/14; flip angle, 90°) with and without Gd-DTPA; axial TSE T2-weighted image (TR/TE, 2,500/88; flip angle, 90°); axial FLAIR FS+Gd (TR/TE, 9,000/127); axial SWI (TR/TE, 78/47; section thickness, 1.5 mm; flip angle, 15°) or coronal T2*-weighted GRE (TR/TE, 700/20; flip angle, 25°). DWI was performed using a single-shot echoplanar imaging pulse sequence (TR/TE, 8,000/90 ms). Diffusion-sensitizing gradients were applied sequentially along the three orthogonal planes, and images were obtained at b values of 0 and 1,000 s/mm².

On the 1.5-T scanner (Philips Healthcare, Best, the Netherlands), the following sequences were acquired: axial 3D TSE T1-weighted image (TR/TE 560/29; flip angle, 90°) with and without Gd-DTPA; axial TSE T2-weighted image (TR/TE, 4,300/98; flip angle, 90°); axial FLAIR FS+Gd (TR/TE, 4,800/300); axial SWI (TR/TE, 52/12; section thickness, 2 mm; flip angle, 20°) or coronal T2*-weighted GRE (TR/TE, 682/16; flip angle, 25°). DWI was performed using a single-shot echoplanar imaging pulse sequence (TR/TE, 5,900/98 ms). Diffusion-sensitizing gradients were applied sequentially along the three orthogonal planes, and images were obtained at b values of 0 and 1,000 s/mm².

ADC maps were generated for all patients using the present study vendors' standard software, including IntelliSpace Portal 12 and Signa Works.

MRI analysis

The MRI studies of the brain were initially reviewed on FLAIR sequence to evaluate the demyelinating lesions in each patient by two experienced neuroradiologists (PP, TP) in consensus. Each demyelinating lesion was marked and assigned with a specific numeric value. The neuroradiologists then evaluated the corresponding location of the demyelinating lesion on post-contrast T1WI. Each lesion was categorized into two groups, non-enhancing or enhancing lesions, based on the presence of enhancement on post-contrast T1WI. The ADC values were separately measured in all demyelinating lesions by two readers, including a neuroradiologist (PP) and a radiology trainee physician (BC). The readers were blinded to clinical history.

For ADC value measurement, the circular regions of interest (ROIs) were placed at the same location as the lesions on FLAIR FS and post-contrast

