# Is It Possible to Discriminate Active MS Lesions with Diffusion Weighted Imaging?

Sena Unal[1], Elif Peker[1], Seyda Erdogan[2], Memet Ilhan Erden[1]


## ABSTRACT

**Objective:** Patients with multiple sclerosis (MS) are at a risk of gadolinium deposition because of multiple control imaging. Therefore, it is important to determine biomarkers that can differentiate active and chronic lesions without using contrast agent. This study aimed to assess mean apparent diffusion coefficient (ADC) values and signal intensities (SI) on diffusion weighted imaging (DWI) values of active and nonactive lesions.

**Materials and Methods:** We included 25 patients in this study. We measured mean ADC values and SI on DWI of the randomly selected active and nonactive lesions and normal appearing white matter (NAWM) for all patients with MS. SI on DWI and ADC values were normalized to the SI of the CSF. We compared all of the measurements between active and nonactive lesions, active lesions and NAWM, and nonactive lesions and NAWM. SI on DWI and mean ADC values of normal healthy white matter (NHWM) of control group were measured. A comparison was made between NHWM and NAWM.

**Results:** For patients with active lesions, the mean nADC value was 0.35±0.06 for active lesions and 0.30±0.07 for nonactive lesions ($p>0.050$). The mean nDWI-SI value was 3.69±0.68 for active lesions was 3.39±0.68 for nonactive lesions ($p<0.050$). When patients with and without active lesions were compared, both nDWI values and nADC values for active and nonactive lesions were statistically insignificant ($p>0.050$).

**Discussion:** In MS lesions, diffusion alternations can be quantitatively evaluated with ADC mapping. Lesions seen in patients with MS have higher mean ADC values than NAWM and NHWM.


**Keywords:** Diffusion, multiple sclerosis, active, apparent diffusion coefficient

## Introduction

Multiple sclerosis (MS) is a common autoimmune neurologic disorder. Demyelination due to myelin breakdown, axonal injury, perivascular inflammation, and gliosis are seen in MS lesions [1]. Although various imaging modalities can help to diagnose MS, magnetic resonance imaging (MRI) is the most sensitive one. MRI has an important role in guiding treatment and disease prognosis by enabling early diagnosis [1, 2]

For the first imaging and follow-up of patients with MS, conventional sequences include T1 weighted images (WI), T2WI, FLAIR images, and contrast-enhanced T1WI [2]. Changes on diffusion WI (DWI) and apparent diffusion coefficient (ADC) maps can be seen because of the inflammatory processes causing cytotoxic and then vasogenic edema [3]. Since various pathologies can cause hyperintensities on T2WI and FLAIR images, using conventional MRI alone has low specificity. Furthermore, it is inadequate to reveal the injury of normal appearing white matter (NAWM) [4].

Recently, studies have shown gadolinium deposition in the brain after contrast-enhanced MRI. The patients with MS are at a risk of gadolinium deposition because of multiple control imaging. It is known that repeat doses of gadolinium are correlated with an increase in intensity on T1WI in the dentate nucleus of the cerebellum in patients with MS [5]. This finding is associated with secondary-progressive MS and clinical disability [6]. Therefore, it is important to determine biomarkers that can differentiate active and chronic lesions without using contrast agent [7].

***Cite this article as:*** *Unal S, Peker E, Erdogan S, Erden MI. Is It Possible to Discriminate Active MS Lesions with Diffusion Weighted Imaging? Eurasian J Med 2019; 51(3): 219-23.*

***ORCID IDs of the authors:***
*S.U. 0000-0001-6680-0789*
*E.P. 0000-0003-3585-6848*
*S.E. 0000-0002-4113-2080*
*M.I.E. 0000-0002-6274-3841*

[1]Department of Radiology, Ankara University School of Medicine, Ankara, Turkey
[2]Department of Neurology, Ankara University School of Medicine, Ankara, Turkey

**Received:** December 25, 2018
**Accepted:** June 18, 2019

**Correspondence to:** Elif Peker
**E-mail:** elifozyurek0@yahoo.com

DOI 10.5152/eurasianjmed.2019.18473

DWI shows the movement of water molecules in tissues, and the ADC maps show the quantitative measurement of myelin breakdown [8]. The mean ADC values of MS lesions may show alterations depending on the type of edema during active and chronic periods [3]. The MS lesions may have higher mean ADC values than NAWM [3, 8]. Even though conventional MRI cannot depict any intensity changes in NAWM, microscopic injuries may be present. The measurement of ADC values may allow the detection of NAWM injuries [8].

