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Forniceal and hippocampal atrophy in temporal lobe epilepsy patients with a history of complex febrile convulsion

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Abstract

Objectives: Temporal lobe epilepsy (TLE) is the most common seizure type in adults. Recent studies showed that 28–58% of TLE patients had a previous history of complex febrile convulsions (CFC). We compared the hippocampal volumes and volumes of amygdaloid body and widths of fornix and mammillary bodies on magnetic resonance imaging (MRI) of TLE patients with and without history of CFC.

Methods: MRI scans of 42 subjects retrospectively examined. The amount of atrophy in hippocampus, amygdaloid body, fornix and mammillary bodies were determined by two formulas depending on the mean values of the controls.

Results: We found no difference between TLE patients with a history of CFC and TLE patients without such a history in terms of all the quantitative measurements results ($p>0.05$) except the absolute right-left hippocampus volume and fornix % difference rate ($p<0.01$, $p<0.05$ respectively).

Conclusion: Forniceal atrophy was more prominent in the TLE group of patients with previous CFC history when compared to those patients without a CFC history. The CFCs should not be underestimated in the childhood, as they are associated with more atrophy in the particular brain structures in patients with TLE.

Keywords: complex febrile convulsion; limbic system; magnetic resonance imaging; morphometry; temporal lobe epilepsy

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Introduction

Epilepsy is an umbrella term characterized by epileptic seizures. An epileptic seizure results from the transient occurrence of several clinical symptoms due to abnormal discharge of the neurons in the brain.[1] The lifetime prevalence of epilepsy has been reported as 7.60 per 1000 persons.[2] Temporal lobe epilepsy (TLE) is the most common type of epilepsy in both adolescents and adults being 2/3 of all the epileptic patients undergoing surgery.[2,3] Previous studies revealed that 40% of TLE patients suffer from Ammon's horn sclerosis, hippocampal sclerosis or by its more appropriate name mesial temporal sclerosis (MTS).[4,5] Volumetric changes are typical in TLE patients; moreover, reduction in hippocampal volume is one of the diagnostic criteria for MTS.[6] Enlargement in amygdaloid body[7,8] and decreases in the volumes of extratemporal structures such as thalamus[9] are of most commonly reported findings in TLE patients.

The size of the fornix, which constitutes the major output pathway of the hippocampus has also been reported to decrease in TLE patients compared to the controls.[10,11] In addition, the width of mammillary body on MRI was investigated to uncover its role in seizure lateralization by Ng et al.[11]

MRI serves as a useful tool that can be used in diagnosis of TLE and for evaluating the morphometric changes and understanding the etiopathogenesis of TLE. However, morphological changes in limbic system structures other than hippocampus and amygdaloid body were not evaluated sufficiently.[12]

In TLE one of the most important concepts the MRI morphometric studies focused at is its relation with complex febrile convulsion (CFC) of the childhood.[13] Febrile convulsions are convulsions induced with fever caused by infections other than central nervous system infection. To differentiate febrile convusions from epilepsy, the patients should not have a history of any afebrile convulsion except neonatal convulsions which is seen between 1 month-5 years old in early childhood.[14,15] They are seen in 2–4% of all the children.[16] 2–10 % of the children who suffer from febrile seizures later have one or more unprovoked seizures.[16] 75% of these febrile seizures are actually complex febrile convulsions in nature.[5] A CFC is characterized by one or more of the following aspects : (a) the onset should be a partial onset, (b) it must have a duration of more than 10–15 minutes,[16] (c) multiple seizures should occur in 24 hours.[5] Sometimes 30 minutes is used as a criterion for longer duration.[17] 28–58% of TLE patients were reported to have history of CFC (TLE-CFC[+] patients).[17–19] Especially long duration of CFC is an important predictor for determining risk for developing TLE.[20] In an animal study it was shown that the number of febrile convulsion attacks were related to development of TLE.[21] In the studies with the post-operative specimens the number of neurons in TLE-CFC[+] patients tended to decrease more than the patients without a history of CFC (TLE-CFC[-] patients).[22,23] Several theories had been proposed by different authors to explain the relation between CFCs of the childhood and TLE including TLE patients having a predisposition for CFCs[24] and inflammatory mechanisms.[25]

