RESEARCH

Evaluation of Epileptogenic Focus by DWI in Temporal Lobe Epilepsy

Neslihan Kose[1], Bulent Yildiz[2], Burhanettin Cigdem[3]

[1] Department of Radiology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Turkey
[2] Department of Radiology,Faculty of Medicine, Sivas Cumhuriyet University, Sivas,Turkey
[3] Department of Neurology, Faculty of Medicine, Sivas Cumhuriyet University, Sivas, Turkey

ORCID; 0000-0002-3741-5133, 0000-0003-3836-3184, 0000-0003-4941-9497

Abstract: Temporal lobe epilepsy (TLE) is the most common focal epileptic syndrome in population. Mesial temporal sclerosis (MTS) is a frequent structural abnormality in medically intractable TLE. In this study, we aimed quantitative evaluation of epileptogenic focus using interictal diffusion-weighted magnetic resonance imaging (MRI) method in patients with temporal lobe epilepsy. A total of 72 TLE patients who underwent cranial MRI and 35 control cases were included in this study. 34 hippocampal sclerosis (HS) patients and 38 normal patients were evaluated. Patients were divided into two subgroups as MTS+ and MRI-negative TLE. The measurements of ADC were obtained from the hipocampus head, corpus, tail, amygdala, temporal lobe white matter and cortex bilaterally in the axial ADC map and compared between the groups. In the MTS group, predictive cutoff levels of hippocampal ADCs for identifying pathologic areas were established through receiver operating characteristic (ROC) curve analysis. MTS + group had significantly higher ADC values compared to control group, MTS-negative TLE group and contralateral side ($p<0.05$). We obtained significantly higher ADCs in right hippocampus corpus and tail, left temporal lobe cortex in MRI-negative TLE group than the contralateral side ($p<0.05$).

INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common focal epileptic syndrome in children and adults[1,2]. Mesial temporal sclerosis (MTS) is a frequent structural abnormality in 60-80% of medically intractable TLE [3, 4]. Although MTS mostly presents with hippocampal sclerosis (HS) on magnetic resonance imaging (MRI), other limbic structures are often involved [2,5,6]. The histopathology of HS is characterized by neuronal loss and gliosis. HS is usually observed as atrophy and/or high signal intensity on T2-weighted images [7,8]. Nonlesional or MRI-negative TLE is an important subgroup that accounts for about 30% of all TLE patients. It is characterized by no significant alteration on conventional MRI [9,10]. MTS is the most common pathological finding in MRI-positive TLE.Conventional MRI can be insufficient to detect the epileptogenic focus in MRI-negative TLE or bilateral HS. Quantitative methods can be used to show the epileptogenic focus.Diffusion-weighted imaging (DWI) is a quantitative MRI technique that shows molecular motion of water within brain tissue. Apparent diffusion coefficient (ADC) is calculated from DWI [11]. Loss of neurons lead to the expansion of extracellular space, resulting in increased ADC in the sclerotic hippocampus [12].Several studies have shown that the ADC values of pathological hippocampus were increased in patient with MTS positive TLE [5, 11, 14-20]. In this study, we investigate the ADC values between MTS positive TLE patients and MRI-negative TLE patients. ADC was measured in the bilateral hippocampus, amygdala, and temporal lobes. The literature contains no study on this, and as far as we know, this is the first study to make this assessment. We aimed to detection of epileptogenic focus quantitatively by using interictal DWI in patients with TLE in this study.

MATERIALS and METHODS

In this study, 87 cases diagnosed as TLE were enrolled. Four patients had no MR images, 2 patients had no preoperative MR images, 1 patient was thought to have Dyke-Davidoff Masson syndrome, 3 patients were thought to have dysembryoplastic neuroepithelial tumor (DNET), 2 patients had inadequate MR images. These 16 patients were excluded.

