Neurology Asia 2014; 19(4) : 387 – 391

ADC evaluations of the hippocampus and amygdala in multiple sclerosis

[1]Mikail Inal, [1]Birsen Unal Daphan, [1]Yasemin Karadeniz Bilgili, [2]Yakup Turkel, [3]Ibrahim Kala

[1]Department of Radiology, [2]Department of Neurology, Kirikkale University School of Medicine, Kirikkale; [3]Department of Radiology, Cizre State Hospital, Sırnak, Turkey

Abstract

*Background & Objective:*Diffusion-weighted MR imaging and apparent diffusion coefficient (ADC) values provide significant structural information about tissues in multiple sclerosis (MS).The goal of this study was to evaluate the ADC values in the hippocampus and amygdala in MS. *Methods:*Thirty-eightpatients with MS and 41 healthy individualswere included in the study. ADC values were measured bilaterallyfrom three different pointsin the hippocampus and amygdala in MS patients and were compared with those of the controls. An analysis of varianceposthoc test was used to analyse the differences among mean ADC values between MS and control groups.*Results:*The mean ADC values of both sides of thehippocampus and the left amygdala in MS patients were lower than the control group. The mean ADC values of the right amygdala in MS patients were lower than the control group, but the difference was not statistically significant.
*Conclusion:*We observed restricted diffusion in the hippocampus and amygdala in MS patients contrary to information in the literature.

INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory,demyelinating, and neurodegenerative disease of the central nervous system and the most common cause of non-traumatic disablement in young adults.[1]Patients with MS frequently develop psychiatric disorders, and thehippocampus, which plays a basic role in memory processing[2], has been implicatedthrough a retrospective discovery of a correlation between psychosis in MS patients and temporal lobe pathology.[3,4] There is evidence of selective atrophy within the hippocampus in MS that is associated with impaired performance on a cognitive test of verbal memory. These findings implicate distinct disease mechanisms leading to grey matter loss in MS and are consistent with emerging evidence of an early neurodegenerative process affecting the grey matter in MS patients.[5]

The literature lacks adequate information on the apparent diffusion coefficient (ADC) values of the hippocampus and amygdala in MS patients. Therefore, we aimed to compare the ADC values of hippocampus and amygdala in MS patients with an age-matched control group.

METHODS

Thirty-eight MS patients (8 male and 30 female, age range 23–48 years, mean 35.9±6.4 years) diagnosed as relapsing-remitting multiple sclerosis (RRMS) according to the McDonald criteria[6] were included in the study. All patients in the study was the RRMS patients. Magnetic resonance (MR) examinations obtained from the patients evaluated in the study were taken after an average of 8.7 ± 6.9 (r = 1-25) days from the most recent relapse episode. The control group consisted of 41 healthy individuals(15 male, 26 female, age range 22–57 years, mean 35.8 ± 9.6 years) with no neurologic disability or intracranial pathology found uponMR examination. The study was approved by the hospital ethics committee.

All experiments were performed by using a head coil in conduction with a 1.5-T whole-body imager (Infinion; Philips Medical Systems, Cleveland, OH) with a maximum gradient amplitude of 50 mT/m and a maximum gradient slew rate of 100 mT/m/s. The head coil had an inner diameter of 27 cm.

ADC values were measured bilaterally from three different points in the amygdala and hippocampus in MS patients and were compared with those of thecontrols.

Address correspondence to: MikailInal, Kirikkale University School of Medicine Research and Training Hospital, Radiology Department 71450Yahsihan/KIRIKKALE, TURKEY.Mobile: +90 555 538 15 38, Fax: +90 318 224 07 86, E-mail: inal_m@hotmail.com

Conventionalmagnetic resonance examinations

Before diffusion-weighted MR imaging (DWI), T1-weighted images were acquired in the transverse plane by using the following parameters: TR/TE, 407/10; bandwidth, 20.83 kHz; matrix size,256 × 256; field of view (FOV), 22 × 22 cm; number of sections, 20; section thickness, 5 mm; and gap, 1 mm. T2-weighted fast spin-echo images were acquired with the following parameters: TR/TE, 4555/125; bandwidth, 20.83 kHz; matrix size, 256 × 256; FOV, 22 × 22 cm; number of sections, 20; section thickness, 5 mm; and gap, 1 mm.