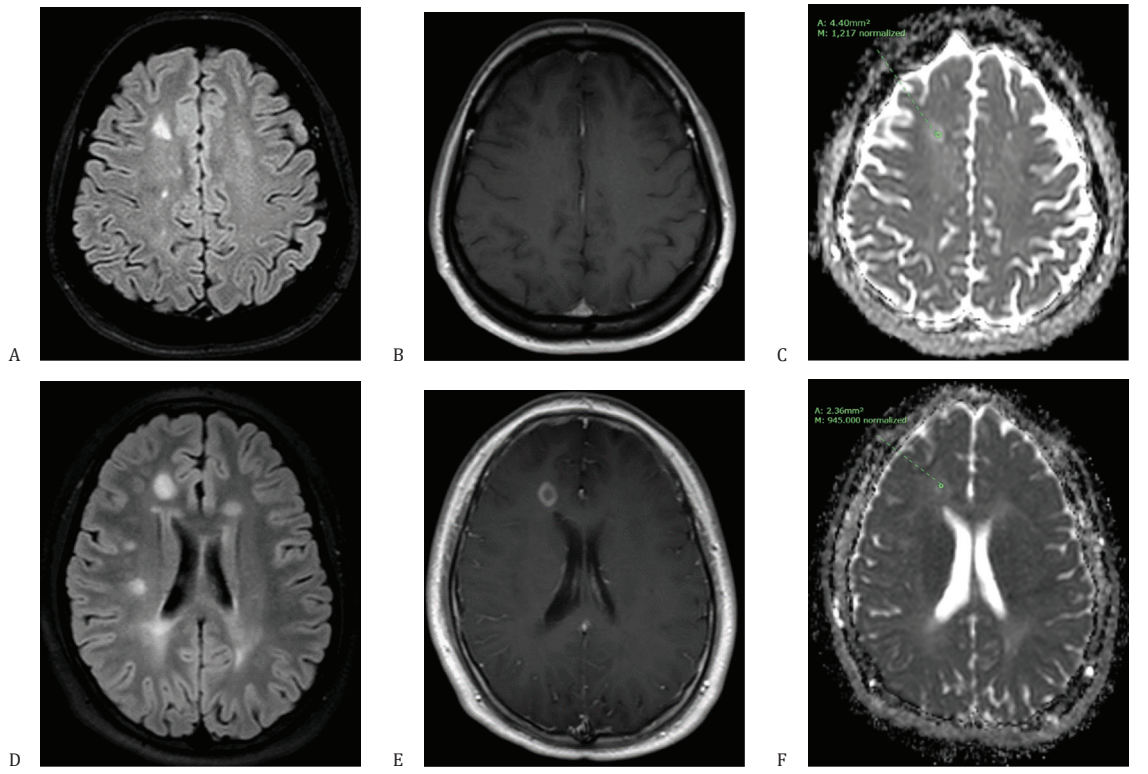

Figure 1. Axial FLAIR FS (A), post-contrast T1WI (B), and ADC map of a patient diagnosed with multiple sclerosis (C) demonstrate non-enhancing demyelinating lesion at the right frontal white matter. The ROI (green circle in C) was placed centrally within the lesion. Axial FLAIR FS (D), post-contrast T1WI (E), and ADC map (F) of another patient demonstrate a ring-enhancing demyelinating lesion at the right frontal white matter. The ROI (green circle in F) was placed only in the enhancing portion at the periphery.

T1WI sequences (Figure 1). The ROIs were placed centrally within the homogeneously enhancing lesions and non-enhancing lesions. In ring-enhancing and heterogeneously enhancing lesions, ROIs were placed in the enhancing portions. The size of the ROIs ranged between 1 to 5 mm^2. Only one ROI was placed in each lesion.

Statistical analysis

The ADC value of each lesion was categorized into two groups, enhancing and non-enhancing lesions, based on the presence or absence of enhancement on the post-contrast T1WI sequence. The mean of the measured ADC values of each lesion between the two observers was calculated. The t-test was used to calculate the difference between quantitative data in the two groups. Receiver operating characteristic (ROC) analysis was also performed to determine sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and 95% confidence interval (CI) and cutoff ADC value to differentiate the enhancing MS lesions from non-enhancing MS lesions. A significant difference was set at a p-value of less than 0.05. The interobserver correlation was calculated using Pearson correlation.

Results

Based on a retrospective analysis of the data profiles in the present study institution between January 2015 and December 2019, there were 23 patients diagnosed with definite MS. One case was excluded due to an inadequate MRI study. Therefore, 22 patients were included in the study, with a total of 194 demyelinating lesions. The details of the patients' characteristics are shown in Table 1. The measured ADC values by the two observers ranged from 0.566×10^{-3} to 2.106×10^{-3} mm^2/second. There were 33 enhancing lesions and 161 non-enhancing lesions. Mean ADC values were $0.891\pm0.164\times10^{-3}$ mm^2/second in the enhancing lesions and $1.303\pm0.280\times10^{-3}$ mm^2/second in the non-enhancing lesions. The ADC differences between enhancing, and non-enhancing lesions were statistically significant, with a $p<0.001$ (Table 2). Interobserver agreement using Pearson correlation was 0.916 (Figure 2). By using the Euclidean index, a cutoff ADC value of 1.117×10^{-3}

Table 1. Demographic data

Patients (n=22)	
Sex; n (%)	
Male	6 (27.27)
Female	16 (72.73)
Age (year); mean±SD	35±16.12

SD=standard deviation

Table 2. ADC values of each enhancing pattern

Enhancing pattern	No. of lesions	ADC value ($\times10^{-3}$ mm^2/second)		p-value
		Range	Mean±SD	
Enhancing lesions	33	0.566 to 1.467	0.891±0.164	<0.001
Non-enhancing lesions	161	0.867 to 2.106	1.303±0.280	
Total	194	0.566 to 2.106	1.233±0.306	

ADC=apparent diffusion coefficient; SD=standard deviation

Table 3. Number of true positive, false negative, false positive, and true negative, using the cutoff ADC value at 1.117×10^{-3} mm^2/second

Enhancing pattern	Lesions; n (%)		Total
	ADC value <1.117 $\times10^{-3}$ mm^2/second	ADC value ≥1.117 $\times10^{-3}$ mm^2/second	
Enhancing lesions	31 (93.9)	2 (6.1)	33
Non-enhancing lesions	46 (28.6)	115 (71.4)	161
Total	77 (100)	117 (100)	194

ADC=apparent diffusion coefficient

Table 4. Diagnostic performance of the cutoff ADC value at 1.117×10^{-3} mm^2/second in differentiating enhancing MS lesions from non-enhancing MS lesions

Parameters	Results (%)	95% confidence interval
Sensitivity	93.9	79.8 to 99.3
Specificity	71.4	63.8 to 78.3
ROC area	0.827	0.773 to 0.881
Positive predictive value	40.3	29.2 to 52.1
Negative predictive value	98.3	94.0 to 99.8
Accuracy	75.3	68.6 to 81.2

ROC=receiver operating characteristic

mm²/second was selected to distinguish between the enhancing and the non-enhancing lesions. The best results were obtained with a sensitivity of 93.9%, specificity of 71.4%, positive predictive value (PPV) of 40.3%, negative predictive value (NPV) of 98.3%, false positive rate (FPR) of 28.6%, false negative rate (FNR) of 6.1%, and accuracy of 75.3% (Figure 3, Table 3, 4).