A total of 72 patients with TLE who underwent cranial MRI, and 35 control cases between January 01, 2013 and April 01, 2019 were included in the study and analyzed retrospectively. The diagnosis of

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Corresponding Author:
Bulent Yildiz
E-mail; bulent.yildiz@hotmail.com
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TLE was made according to MRI findings, clinical examination and EEG results by a 10 years experienced neurologist. Control cases who presented with headache were screened and included in the study if there was no abnormality on MRI**.**

34 patients with HS on cranial MRI and 38 patients with normal MRI were divided into two subgroups as MTS+ and MRI-negative TLE, respectively. 16 patients had right HS, 13 patients had left HS and 5 patients had bilateral HS. MTS+ patients included 14 men and 20 women, aged 18 to 67 (average 35.23 years). MRI-negative TLE patients included 14 men and 24 women, aged 18-69 (average 31.34 years). Control cases included 13 men and 22 women, aged 18 to 64 (average 34.85 years). The age and sex of TLE patients and control cases were not significantly different ($p>0.05$).

Seizure type, frequency of seizure, seizure onset, seizure duration, family history, history of febrile convulsion and trauma were extracted from medical records. According to international classification of epileptic seizures by International League Against Epilepsy (15), the seizure types of the subjects were as follows: simple partial seizures (n=2), complex partial seizures (n=30), generalized tonic-clonic seizures (n=7), secondary generalized tonic-clonic seizures (n=16) and complex partial seizures+ secondary generalized tonic-clonic seizures (n=17). Approval of ethical committee was obtained from Ethics Committee of Sivas Cumhuriyet University Faculty of Medicine in compliance with the Helsinki Declaration (Decision number : 2019-04/09, Date:17.04.2019)

Interictal MRI

All patients and control cases were scanned on the same 1.5T scanner (Magnetom Area, Siemens Healthcare, Erlangen, Germany), using a 20-channel head coil. Imaging protocol included MPRAGE sections (TE: 2.35 ms, TR: 1420 ms, field of view (FOV): 270X93.8 mm, matrix size: 224X100, slice thickness: 1.3 mm), coronal 2D fluid attenuated inversion recovery (FLAIR) (TE: 86 ms, TR: 9000 ms, FOV: 260X65.6 mm, matrix size: 256X100, slice thickness: 3 mm), axial 2D-FLAIR (TE: 86 ms, TR: 8000 ms, FOV: 220X96.9 mm, matrix size: 256X90, slice thickness: 5 mm), coronal T1-IR (TE: 15 ms, TR: 5390 ms, FOV: 200X100 mm, matrix size: 320X80, slice thickness: 3 mm), axial T2 FSE (TE: 106 ms, TR: 4350 ms, FOV: 260X75 mm, matrix size: 320X90, slice thickness: 5 mm), coronal T2 FSE (TE: 97 ms, TR: 3470 ms, FOV: 250X81.3 mm, matrix size: 384X70, slice thickness: 4 mm), SWI (TE: 40 ms, TR: 49 ms, FOV: 260X65.6 mm, matrix size: 256X80, slice thickness: 4 mm).

DW images were performed using a single-shot, spin echo, echo planar imaging sequence (TE: 89 ms, TR: 6300 ms, FOV: 230X100 mm, matrix size: 192X100, axial slice thickness: 3 mm). The diffusion -sensitizing gradients were applied in three directions (x, y, z) with b=0 mm2/s and b=1000 mm2/s. DW images were obtained angled along the long axis of the hippocampus. Images were postprocessed to produce ADC maps.

Data analysis

Two radiologists who are 5 years (N.K.) and 13 years (B.Y.) experienced evaluated all studies qualitatively for the presence of HS on conventional MRI. The diagnostic criteria for HS were presence of hippocampal atrophy and hyperintensity on T2-weighted and FLAIR images. Hippocampal atrophy was decided by visual analysis. Differences in opinions were resolved by consensus. The measurements of ADC were obtained from the hippocampus head, corpus, tail, amygdala, temporal lobe white matter and cortex bilaterally in the axial ADC map. The region of interest (ROIs) were drawn on the axial plane manually. It is between 4-10 mm2 avoiding the adjacent cerebrospinal fluid regions to decrease the partial volume effects of fluid. All measurements were performed by two radiologists independently without knowledge of any clinical and conventional MR imaging information. An example of case is shown in Figure 1.