Reduction in size of hippocampus in TLE-CFC[+] patients was reported to be more than the patients without such a history.[13,26–28] However, some authors contradicts this result and reported no relation with hippocampal volume reduction and existence of history of CFC in TLE patients.[29]

It is evident that not every TLE patient with a hippocampal atrophy has a history of CFC.[30] Hippocampal volume reduction after CFC detected by MRI was observed as a marker of acute damage.[31] The size of amygdaloid body seems to reduce more in TLE-CFC[+] patients than the TLE-CFC[-] patients. But this change revealed to be relatively less when compared with reduction in hippocampal volume.[28]

Fornix is the primary efferent pathway of the hippocampal formation and the forniceal fibers mostly end in the mammillary bodies. Although TLE-CFC[+] patients and TLE-CFC[-] patients were compared according to reduction in size of hippocampus and amygdaloid body, no comparison was made between the sizes of fornix and mammillary bodies. In this study, we aimed to asses the relation between hippocampus and amygdaloid body volumes, the width of fornix and mammillary bodies and the presence of history of CFC in TLE patients.

Materials and Methods

The study was conducted in 84 adults with equal number of patients and controls; the patient group included 42 cases (23 males, 19 females) having complex partial seizures originating from the temporal lobe. The patients had a mean age of 30.69±13.34 and they were outpatients of the Neurology Clinic of Medical Faculty of Uludağ University. The patients with space-occupying lesions (tumor, scar etc.) were not included to the study. The patients were taking their anti-epileptics in the prescribed doses and free of any seizure during the study period. The control group included 42 healthy volunteers with a mean age of 31.09±12.06. The controls were not taking any medication or hormones etc. One case in each group was left-handed and all the other cases in both groups were right handed. The history of CFC in childhood was questioned and recorded. CFC was defined as febrile seizures occurred before 5 years of age, lasting 20 minutes or longer without any underlying pathology of the central nervous system. The "age of epilepsy onset" was defined as the age when the first unprovoked afebrile seizure was seen. The "epilepsy duration" referred to the time interval between the first afebrile seizure and the time when MRI was performed.

MRI investigations were performed with 1.5 Tesla MRI scanner (Magnetom, Siemens, Erlangen, Germany). The measurement of intracranial area was performed at the midsagittal plane using sagittal T1 weighted Spin Echo (SE) sequences. The images of hippocampus and amygdaloid body were acquired at oblique coronal plane using a section thickness of 3 mm without any gap and using T1 turbo Inversion Recovery (IR) sequence.

The volume of hippocampus and amygdaloid body and the width of fornix and mammillary bodies were measured on 1.5 T MRI unit in both TLE and the control group. Assessing the images by the raw data without being normalized according to brain size one can get wrong results especially when bilateral atrophy exists.[32–35] Since the brain size can affect the volumes of hippocampus and amygdaloid body; we normalized the volume of hippocampus and amygdaloid body according to the following formula:

[Mean mid-intrasagittal area of the control group × volume of hippocampus or amygdaloid body] / mid-sagittal area of the patient (**Figure 1**).[10]

We used Cavalieri's principle while performing volumetric measurements.[35,36] Normalized hippocampus volume, the width of fornix and mammillary bodies were acquired after performing measurements using the images acquired from T1-weighted oblique coronal sections in 42 cases with TLE. One of the patients had artefacts in the scans; therefore, it is excluded. The hippocampus and amygdaloid body were drawn manually by a cursor in each section where they were seen, and the area measurement was calculated automatically. The sum of the areas were then multiplied by the section thickness (0.3 cm).[11] We then normalized the volumes accordingly.

Hippocampus was delineated on the coronal slices by the following borders;[12] posterior border: crus of fornix; superior border: choroid plexus; inferior border: subiculum and parahippocampal gyrus; lateral border: temporal horn of the lateral ventricle; median border: cisterna ambiens (**Figure 2**). For the amygdaloid body, following borders on the coronal plane were used to asses its volume;[12] posterior border: optic tract; superior border: a horizontal line drawn from the entorhinal sulcus; inferior and lateral borders: temporal horn and white matter of temporal lobe; medial border: ambient gyrus. The gyrus ambiens was seperated from gyrus parahippocampalis by the free margin of tentorium; uncal recess (**Figure 3**).