This study aimed to assess mean ADC values and signal intensity (SI) on DWI of active and nonactive lesions and NAWM and to compare their measurements with each other and with normal healthy white matter (NHWM) of patients with normal brain MRI findings and no clinical suspicion of MS.

## Materials and Methods

### Patients

The institutional review board approved this retrospective, single-center study protocol and waived informed consent.

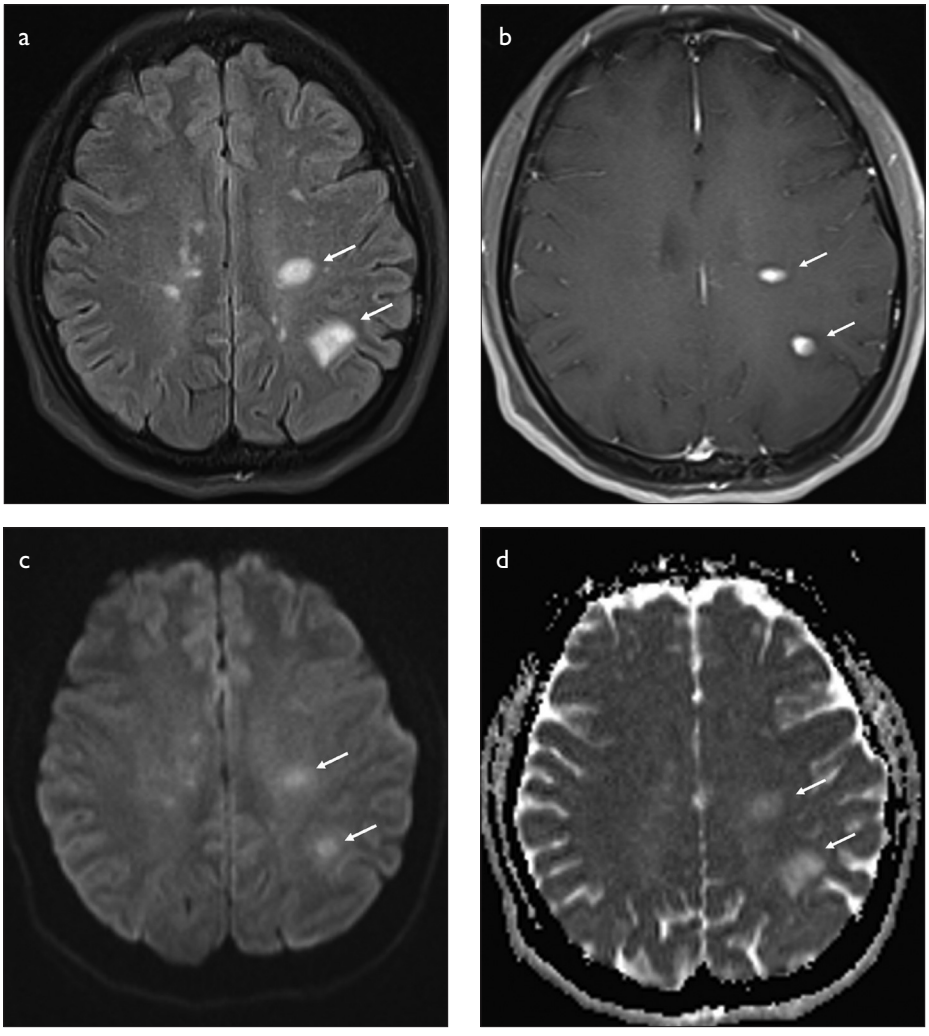


**Figure 1. a-d.** a) Axial plane FLAIR image of a patient with active MS lesions at the left centrum semiovale (arrows). b) Axial plane contrast enhanced image of a patient with active, enhancing MS lesions at the left centrum semiovale (arrows). c) Axial plane diffusion weighted image of a patient with active MS lesions at the left centrum semiovale. Lesions are hyperintense on diffusion weighted image (arrows). d) Axial plane ADC map of a patient with active MS lesions at the left centrum semiovale. Lesions show no difffusion restriction (arrows).