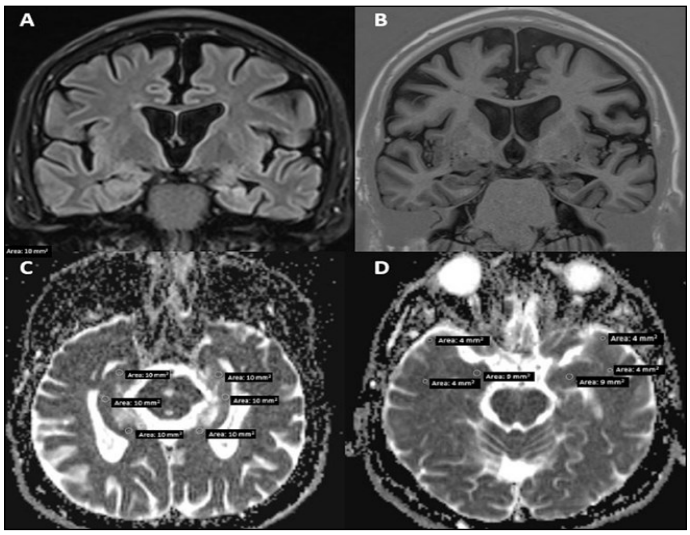

Figure 1. 56 year-old male patient. On the left hippocampus, high signal on coronal plane FLAIR (A), atrophy and dilatation in the temporal horn of left lateral ventricle on coronal plane T1-IR (B). On ADC map (C, D), ROIs examples in the head, corpus and tail of hippocampus, amygdala, cortex and white matter of temporal lobe.

Statistical analysis

The data obtained from the study were entered into SPSS 22.00 (IBM Corp., Armonk, NY., USA) software. independent sample test was used when comparing two independent groups. One-way ANOVA, tukey test and Pearson correlation analysis were used when comparing more than two independent groups. Chi-square test was used when comparing the data obtained by counting. In the MTS group, predictive cutoff levels of hippocampal ADCs for identifying pathologic areas were established through receiver operating characteristic (ROC) curve analysis and accordingly percentage of sensitivity , specificity values were calculated and present in Figure2, Tables 1 and 2. A P-value of less than 0.05 was considered statistically significant.

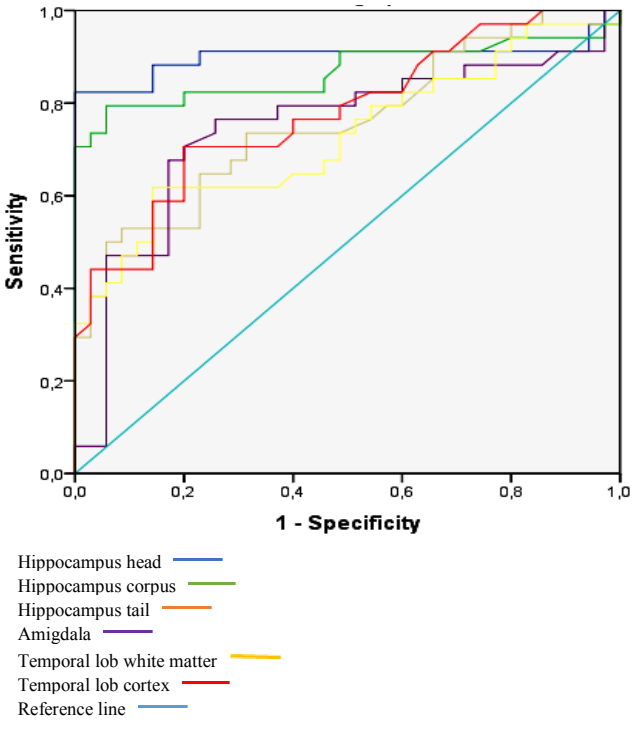

Figure 2.Source of the curve

Table 1: Area under the curve[a]

Test Result Variable(s)	Area	Std. Error[b]	Asymptotic Sig.[c]	Asymptotic 95% Confidence Interval (CI) Lower Bound	Upper Bound
Hippocampus head	0,901	0,047	0,000	0,809	0,993
Hippocampus corpus	0,868	0,050	0,000	0,771	0,965
Hippocampus tail	0,758	0,058	0,000	0,644	0,871
Amigdala	0,745	0,063	0,000	0,621	0,869
Temporal lobe white matter	0,727	0,062	0,001	0,606	0,849
Temporal lobe cortex	0,777	0,056	0,000	0,668	0,886

Table 2: Cut of values

	Cut of value	Sensitivity	Specificity
Hippocampus head	964	%88.2	%82.9
Hippocampus corpus	940	%79.4	%94.3
Hippocampus tail	810	%79.4	%62.9
Amygdala	819	%73.5	%74.3
Temporal lobe white matter	874.50	%61.8	%82.9
Temporal lobe cortex	821.50	%70.6	%80

RESULTS

In this study, 72 cases (28 men and 44 woman) diagnosed as TLE and 35 control cases (13 men and 22 women) were included. The mean age of the TLE cases were 33.18±13.10 (range 18 to 69 years) and the control cases were 34.85±13.82 (range 18 to 64 years). In TLE cases, nine patients (12.5%) had family history, 26 patients (36.1%) had febrile convulsions and six patients (8.3%) had trauma history.