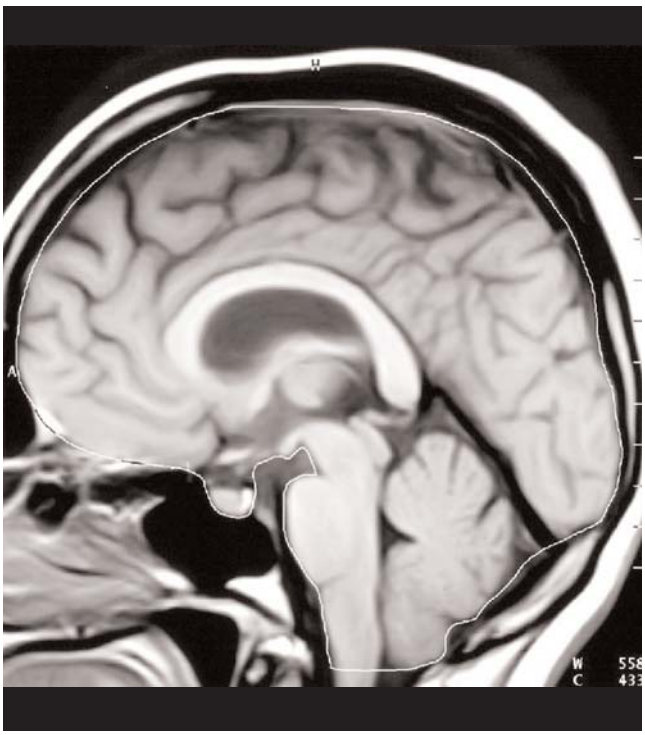

Figure 1. Intracranial measurement of mid-sagittal area of a subject. From "Morphometry of some elements of limbic system in normal population: a quantitative MRI study" by Yücel K, Hakyemez B, Parlak M, Oygucu IH. Neuroanatomy 2002;1:15–21.[33] ©neuroanatomy.org. Reprinted with permission.

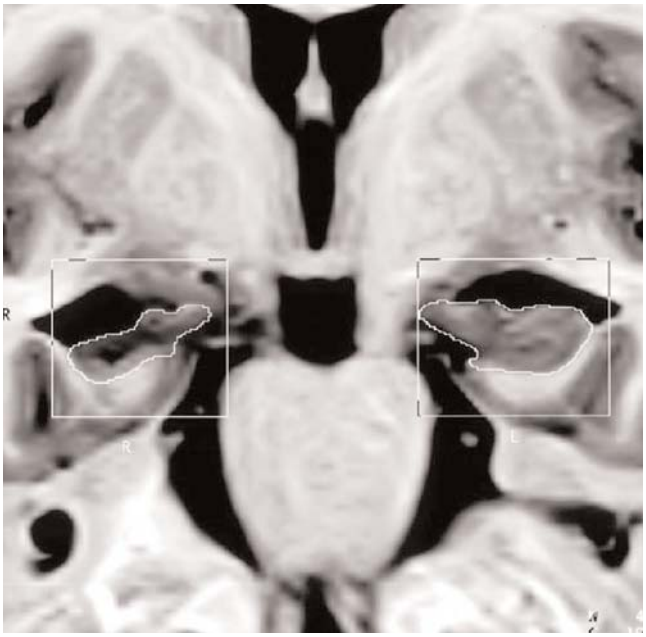

Figure 2. Hippocampal area measurement. From "Morphometry of some elements of limbic system in normal population: a quantitative MRI study" by Yücel K, Hakyemez B, Parlak M, Oygucu IH. Neuroanatomy 2002;1:15–21.[33] © neuroanatomy.org. Reprinted with permission.