We retrospectively evaluated 35 patients examined with brain MRI between November 2011 and November 2016. Patients who did not get contrast administration and patients without b=1000 DWI sequences were excluded from the study. Twenty-five patients were included in the study. Twenty-two patients had relapsing-remitting MS, two patients had seconder progressive MS, and one patient had primer progressive MS. For comparison, a control group consisted of 25 patients without any history of radiotherapy, chemotherapy, and hypertension; without significant abnormalities on brain MRI; and the same age and gender as the patient group.

### MRI Protocol and Evaluation of Images

All images were obtained with 3 Tesla MR scanner (Siemens Magnetom Verio, Erlangen, Germany). All the patients included in the study had FLAIR images (axial plane, TSE, TR>6000, TE:100-140, TI: 2000-2500, FOV: 240, slice thickness/gap:4/0), DWI (b=1000, SS-EPI, axial plane, TSE, TR>5000, TE:min, FOV: 240, slice thickness/gap:4/0), ADC maps, and contrast-enhanced 3d-T1WI (MPRAGE, 3D, TR>2100, TE:min, TI: 1100, FOV: 256, slice thickness/gap:4/0). For contrast-enhanced imaging gadobutrol (Gadovist, Bayer Schering Pharma, Berlin, Germany) or gadoterate meglumine (dotarem; Guerbet, Aulnay-sous-Bois, France) were administered at a single dose of 0.1 mmol/kg by intravenous bolus injection at a rate of 2 mL/s. The presence of contrast-enhancing lesions and diffusion restriction was noted. Contrast-enhancing lesions were considered as active lesions. For patients with active MS lesions, mean ADC values and signal intensities (SI) on DWI of the randomly selected active and nonactive lesions were measured. In patients with MS with acute disease, 31 active lesions and 31 nonactive lesions were assessed; in patients with chronic disease, 38 nonactive lesions were assessed. These parameters were also measured from the frontal NAWM for all patients with MS. Measurements were made using region of interests (ROI). ROIs were located centrally in the lesions. SI on DWI and ADC values were normalized (n) to the signal intensities of the cerebrospinal fluid (CSF) ($SI_{lesion}/SI_{CSF}$) for correction between examinations. SI of the CSF was measured from the body of the lateral ventricle. All of the measurements were compared between active and nonactive lesions, active lesions and NAWM, and nonactive lesions and NAWM and NAWMs of patients with active and nonac-

**Table 1.** Normalized SI values of active and nonactive lesions on DWI and ADC maps

| | Active lesions | Nonactive lesions | p | Active lesions | NAWM | p | Nonactive lesions | NAWM | p |
|---|---|---|---|---|---|---|---|---|---|
| nSI on b=1000 | 3.69±0.91 | 3.39±0.68 | 0.011 | 3.65±0.91 | 2.32±0.70 | <0.001 | 3.37±0.72 | 2.60±0.86 | <0.001 |
| nADC | 0.35±0.06 | 0.30±0.07 | 0.961 | 0.35±0.06 | 0.24±0.02 | <0.001 | 0.38±0.07 | 0.23±0.02 | <0.001 |

N: normalized; DWI: diffusion weighted imaging; ADC: apparent diffusion coefficient; NAWM: normal appearing white matter

tive lesions. SI on DWI and mean ADC values of NHWM of control group were measured. A comparison was made between NHWM and NAWM.

### Statistical Analysis

Statistical analyses were performed using The Statistical Package for the Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, USA). Mean±standard deviation [median (min-max)] for metric variables and frequency (percent) for categorical variables were used as descriptive statistics. For the comparison between the two independent groups, the Mann–Whitney U test was used for metric variables.

**Table 2.** Normalized SI values of normal appearing white matter of patients with active and nonactive lesions on DWI and ADC maps

| | Patient with active lesion | Patient without active lesion | |
|---|---|---|---|
| | NAWM | NAWM | p |
| nSI on b=1000 | 2.32±0.70 | 2.60±0.86 | 0.145 |
| nADC | 0.24±0.02 | 0.23±0.02 | 0.445 |

N: normalized; DWI: diffusion weighted imaging; ADC: apparent diffusion coefficient; NAWM: normal appearing white matter

## Results

Of the 25 patients with MS, 19 were women and six were men. Ages ranged from 22 to 58 years. The mean age was 39.3±9.3 years. The MR images were acquired with an average of 14±9 days after the onset of symptoms.