Diffusion-weighted images

DWI was performed by using a diffusion-weighted, single echo-planar, MR-imaging sequence. During the MR studies, the two experienced radiologists evaluated the quality of the diffusion-weighted images and selected by consensus those images that had a minimum of distortion from susceptibility artefacts and ghosting for further analysis. We selected b values of 0 and 1000 s/mm^2 for the calculation of ADCs in this study. Diffusion-weighted images were obtained over 43 s. DWI was performed with the following parameters: TR/TE, 7216/122.8; flip angle, 90°; FOV, 24 × 24 cm; and matrix size, 128 × 128 mm. Between 20 and 24 axial sections were obtained, with a section thickness of 5 mm and an intersection gap of 2.5 mm.

The reconstructed magnitude images were transferred from the MR system to an independent workstation for the calculation of the trace images and ADC values.

Apparent diffusion coefficient measurements

All measurements were performed by one radiologist. To ensure accurate localization and consistency of measurements, radiologist independently placed region of interest (ROI) areas on the right and left side of the brain in different characteristic localisations (hippocampus, amygdala) on the images obtained with a *b* value of 1000 s/mm^2. At each pre-specified site, three ADC values were obtained by using three different-sized ROI areas. Each measurement was repeated by using three ROI areas (average areas of regions of interest were 18± 2 mm^2).

The ADC values were noted according to each location, which were the right and the left sides of the hippocampus (three different measurements per side)(Figure1) and the right and left amygdala (three different measurements per side). Mean values were used for statistical comparisons.

Statistical analysis

Statistical analyses were performed with SPSS 16.0 using one-waydescriptive to calculate mean and standard deviation values, upper and lower bounds, and minimum and maximum values. An analysis of variance (ANOVA) post-hoc test was used to analyse the differencesamong ADC values between patients and control groups and to calculate p values in different localisations. Cross-tabulation and chi-square tests were used to calculate compliance with gender; one-way descriptiveand ANOVA tests were used to calculate age compliancebetween patients and

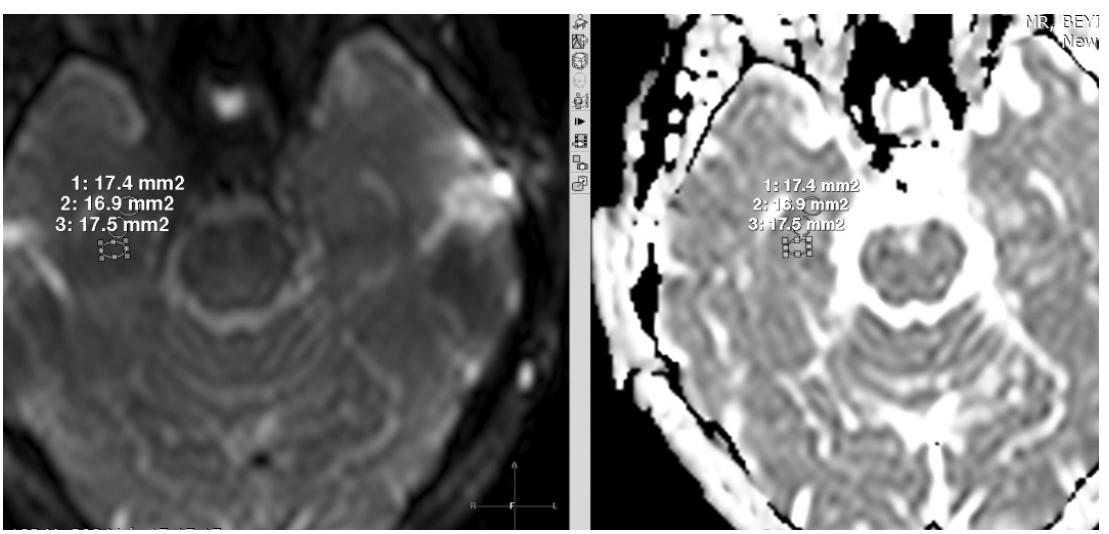

Figure 1 ROI placement onto the hippocampus, b= 0, T2-weighted image on the left. The ROIs were copied onto the ADC map images on the right.

Table 1: The study group descriptive

	Multiple sclerosis n = 38	Control group n = 41	P value
Age	35.9 ± 6.4	35.8 ± 9.6	0.9
Gender (M/F)	8/30	15/26	0.145

control groups; and paired samples statistics were used to calculate analysis in the control and patient groups separately.

RESULTS

Descriptive statistics of the study group are summarized in Table 1. The gender distribution and the mean age of the MS patients were similar to those of the control group (p=0.145, p=0.9, respectively). Mean duration of illness of the patients in the study was 4.1 ± 4.2 (r = 1-16) years.Two male and six female patients showed cerebral atrophy and there were no lesion in the targetted area of amygdala and hippocampus.