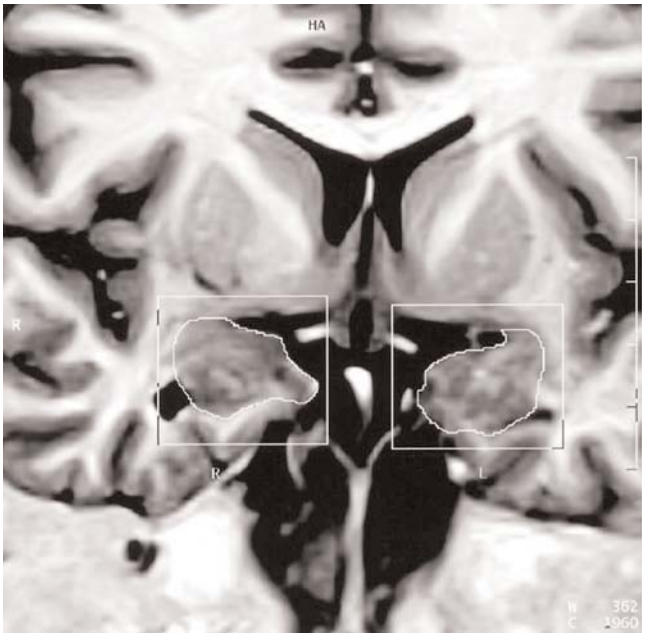

Figure 3. Amygdaloid body area measurement. From "Morphometry of some elements of limbic system in normal population: a quantitative MRI study" by Yücel K, Hakyemez B, Parlak M, Oygucu IH. Neuroanatomy 2002;1:15–21.[33] © neuroanatomy.org. Reprinted with permission.

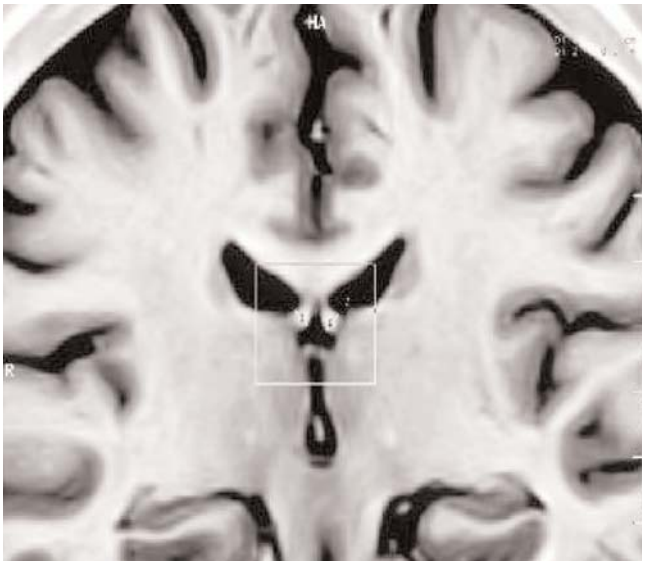

Figure 4. Fornix width measurement on a coronal section. From "Morphometry of some elements of limbic system in normal population: a quantitative MRI study" by Yücel K, Hakyemez B, Parlak M, Oygucu IH. Neuroanatomy 2002;1:15–21.[33] © neuroanatomy.org. Reprinted with permission.

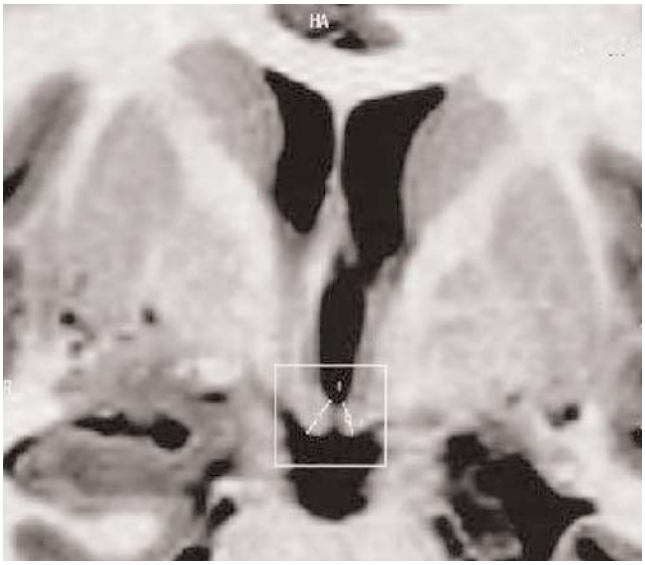

Figure 5. Mamillary body width measurement on a coronal section. From "Morphometry of some elements of limbic system in normal population: a quantitative MRI study" by Yücel K, Hakyemez B, Parlak M, Oygucu IH. Neuroanatomy 2002;1:15–21.[33] © neuroanatomy.org. Reprinted with permission.