For patients with active lesions, the mean nADC value was 0.35±0.06 for active lesions and 0.30±0.07 for nonactive lesions. This difference was not statistically significant (Figures 1, 2). The mean nSI on DWI value was 3.69±0.68 for active lesions and 3.39±0.68 for nonactive lesions. This difference was statistically significant. There was a statistically significant difference the mean nADC and nSI on DWI of both active and nonactive lesions with NAWM (p<0.001). When patients with and without active lesions were compared, both nDWI values and nADC values for active and nonactive lesions were statistically insignificant (p>0.050) (Table 1). No significant difference was detected between NAWM of patients with and without active lesions (Table 2).

The mean normalized ADC value was 0.24±0.02 for NAWM and 0.24±0.02 for NHWM (p=0.320). The mean normalized DWI value was 2.47±0.80 for NAWM and 2.33±0.66 for NHWM (p=0.264).

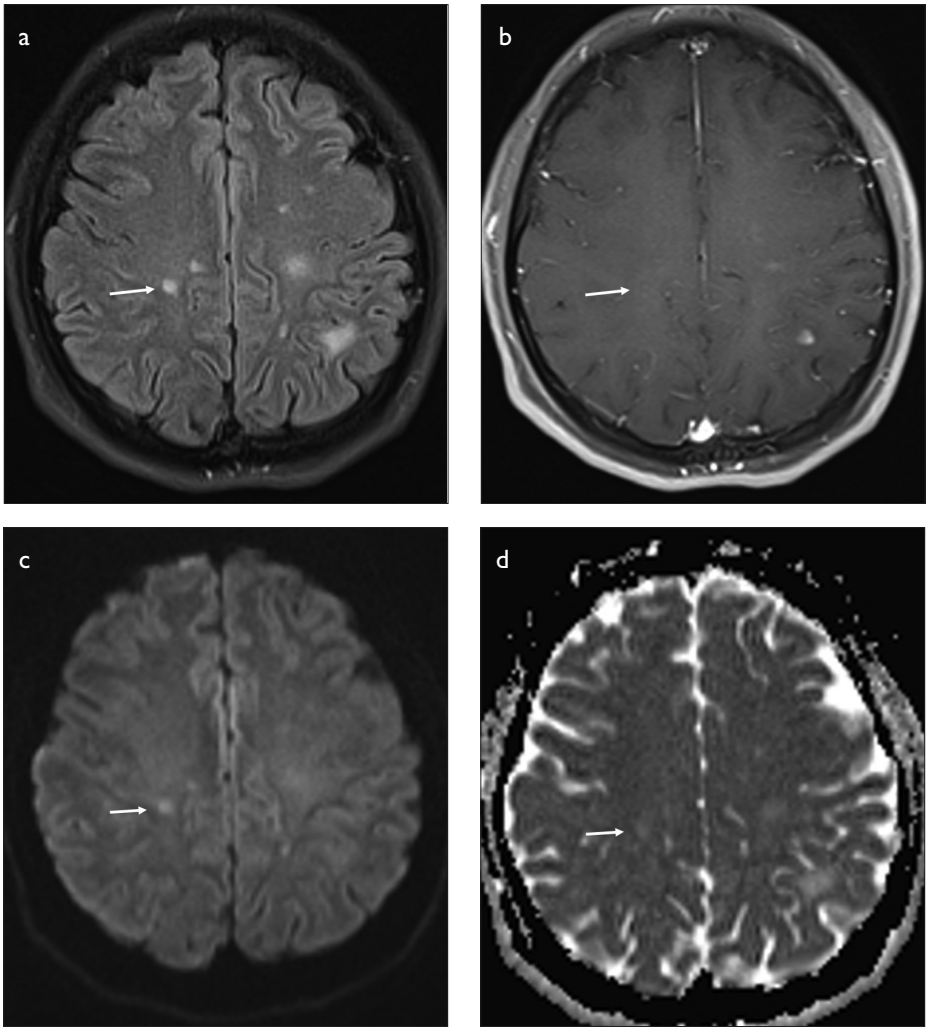


**Figure 2. a-d.** a) Axial plane FLAIR image of a patient with non-active MS lesion at the right centrum semiovale (arrow). b) Axial plane contrast enhanced image of a patient with non-active MS lesion at the right centrum semiovale. Lesion is not enhancing (arrow). c) Axial plane diffusion weighted image of a patient with non-active MS lesion at the right centrum semiovale. Lesion is hyperintense on diffusion weighted image (arrow). d) Axial plane ADC map of a patient with non-active MS lesion at the right centrum semiovale. There is no diffusion restriction (arrow).