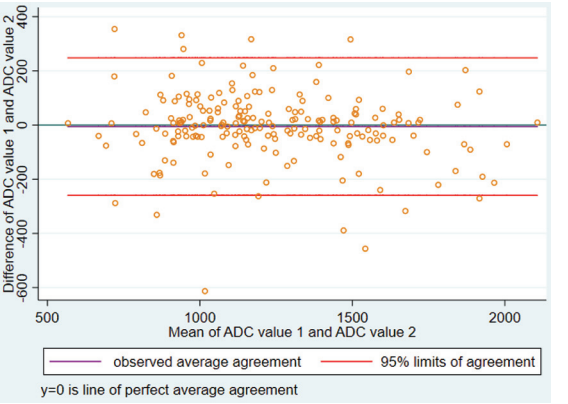

Figure 2. Interobserver agreement by using Pearson correlation.

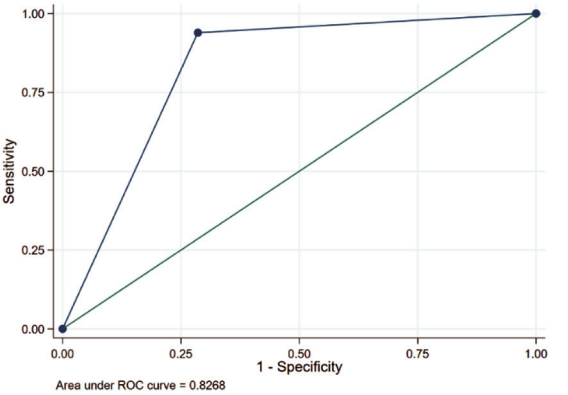

Figure 3. The optimal cutoff ADC value predicting enhancement of MS plaque was 1.117×10^{-3} mm^2/second [area under ROC curve (AUC) 0.827].

Discussion

In the present study, the authors found a significant difference in ADC values between the enhancing and the non-enhancing MS lesions. The enhancing MS lesions have significantly lower ADC values than the non-enhancing MS lesions. In multiple sclerosis, the pathogenesis of active demyelinating plaque is hypothesized to be associated with cytotoxic tissue damage caused by T lymphocytes[11-14], which explains why the enhancing lesions tend to have lower ADC values than the ADC values of the non-active chronic MS plaques.

In the present study, the authors selected the ADC value of 1.117×10^{-3} mm²/second as an optimal cutoff point to predict the enhancement of the MS plaques due to its high sensitivity, good specificity, and high negative predictive value. There was also a good interobserver agreement, which suggests good reproducibility of this method. This cutoff

point can serve as a screening tool to predict active demyelinating MS plaque. Only the patients who have the MS plaque with the ADC value lower than 1.117×10^{-3} mm²/second need a contrast-enhanced MRI study to confirm the presence of active MS plaque. The physician can omit unnecessary Gd administration in patients with no MS plaque with the ADC value lower than this cutoff point, which helps lower Gd exposure.

The present study result correlates with that of Abdoli et al[15] and that of Mohamed et al[16], which found that the non-enhancing lesions have higher ADC values than the enhancing lesions. Mohamed et al[16] also found that the ring-enhancing lesions also had lower ADC values than the non-enhancing lesions but more than the homogeneously enhancing lesions. This result may be due to the measurement of the ADC values of the ring-enhancing lesions in which they had to include both enhancing and non-enhancing portions of the lesion, making their ADC values less than that of the non-enhancing lesions but more than that of the homogeneously enhancing lesions. The authors also agree with Phuttharak et al[17], who found that the enhanced rim of ring-enhancing lesions had lower ADC than the central non-enhanced portions. The authors disagree with Unal et al[18] in measuring ADC values between enhancing and non-enhancing MS plaque, which they reported as insignificant.

The present study has limitations. The major limitation is the difficulty in identifying the same location of the lesion on the ADC map due to the small size of the majority of the demyelinating lesions. Second, this was a retrospective study with a small sample size.

Conclusion

ADC value measurement can be used to predict the enhancement of the MS plaque, which may be helpful as a screening tool for active demyelinating plaque in MS patients.

What is already known on this topic?

The presence of enhancement of the MS plaque represents the active demyelinating process of the lesion.

What this study adds

The enhancing MS lesions have significantly lower ADC values than the non-enhancing MS lesions. With an appropriate cutoff point, the ADC value can be used as a screening tool for active demyelinating plaque in MS patients.

Conflicts of interest

The authors declare no conflict of interest.

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