According to first seizure onset, TLE cases were classified into two groups as ≤18 years old (early onset) and >18 years old (late onset). 47 patients (65.3%) had early onset and 25 patients (34.7%) had late onset. The first seizure onset of MTS positive TLE cases and MRI-negative TLE cases were not significantly different (p>0.05) (Figure 3a) .Seizure duration of TLE cases were classified as <10 years and ≥10 years. 30 cases (41.7%) had seizures less than 10 years and 42 cases (58.3%) had seizures more than 10 years. Seizure duration more than 10 years of TLE cases was higher than other group (p<0.05) (Figure 3b).

The seizure types of the cases were as follows: simple focal seizures (n=2), complex focal seizures (n=30), generalized tonic-clonic seizures (n=7), secondary generalized seizures (n=16), and complex focal+secondary generalized seizures (n=17). The seizure types of MTS positive TLE cases and MRI-negative TLE patients was not significantly different (p>0.05) (Figure 3c).

Frequency of seizure was classified as daily (n=4), frequently (n=34), rare or seizure-free (n=16) and uncertain (n=18). Seizure frequency of MTS+TLE patients and MRI-negative TLE patients was not significantly different (p>0.05) (Figure 3d).

Seventeen of TLE+MTS patients and 9 of MRI-negative TLE patients had febrile convulsions. The number of febrile convulsion of MTS+TLE patients was higher than the MTS (-) TLE group. It was significantly different between groups (p<0.05). It was significantly different between groups (p<0.05) (Figure 3e).