## Discussion

In MS, alterations of water diffusion are seen because of tissue damage. Thus, DWI can be used to evaluate the quantitative assessment of tissue damage in patients with MS. The DWI and ADC maps may show changes before blood-brain barrier leakage occurs and MS lesions become evident [9]. For the evaluation of the severity and the disease extension to NAWM of MS, DWI and ADC maps are used together with routine MRI [4, 8].

Larsson et al. [10] evaluated 25 patients with MS, and they reported that water diffusion is higher in MS lesions than NAWM. They also found that water diffusion is high in acute lesions compared with chronic lesions. They suggested that an increase in water diffusion might be related to an increase in extracellular space and the degree of demyelination. It was stated that measurement of water diffusion could contribute to the assessment of demyelination pathogenesis.

Some articles and case reports suggest that acute MS lesions show restriction on the ADC maps [11-14]. A restricted ADC is seen in the early stages of acute lesions, and subsequently, ADC values normalize or increase. It is assumed that restriction emerges before the contrast enhancement of lesions becomes visible and normalizes long before enhancement disappears [15]. Diffusion restriction is seen before the tissue injuries become prominent on conventional MRI. Restriction is significant in the first seven days in patients with acute MS attack. The ADC values subsequently normalize and then increase in about the fourth week. In the first seven days, contrast enhancement is subtle or absent, and in up to four weeks, enhancement becomes prominent [16]. An increase in ADC values of MS lesions is considered a result of vasogenic edema, axonal injury, and demyelination [17-19]. Balashov et al. [12 ] found nine acute lesions with restricted dif-

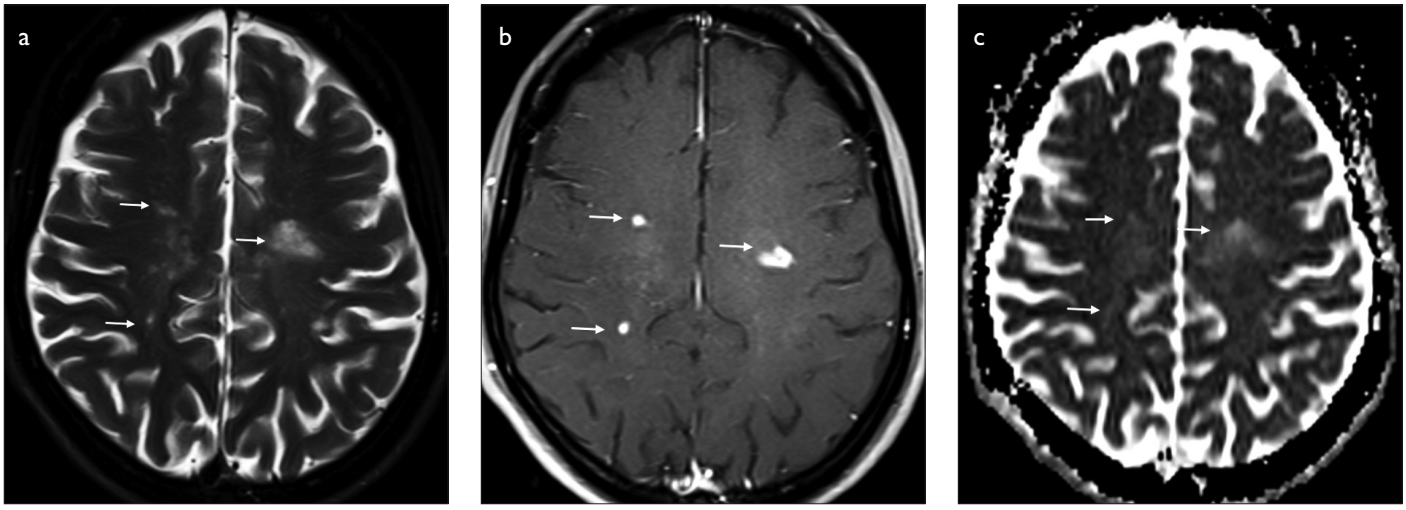


**Figure 3. a-c.** a) Axial plane T2-weighted image of a patient with active MS lesions at both centrum semiovale (arrows). b) Axial plane contrast enhanced image of a patient with active, enhancing MS lesions at both centrum semiovale (arrows). c) Axial plane ADC map of a patient with active MS lesions at both centrum semiovale. Lesions show no difffusion restriction (arrows).

fusion in six patients with relapsing-remitted MS. Follow-up images showed that ADC values normalize or increase at least 13 days after the onset of clinical symptoms. In our study, MR images were acquired with an average of 14 days after the onset of symptoms; and none of the active lesions showed restricted diffusion.