The ADC values of both groups are summarised in Table 2. ADC values observed in the left and right amygdala were lower than the ADC values observed in the right and left sides of the hippocampus in both the MS group and the control group. In the control group, the mean ADC values of the right amygdala and left amygdala did not differ statistically from each other (p = 0.648), nor was there any difference in the mean ADC values between the left and right sides of the hippocampus(p = 0.233). In the MS patients, the mean ADC measurements of the right amygdala were slightly higher than those of the left amygdala but with no difference statistically (p = 0.345). ADC measurements of the right side of the hippocampus were slightly lower than the left side in the MS patients, but again there was no statistical difference (p = 0.151). The mean ADC values of the right amygdala in the MS patients were lower than those of the control group but not significantly (p = 0.149); however, the mean ADC values of the left amygdala and the right and left sides of the hippocampus were significantly lower than those of the control group (p = 0.047, p = 0.000,p = 0.023, respectively).

DISCUSSION

Demyelination is accepted to be the primary pathological course in MS, although the exact mechanisms causing it are not well understood.[7,8]

In MS investigations, nonconventional MR imaging techniques, such as DWI, play a significant role in highlighting brain microstructural injury not visible when conventional sequences are used. DWI principles are attributed to the measurement of the motion of water molecules within tissues and can be used to search the structural characteristics of tissue.[9-11] Diffusion of water molecules are influenced by microstructures and microdynamic processes, and ADC can be measured quantitatively. The diffusion is constricted in MS plaques, and normal-appearing white matter is actually affected in these patients.[12]

The latest studies have defined abnormalities, including bothfractional anisotropy and mean diffusivity changes, in the cortical or subcortical normal appearing grey matter of RRMS patients when compared tocontrols. While mean diffusivity usually rıses, fractional anisotropy has been found to either increase or decline.[13-15]

Table 2: The mean ADC values (ADC×10–3 mm2/s) of the left and right amygdala and hippocampus

	MS group	Control group	MS vs Control	MS R vs L	Control R vs L
	Mean ± SD	Mean ± SD	P value	P value	P value
Right amygdala	821.3 ± 68.6	854.5 ± 123.9	0.149	0.345	0.648
Left amygdala	807.1 ± 64.0	849.9 ± 117.5	0.047		
Right hippocampus	823.0 ± 56.1	905.6 ± 103.0	0.000	0.151	0.233
Left hippocampus	838.0 ± 64.6	891.4 ± 127.0	0.023		

Larsson *et al*.[13] found that acute lesions less than 3-months old (by review of serial examinations) had higher diffusion coefficient ratios than did chronic lesions. A relationship exists between trace ADC and the pattern of enhancement in MS lesions. There are significant increases in trace ADC in non-enhancing lesions and ring-enhancing lesions, which show histopathological evidence of increased myelin loss relative to homogeneouslyenhancing lesions, which are predominantly inflammatory with more myelin preservation.[16]

Diffusion in enhancing portions of enhancing lesions was decreased when compared with non-enhancing portions. This finding concurs with diffusion-tensor measurements reported in acute MS lesions as defined by contrast enhancement. This relatively decreased diffusion may be the resultof cellular infiltration. Alternatively, restriction of diffusion may reflect remyelination or relative preservation of structural integrity (e.g., preservation of axons). Although the precise histopathological correlatesof these various areas seen on MR imaging are uncertain, the data are consistent with the hypothesis that the presence of a macromolecularstructure (e.g.,remyelination, proteins) is the common substrate in enhancing lesions.[17]

In contrast to most studies, which revealed increased diffusion in different parts of the central nervous system, except in some acute plaques, we observed restricted diffusion in the hippocampus and amygdala. This is a new finding. All of these may be the result of neuronal degeneration observed in the hippocampus and amygdala as in the study of Wall *et al*.[18] This decreased diffusion may be the result of a shift in intracellular water protons, ischaemia, cellular infiltration, demyelination processes, or remyelination. Asthe diffusion restriction in acute plaques is related to acute inflammation, we can conclude that the hippocampus and amygdala are involved through inflammatory reaction, even though they appear normal.

There is contradictory information about normal-appearing white matter. Normal-appearing white matter changes are more likely to be found in patients with MS than in other conditions that can mimic MS clinically and radiologically.[19]One study found that ADC values were abnormal in all white matter regions assessed in a population of patients with MS[20]; however, in another study, although ADC values were significantly altered in plaque and periplaque regions, a significance difference was not found in normal-appearing white matter.[11]

Since there is no published information on ADC values of normal appearing hippocampus and amygdala, our study needs to be supported by multicenter DWI and diffusion tensor imaging studies.