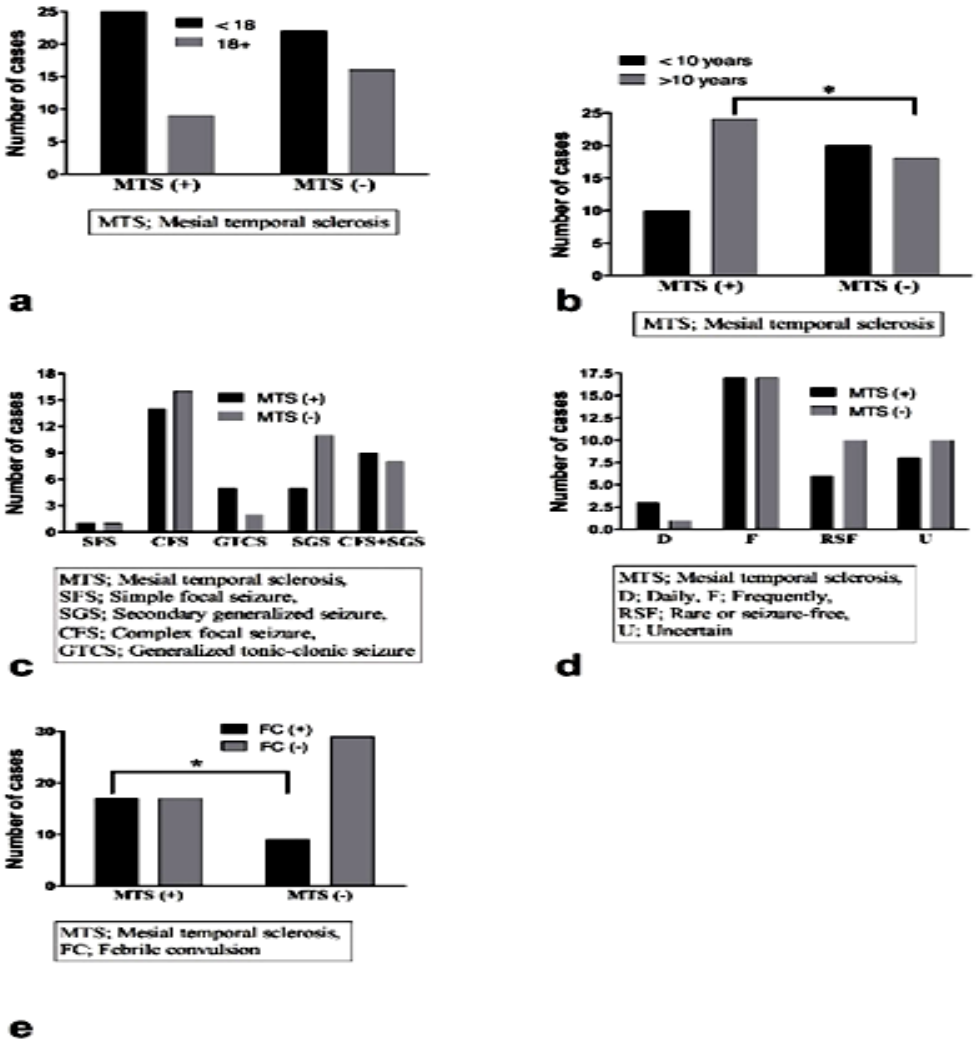

Figure 3. According to first seizure onset (a), seizure duration (b), seizure types (c), frequency of seizure (d), febrile convulsion condition (e) of MTS groups. *p<0.05

Convansional MRI Findings

The diagnostic criterias for HS were presence of hippocampal atrophy and hyperintensity on T2-weighted and FLAIR images. According to this; 34 patients (47.2%) had MTS and 38 (52.8%) had not MTS. In MTS+ group; 16 patients (41.7%) had right, 13 patients (38.2%) had left and 5 patients (14.7%) had bilateral HS. .Other pathologies in TLE patients were as follows: 1 patient had multiple periventricular and juxtacortical demyelinating plaques. 2 patients had arachnoid cyst in middle cranial fossa and compression in hippocampus due to the cyst. 1 patient had encephalomalasia and gliosis in occipital lobes. 1 patient had perivascular space 13 mm in diameter on the left. 1 patient had partial corpus callosal dysgenesis and colpocephaly. 1 patient had mega cisterna magna. 1 patient had atrophy and gliosis in the left temporal lobe and gliosis in the right cerebellar lobe. Because of the morphology of hippocampus was normal in those cases , it was included to the study.

Interictal DWI Findings

Mean ADC values were higher in the ipsilateral hippocampus in all three segments than in the contralateral hippocampus both in right and left MTS groups ($p<0.05$). In the right MTS group, right amygdala and temporal lobe cortex ADC measurements were significantly higher than that of the left side ($p<0.05$). In the right MTS group, the right hippocampus head, body ,tail, amygdala right temporal lobe white matter and cortex ADC values were significantly higher than that of the no MTS, and control groups ($p<0.05$).

In the left MTS group, left temporal lobe white matter ADC measurements were significantly higher than that of the right side ($p<0.05$). In the left MTS group, the left hippocampus head, body, tail, amygdala, left temporal lobe white matter and cortex ADC values were significantly higher than that of the no MTS, and control groups ($p<0.05$).

In the no MTS group , the left hippocampus body and tail and left temporal lobe white matter ADC measurements were significantly higher than that of the right side ($p<0.05$), however, the right and left hippocampus head, amygdala, and temporal lobe cortex ADC values were found comparable ($p>0.05$).Mean ADC values were similar in hippocampus, amygdala and temporal lobes on the right and left sides in the bilaterally MTS group ($p>0.05$).In the bilaterally MTS group, the right hippocampus head, body, and tail ADC values were significantly higher than that of the no MTS and control groups ($p<0.05$).

In the bilaterally MTS group, the left hippocampus head , body , and tail, and left temporal lobe cortex ADC measurements were significantly higher than that of the no MTS and control groups ($p<0.05$).

Mean ADC values were shown in Table 3

We did not find any significant differences between two groups when we compare it in terms of other clinical data ($p>0.05$). In addition, we compared our clinical data with the pathological side ADC measurements of the MTS+ TLE patients and found no significant results in any of them ($p>0.05$).