Several studies showed that ADC values of NAWM are higher than NHWM [8, 9 ]. Microscopic injuries are also seen in NAWM, not merely in visible lesions [4]. Werring et al. [9] suggested that there is an increase in ADC values of prelesion NAWM (approximately six months before contrast-enhancing lesions are seen), and at the same time, ADC values of contralateral NAWM are stable. The ADC values of contralateral NAWM are initially stable and eventually increase. An increase in ADC values indicates microscopic injuries in NAWM, and MS lesions may develop from these areas in time. This shows that MS is a white matter disease with multiple involvement areas [20]. Pathological changes in NAWM include astrocyte hyperplasia, microglia activation, perivascular inflammation, and myelin breakdown [9, 21]. These changes cause tissue damage and enlargement of extracellular space and lead to an increase in ADC values [9]. In a study of Caramia et al. [22] in which they evaluated clinically isolated patients with MS, they found no significant changes in ADC values on initial MRI, but after one year, follow-up imaging showed that ADC values of NAWM had increased. These data indicate that in the early stages of MS disease, microscopic injuries are not significant, but subsequently, diffusion abnormalities can occur. In our study, no statistically significant difference was found between the ADC values of NAWM and NHWM.

Almolla et al. [8] evaluated patients with MS with chronic lesions and found a significant increase in ADC values of chronic lesions compared with NAWM and NHWM. In a study in which patients with MS with acute attack were assessed, Yurtsever et al. [3] reported that ADC values of acute lesions have higher ADC values than NAWM and NHWM. Terzi et al. [20] found no significant difference between ADC values of active and chronic lesions, but they indicated that active lesions have higher ADC values than NAWM.

There are several limitations of this study. First is the small sample size. Second, when evaluating the NAWM and NHWM, ADC measurements were made from a single frontal white matter region where there were no hyperintensities seen on T2WI and FLAIR images. Taking measurements from one region instead of averaging measurements from different regions might have affected our results. Not all of the MS lesions were sampled, but they were randomly selected.

Our results also showed no statistically significant difference between active and chronic lesions, and both lesion groups had statistically significant higher ADC values than NAWM and NHWM. These findings were consistent with other studies mentioned before.

In conclusion, in MS lesions, diffusion alternations may be seen because of tissue damage caused by demyelination. These alternations in diffusion between NAWM and active/nonactive MS lesions can be quantitatively evaluated with DWI.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the Ethics Committee of Ankara University School of Medicine.

**Informed Consent:** Informed consent is not necessary due to the retrospective nature of this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – S.U., E.P.; Design – S.U., E.P., I.E.; Supervision - I.E.; Resources – E.P., S.E.; Materials – E.P., S.E.; Data Collection and/or Processing – S.U., E.P., S. E.; Analysis and/or Interpretation -S.U., E.P.; Literature Search - S.U., E.P., M.A.A.; Writing Manuscript - S.U., E.P.; Critical Review – I.E.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

## References

1. Hygino da Cruz LC, Batista RR, Domingues RC, Barkhof F. Diffusion magnetic resonance imaging in multiple sclerosis. Neuroimaging Clin N Am 2011; 21: 71-88. **[CrossRef]**
2. Davoudi 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. **[CrossRef]**
3. Yurtsever I, Hakyemez B, Taskapilioglu O, Erdogan C, Turan OF, Parlak M. The contribution of diffusion-weighted MR imaging in multiple sclerosis during acute attack. Eur J Radiol 2008; 65: 421-6. **[CrossRef]**
4. Iannucci G, Rovaris M, Giacomotti L, Comi G, Filippi M. Correlation of multiple sclerosis measures derived from T2-weighted, T1-weighted, magnetization transfer, and diffusion tensor MR imaging. AJNR Am J Neuroradiol 2001; 22: 1462-7.
5. Stojanov DA, Aracki-Trenkic A, Vojinovic S, Benedeto-Stojanov D, Ljubisavljevic S. Increasing signal intensity within the dentate nucleus and globus pallidus on unenhanced T1W magnetic resonance images in patients with relapsing-remitting multiple

sclerosis: correlation with cumulative dose of a macrocyclic gadolinium-based contrast agent, gadobutrol. Eur Radiol 2016; 26: 807-15. **[CrossRef]**