Fornix width was measured at the coronal section where crus of fornix from the right and left side gather to form the corpus fornicis (**Figure 4**).[10] The width of mamillary body was measured at the section where hippocampal digitations were seen at the hippocampal head (**Figure 5**).[11] In the epilepsy neuroimaging literature particularly, in order to define atrophy in the hippocampus and amygdaloid body, normative data from a properly matched control group has been used.[37,38] Accordingly, the values 2 standart deviations below the mean volumes of the control group for hippocampus and amygdaloid body and the width of fornix and mammillary bodies were considered as "atrophic". In order to compare the sizes of the anatomical structures measured between TLE-CFC[+] patients and TLE-CFC[-] patients we took the amount of atrophy into consideration. We used two different formulas to detect the amount of atrophy quantitatively in hippocampus/amygdaloid body and fornix/mammillary bodies. The first formula was for assessing hippocampal and amygdaloid atrophy calculating the absolute difference between right and left hippocampal and amygdaloid volume (R-L) in the TLE group. The second formula was the "% difference rate" for measuring the width of fornix and mamilary body as demonstrated below:

$$\%\ \text{difference rate} = \frac{(\text{larger side} - \text{smaller side})}{\text{larger side}} \times 100$$

% difference rate was also helpful detecting the number of patients with and without atrophy of these two structures when compared with the 2 standard deviations above the mean of the control group as an overlapping exists in fornix and mamillary body sizes between the normal cases and pathological cases.[11] Regarding fornix or mamillary body % difference rates of standart deviations above the mean of control group for these was considered as "atrophic."

The results of our study were assessed using Statistical Package for Social Sciences (SPSS Version 7, Armonk; NY, USA). In comparing the results of patient and control group t-test and Mann–Whitney U test were used. For the correlations Pearlson's correlation rate was used. For all the comparisons, p-values less than 0.05 were considered as significant.

Results

We found no difference between TLE and control group in terms of age ($p>0.05$). The years of education were different between the two groups ($p>0.05$). The demographic data of the TLE and control group are shown in **Table 1**. The mean of seizure frequency in the patient group was 5.66 seizures/per month (0.08–25). After performing partial correlations it was found that this variable had an effect on normalized amygdaloid body volume and fornix % difference rate. After control-

Table 1

Demographic data in TLE and control group including age, education, age at onset of epilepsy, epilepsy duration.

Group	Age Mean±SD (min-max)	Education (years) Mean±SD (min-max)	Age at onset of epilepsy Mean±SD (min-max)	Epilepsy duration (years) Mean±SD (min-max)
TLE	30.69±13.34 (10–67)	7.76±3.97 (0–15)	14.59 (9 month–42 years)	16.24 (2–54)
Control	31.09±12.06 (13–62)	11.97±4.21 (0–17)	-	-
Statistical significance	0.775	<0.05	-	-

Max: maximum value; **min:** minimum value; **SD:** standart deviation.

Table 2

The dispertion of cases with history of CFC in the TLE and control group.

Group	Number of cases with a history of CFC	Number of cases without a history of CFC
TLE (n=42)	19 (8 females, 11 males)	23 (11 females,12 males)
Control (n=42)	2 (1 male, 1 female)	40 (18 females, 22 males)
Statistical significance	p<0.01	p<0.01

ling for numbers of years of education variable, the results of the study with statistical significance remained the same.