Table 3: Mean ADC values

	Right MTS	Left MTS	Bilateral MTS	Non-MTS	Control
Right HH	1126,25±126,09	924,23±63,9	1009,6±188,64	909,34±69,58	919,71±55,75
Right HB	1007,12±109,63	895,76±126,63	955±156,6	847,86±55,08	876,54±41,36
Right HT	914,37±100,74	822,23±70,99	882,4±63,46	800,63±47,25	839,94±58,87
Right Amygdala	848,18±44,45	814,15±71,78	838,6±69,35	806,21±46,7	808,62±44,32
Right TLWM	873,68±81,38	820,23±82,41	883,6±79,22	835,63±47,28	830,82±53,46
Right TLC	853,12±50,63	818,3±66,88	822,4±56,62	814,97±63,4	793,65±47,26
Left HH	920,5±78,38	1141±168,59	1058±144,3	913,86±66,27	926,22±54,71
Left HB	890,68±70,71	1056,23±172,26	967,6±157,28	878,02±72,03	889,65±49,23
Left HT	863,18±68,95	963±86,07	979,4±199,6	837,07±62,93	864,97±55,41
Left Amygdala	811,5±42,44	848,92±54,32	844,4±54,28	803,23±39,3	808,91±48,56
Left TLWM	875,75±57,55	908,84±68,46	832±62,32	860,31±57,49	838,11±51,98
Left TLC	818,12±37,78	850,15±47,33	855,2±52,51	833,6±42,47	811,25±39,41

Data are mean values ± SD ($1x10^{-6}mm^2/s$). HH: Hippocampus head, HB: Hippocampus body, HT: Hippocampus tail, TLWM: Temporal lobe white matter, TLC: Temporal lobe cortex

DISCUSSION

In our study, the ADC values of pathological hippocampus were significantly higher than those of the MRI-negative TLE patients, the controls and the controlateral side for those of unilateral HS patients ($p<0.05$). In bilateral HS patients, the difference was not statistically significant between both pathological hippocampus. This result was due to elevated ADC values in both sides. Our results are compatible with those of published reports[5,11,14-20]. Hakyemez et al. in a study involving 13 patients with unilateral HS and 21 controls, reported higher ADC values in the pathological hippocampus than those of the controlateral side and the controls[5]. Moreover, they found higher ADCs at the head of the hippocampus than the body and tail parts as in our study. In a study, it was found significantly higher ADCs in the controlateral hippocampus compared with controls[15]. In our study, there was no significant difference in ADC values between the controlateral hippocampus in the group of 29 patients with unilateral HS and the control group ($p>0.05$).We compare the ADC values between MTS+ TLE patients and MRI-negative TLE patients. The literature contains no study on this, and as far as we know, this is the first study to make this assessment. ADCs of the hippocampus were significantly different and higher in the MTS+ TLE patients ($p<0.05$).

The major histopathological findings of MTS are gliosis and neuronal loss. In the brain, extracellular space expands when cell membranes, axons or myelin disrupt that normally restrict the random movement of water molecules [12]. In DWI, which is basically measures the water diffusion at the extracellular distance, increased ADC values are detected in the presence of MTS[5,13]. In some studies, correlated with histopathology, HS was found in the patients with a significant increase in ADC in hippocampus[13,15,19]. These results reflect the success of DWI in showing the focus side correctly in the patients with MTS. In our study, DWI was successful in detecting the

pathological hippocampus in the patients with MTS. The epileptogenic lesion may include the amygdala along with the hippocampus. HS-related amygdala damage is observed, ranging between 7-76%[21, 22]. Moreover, a small group (1-10%) called, "amygdala sclerosis" may have amygdala damage without HS[22]. Quantitative MRI techniques are preferred because it is not usually possible to detect the damage of amygdala by visual assessment in conventional MRI. In previous studies, quantitative MRI techniques such as MR volumetry and T2 relaxation were performed[19,25]. In a MR volumetry study of amygdala, volume loss was reported on the side of HS, ranging between 10 and 30%[24]. In T2 relaxation studies of the amygdala, T2 time increase was detected up to 54%[25-27].DWI studies of amygdala are rare in the literature. In a study, Hakyemez et al. measured the ADCs of the amygdala together with the hippocampus[5]. They reported no significant difference in the pathological side amgydala compared with the controlateral amygdala and the controls ($p>0.05$) [5]. However, Gonçalves et al. reported higher ADCs of the amygdala on the side of HS than those of the contralateral side, and the controls[17]. In our study, we measured bilateral amydalas along with the hippocampus. We found higher ADCs of the ipsilateral amygdala in the patients with right and left HS than the controls. The ADC values of amygdala for the patients with right HS was significantly higher than for the contralateral side. ADC values of amygdala in the left HS group were not significantly different from the contralateral amygdala ($p>0.05$). In the bilateral HS group consisting of 5 people, ADCs of amygdala were not significantly different from the controls ($p>0.05$). Unlike the studies in the literature, we also compared the ADC measurements of MTS+ group with the MRI-negative TLE group. ADC values of amygdala in the patients with right and left HS were significantly higher than the MRI-negative TLE patients.