6. Roccatagliata L, Vuolo L, Bonzano L, Pichiecchio A, Mancardi GL. Multiple sclerosis: hyperintense dentate nucleus on unenhanced T1-weighted MR images is associated with the secondary progressive subtype. Radiology 2009; 251: 503-10. **[CrossRef]**
7. Gupta A, Al-Dasuqi K, Xia F, Askin G, Zhao Y, Delgado D, Wang Y. The Use of Noncontrast Quantitative MRI to Detect Gadolinium-Enhancing Multiple Sclerosis Brain Lesions: A Systematic Review and Meta-Analysis. AJNR Am J Neuroradiol 2017; 38: 1317-22. **[CrossRef]**
8. Almolla RM, Hassan HA, Raya YM, Hussein RA. Correlation of apparent diffusion coefficient to cognitive impairment in relapsing remittent multiple sclerosis (plaque, peri-plaque and normal appearing white matter). Egypt J Radiol Nucl Med 2016; 47: 1009-18. **[CrossRef]**
9. Werring DJ, Brassat D, Droogan AG, et al. The pathogenesis of lesions and normal-appearing white matter changes in multiple sclerosis: a serial diffusion MRI study. Brain 2000; 123: 1667-76. **[CrossRef]**
10. Larsson HB, Thomsen C, Frederiksen J, Stubgaard M, Henriksen O. In vivo magnetic resonance diffusion measurement in the brain of patients with multiple sclerosis. Magn Reson Imaging 1992; 10: 7-12. **[CrossRef]**
11. Balashov KE, Aung LL, Dhib-Jalbut S, Keller IA. Acute multiple sclerosis lesion: conversion of restricted diffusion due to vasogenic edema. J Neuroimaging 2011; 21: 202-4. **[CrossRef]**
12. Balashov KE, Lindzen E. Acute demyelinating lesions with restricted diffusion in multiple sclerosis. Mult Scler 2012; 18: 1745-53. **[CrossRef]**
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. Hyland M, Bermel RA, Cohen JA. Restricted diffusion preceding gadolinium enhancement in large or tumefactive demyelinating lesions. Neurol Clin Pract 2013; 3: 15-21. **[CrossRef]**
15. Abdoli M, Chakraborty S, MacLean HJ, Freedman MS. The evaluation of MRI diffusion values of active demyelinating lesions in multiple sclerosis. Mult Scler Related Disord 2016; 10: 97-102. **[CrossRef]**
16. Eisele P, Szabo K, Griebe M, et al. Reduced diffusion in a subset of acute MS lesions: a serial multiparametric MRI study. AJNR Am J Neuroradiol 2012; 33: 1369-73. **[CrossRef]**
17. Cercignani M, Iannucci G, Rocca MA, Comi G, Horsfield MA, Filippi M. Pathologic damage in MS assessed by diffusion-weighted and magnetization transfer MRI. Neurology 2000; 54: 1139-44. **[CrossRef]**
18. Christiansen P, Gideon P, Thomsen C, Stubgaard M, Henriksen O, Larsson HB. Increased water self-diffusion in chronic plaques and in apparently normal white matter in patients with multiple sclerosis. Acta Neurol Scand 1993; 87: 195-9. **[CrossRef]**
19. Horsfield MA, Lai M, Webb SL, et al. Apparent diffusion coefficients in benign and secondary progressive multiple sclerosis by nuclear magnetic resonance. Magnetic Reson Med 1996; 36: 393-400. **[CrossRef]**
20. Terzi M, Atalay K, İncesu L, Diren B, Onar M. Diffusion-weighted magnetic resonance imaging of the brain in multiple sclerosis. Turk J Neurol 2007; 13: 310-8.
21. Allen IV, McKeown SR. A histological, histochemical and biochemical study of the macroscopically normal white matter in multiple sclerosis. J Neurol Sci 1979; 41: 81-91. **[CrossRef]**
22. Caramia F, Pantano P, Di Legge S, et al. A longitudinal study of MR diffusion changes in normal appearing white matter of patients with early multiple sclerosis. Magn Reson Imaging 2002; 20: 383-8. **[CrossRef]**