We found no difference between TLE-CFC[+] patients and TLE-CFC[-] patients in terms of age of epilepsy onset, epilepsy duration and seizure frequency (p>0.05). There was no difference between the TLE-CFC[+] patients and TLE-CFC[-] patients according to age and gender (p>0.05). In TLE group the number of cases with a history of CFC was more than the cases with such a history in the control group (p<0.01). The distribution of number of cases with and without history of CFC in both groups are demonstrated in **Table 2**.

There was no difference between TLE-CFC[+] patients and TLE-CFC[-] patients in terms of all the quantitative measurements results (p>0.05) except the atrophy rate of hippocampus and fornix % difference rate (p<0.01, p<0.05 respectively) (**Table 3**).

Table 3

Comparison of quantitative measurements of hippocampus, amygdala, fornix and mamillary body between TLE patients with and without a history of CFC.

	TLE patients with a history of CFC (n= 19) Mean±SD (min-max)	TLE patients without a history of CFC (n=23) Mean±SD (min-max)	Statistical significance
Right hippocampus volume	2968.78±769. 29 (1886.56–4099.55)	3189.77±843.49 (1110.56–4456.81)	p>0.05
Left hippocampus volume	2849.38±583.56 (1889.51–4550.41)	3115.05±583.56 (1889.51–4550.41)	p>0.05
Amount of atrophy in the hippocampus (22 m,16 f)	1471.06±575.17 (47.5–2334.35)	819.90±611.08 (9.19–1919.93)	p<0.01*
Right amygdala volume	1987.73±361.96 (1224.83–2618.22)	2149.12±365.2 (1406.29–2699.11)	p>0.05
Left amygdala volume	1918.57±388.09 (977.27–2552.24)	2085.44±341.09 (1380.9–2561.55)	p>0.05
Amount of atrophy in the amygdala (22 m, 15 f)	358.59±331.82 (6.07–965.31)	292.33±331.82 (6.07–965.31)	p>0.05
Right fornix width	2.3±0.05 (1–3.4)	2.48±0.06 (1.4–3.9)	p>0.05
Left fornix width	2.46±0.05 (1.3–4.8)	2.59±0.05 (1.4–43.9)	p>0.05
% fornix difference rate	23.43±17.99 (0–56.52)	13.74±16.54 (0–47.37)	p<0.05*
Right mamillary body width	4.26±0.06 (3.3–5.3)	4.09±0.06 (2.3–5.6)	p>0.05
Left mamillary body width	4.24±0.06 (3–5.4)	4.17±0.06 (2.7–5.5)	p>0.05
% mammillary body difference rate	7.78±8.66 (0–25)	7.17±8.14 (0–36.36)	p>0.05

F: females; **M:** males; hippocampus and amygdala quantitative values are expressed as mm^3; fornix and mamillary body widths are expressed as mm; *statistically significant.

Ten of the patients with hippocampal atrophy did not have a history of CFC while 14 had. Twelve of 14 patients with normal hippocampal size did not have a history of CFC and only 2 patients with normal hippocampus size had. The difference between the two groups was statistically significant ($p<0.01$). Fourteen of 20 patients without forniceal atrophy, did not have a history of CFC and 6 had. Nine of 22 patients with forniceal atrophy did not have a history of CFC while 13 had. The dispersion of patients with and without a history of CFC between the two groups had tendency to be statistically significant ($p=0.059$). Fourteen of 24 patients without atrophy of mammillary bodies, and amygdaloid body atrophy did not have a history of CFC and 10 had. Nine of 18 patients with atrophy of mammillary bodies and amygdaloid body did not have a history of CFC while 9 had. The dispersion of patients TLE-CFC[+] patients and TLE-CFC[-] patients between the two groups was not significant ($p>0.05$).

Discussion

We found no differences in bilateral hippocampus and amygdaloid body volumes and fornix and mamillary body widths between TLE-CFC[+] patients and TLE-CFC[-] patients. On the other hand, the amount of atrophy in the hippocampus and fornix were more in TLE-CFC[+] patients. We found that TLE-CFC[+] patients had more reduction in hippocampal volume with a mean of 8.36% than TLE-CFC[-] patients.