Pathological changes in MTS may affect the ipsilateral and contralateral temporal lobe cortex and white matter[12]. Although the reason is not clear, microdysgenesis is shown as one of the reasons. Microdysgenesis detected in pathology specimens of the temporal lobes is observed as microscopic structural abnormalities. Microdysgenesis is defined as a frequent pathology of MTS[28]. Other causes of white matter atrophy have been suggested to be due to neuronal heterotopia and dysfunctions in the myelination process[29]. In the literature, we found a study of DWI of the temporal lobes. Lee et al. evaluated temporal lobes with the hippocampus[14]. They reported higher ADCs of the temporal lobes on the side of HS than those of contralateral side, and the controls.

In our study, we measured ADC values of temporal lobe cortex and white matter. We found higher ADCs on the side of HS in the patients with right and left HS than the controls. Our results were consistent with the literature. In the patients with bilateral HS, ADC values of left temporal lobe cortex were higher compared with the controls. There was no significant difference for other localizations. It may be due to the small number of patients with bilateral HS. ADCs of ipsilateral cortex in the right HS and ipsilateral white matter in the left HS were higher than the contralateral side. In the left HS group, ADCs of ipsilateral white matter were higher than the MRI-negative TLE group.

MRI-negative TLE is called for the patients that are characterized by no abnormality on

Structural differences between MTS patients, MRI-negative TLE patients and control groups can be evaluated using quantitative techniques even if the lesion cannot be detected with conventional MRI. Nuclear medicine techniques such as PET, SPECT or advanced MRI techniques such as diffusion tensor imaging, functional MRI, MR spectroscopy are mostly used for this purpose[9]. However, we did not find a study with DWI in the literature. DWI is a quantitative technique that is faster than other techniques, can be easily added to protocols and does not require contrast agents. Therefore, we aimed to evaluate this group of patients with DWI. In our study, when we compared the right and left side ADCs of the MRI-negative TLE patients, it was higher at the body and tail of hippocampus and temporal lobe white matter on the left than the contralateral side. In the comparison with the control group, the body and tail of hippocampus on the left and temporal lobe cortex on the right were higher. Although it is not possible to say the epileptogenic focus side clearly with DWI alone, we think that the high ADC values found in some localizations may be the focus side and may contribute to electroencephalography and other imaging methods.Another reason for increased ADC values other than gliosis and neuron loss may be partial volume artifact[4,14,15,31]. As the volume of the sclerotic hippocampus decreases, adjacent cerebrospinal fluid (CSF) areas will be more likely to enter the ROI. Likewise, close CSF neighbourhood reduces the reliability of ADC measurements in the temporal lobe cortex[32]. Coronal plane is more reliable than axial plane in evaluation of hippocampus[15]. In our study, we measured on axial plane parallel to the long axis of the hippocampus and preferred 3 mm slice thickness, and possible rather small ROI ($\leq$10 mm) to avoid partial volume artifact. We also used small ROI (4 mm) for temporal lobe cortex measurements. The measurements of the amygdala and temporal lobe white matter did not have a similar problem as the anatomical structure was easily distinguishable from adjacent CSF. A limitation of this study is that, our patients did not have a histopathological confirmation. Further study is needed to determine whether the ADC value would be positive in pathologically proved cases. Another limitation of this study is that partial volume effect of fluid due to 3 mm axial slice thickness of DWI.

Conclusion

DWI was successful in detecting the epileptogenic focus for the MTS patients. However, in MRI-negative TLE patients, it was not possible to say epileptogenic focus clearly. Even so, we found elevated ADC values in some localizations, and we think that it may contribute to other diagnostic methods. In the further trials, we think there is a need for comparative studies involving different diagnostic methods with a larger number of patients at multicenter.

Conflict of interest

The authors declare that they have no conflict of interest.

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