DISCLOSURE

Conflicts of interest: None

REFERENCES

1. Raz E, Bester M, Sigmund EE, *et al*. A better characterization of spinal cord damage in multiple sclerosis: A diffusional kurtosis imaging study. *AJNR Am J Neuroradiol* 2013; 34:1846-52.
2. Geurts JJ, Bö L, Roosendaal SD, *et al*. Extensive hippocampal demyelination in multiple sclerosis.*J Neuropathol Exp Neurol*2007; 66:819-27.
3. Reiss JP, Sam D, Sareen J.Psychosis in multiple sclerosis associated with left temporal lobe lesions on serial MRI scans.*J Clin Neurosci* 2006; 13:282-4.
4. Honer WG, Hurwitz T, Li DK, Palmer M, Paty DW.Temporal lobe involvement in multiple sclerosis patients with psychiatric disorders.*Arch Neurol*1987; 44:187-90.
5. Sicotte NL, Kern KC, Giesser BS, *et al*. Regional hippocampal atrophy in multiple sclerosis.*Brain* 2008;131:1134-41.
6. Polman CH, Reingold SC, Banwell B, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria.*Ann Neurol* 2011; 69:292-302.
7. Assaf Y, Chapman J, Ben-Bashat D, *et al*. White matter changes in multiple sclerosis: correlation of q-space diffusion MRI and 1H MRS. *Magn Reson Imaging* 2005; 23:703-10.
8. Vercellino M, Masera S, Lorenzatti M, *et al*. Demyelination, inflammation, and neurodegeneration in multiple sclerosis deep gray matter. *J Neuropathol Exp Neurol* 2009; 68:489-502.
9. Sbardella E, Tona F, Petsas N, Pantano P. DTI measurements in multiple sclerosis: Evaluation of brain damage and clinical implications. *Mult Scler Int* 2013; 2013: 671730.
10. Droogan AG, Clark CA, Werring DJ, Barker GJ, McDonald WI, Miller DH. Comparison of multiple sclerosis clinical subgroups using navigated spin echo diffusion-weighted imaging. *Magn Reson Imaging* 1999; 17:653-61.
11. Anik Y, Demirci A, Efendi H, Bulut SS, Celebi I, Komsuoglu S. Evaluation of normal appearing white matter in multiple sclerosis: comparison of diffusion magnetic resonance, magnetization transfer imaging and multivoxel magnetic resonance spectroscopy findings with expanded disability status scale. *Clin Neuroradiol* 2011; 21:207-15.
12. 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.
13. Filippi M. Magnetic resonance imaging findings

predicting subsequent disease course in patients at presentation with clinically isolated syndromes suggestive of multiple sclerosis. *Neurol Sci* 2001; 22:S49-S51.
14. Griffin CM, Chard DT, Ciccarelli O, *et al*. Diffusion tensor imaging in early relapsing—remittingmultiple sclerosis.*Mult Scler* 2001; 7:290-7.
15. Tovar-Moll F, Evangelou IE, Chiu AW, *et al*. Thalamic involvement and its impact on clinical disability in patients with multiple sclerosis: a diffusion tensor imaging study at 3T. *AJNR Am J Neuroradiol* 2009; 30:1380-6.
16. Roychowdhury S, Maldjian JA, Grossman RI. Multiple sclerosis: comparison of trace apparent diffusion coefficients with MR enhancement pattern of lesions. *AJNR Am J Neuroradiol*2000; 21:869-74.
17. Nusbaum AO, Lu D, Tang CY, Atlas SW. Quantitative diffusion measurements in focal multiple sclerosis lesions: correlations with appearance on TI-weighted MR images. *AJR Am J Roentgenol* 2000;175:821-5.
18. Wall CJ, Kendall EJ, Obenaus A. Rapid alterations in diffusion-weighted images with anatomic correlates in a rodent model of status epilepticus. *AJNR Am J Neuroradiol* 2000; 21:1841-52.
19. Filippi M, Tortorella C, Bozzali M. Normal-appearing white matter changes in multiple sclerosis: the contribution of magnetic resonance techniques. *Mult Scler* 1999; 5:273-82.
20. Guo AC, MacFall JR, Provenzale JM. Multiple sclerosis: diffusion tensor MR imaging for evaluation of normal-appearing white matter. *Radiology* 2002; 222:729-36.