Some studies reported atrophy in the hippocampus of TLE-CFC[+] patients compared to TLE-CFC[-] patients,[13,18,26,28] although some reported no relation between hippocampal atrophy and history of CFC.[29,39] Several different mechanisms have been proposed to explain the role of CFCs in the atrophy of medial temporal structures in MTS. One of the theories suggest a further susceptibility of the hippocampus to seizures in the adulthood following cellular and molecular changes occurred following CFC experienced in childhood.[40] An other mechanism is that an initially pre-existing insult can make hippocampal damage to cause CFC initially and then to TLE.[25] Common genetic mechanisms for the development of CFC and TLE have been suggested as a third theory.[41] However, not each case with hippocampal atrophy has a history of CFC. In fact, there is only a certain small group of TLE-CFC[+] patients. Factors such as head trauma, afebrile status epilepticus and meningitis can also cause MTS.[42] As a result we can say that CFC is not the solely etiologic factor of TLE, but only can be one the factors.

We found that history of CFC was not related to any volumetric changes in the amygdaloid body in TLE patients consistent with the findings of the previous studies.[27,34] Actually, amygdaloid body has been related to the psychogenic auras seen in TLE patients, rather than an insult related to the CFC experienced in the childhood[27,43] and hippocampus has a more dominant role than amygdaloid body has for the origin of epileptic seizures.[44]

In spite of their inconsistencies, there are many studies where correlations were reported between hippocampus and amygdaloid body volumes and epilepsy duration, age of onset and seizure frequency.[13,18,45] Parallel to the findings of Bower et al.[39] and Fuerst et al.,[46] we found no difference between TLE-CFC[+] patients and TLE-CFC[-] patients regarding these three variables. Therefore we do not think that they can affect our findings.

Finally, as far as we know more forniceal atrophy in TLE-CFC[+] patients is a new finding. Thinner fornix has been reported previously in TLE patients compared to the controls.[47] It was proposed that forniceal atrophy was associated with relatively larger hippocampal volume loss in TLE.[48] There is only one study with adults with a history of childhood febrile seziures and the authors did not find any difference in forniceal integrity between this sample and controls.[29] Fornix is one of the pathways for seizure spreading along with other pathways including stria terminalis, amygdalofugal fibers, and uncinate fasciculus.[44] An increase in white matter integrity was observed in a group of subjects whose diffussion tensor imaging (DTI) scans were performed eight years after the prolonged febrile seizures compared to controls.[49] We can speculate that fornix atrophy associated with the history of CFC can be secondary to the hippocampal atrophy seen in TLE patients. Considering the proposed mechanisms for the relationship between hippocampus atrophy and CFC, what has been said about the hippocampus may also apply to the fornix; i.e. fornix atrophy may have occurred due to a trauma before CFC or the direct effect of CFC. In this neuroimaging study of ours, however, we can not explain the mechanism of the relation between forniceal atrophy and history of CFC in TLE patients. TLE patients with relatively more hippocampal atrophy and history of CFC can be a separate clinical group, and more forniceal atrophy might be a feature of this particular group of TLE patients.

The point of view from a perspective on genetics is very important when planning future MRI morphometric measurements to uncover the relation between history of CFC and TLE. For example, why not every child with a history of CFC develops TLE and related hippocamapal damage may be answered partly by planning collaborative prospective studies of genetics and MRI morphometery.

Our study has several limitations. First, it is a cross-sectional study with relatively a small sample size. We do not

have any treatment history, as the antiepileptics also can be a confounding factor. Rather than measuring the width of the fornix, DTI as a relatively new and more advanced technique might have been used to see whether there is any deficit in the white matter integrity in this pathway in this subgroup of TLE patients.[50]

In our study, we replicated the consistent finding of more hippocampal atrophy in TLE-CFC[+] patients with an additional finding of more forniceal atrophy in that group of patients compared to those patients TLE-CFC[-] patients. The CFCs should be taken care of carefully in the childhood, as they are associated with more atrophy in the particular brain structures in patients with TLE.

Conflict of Interest

The authors declare that there is no conflict of interest.

Author Contributions

KY: project development, manuscript writing/editing; BH: data collection and data analysis; İB: supervision of the study and collecting patients.

Ethics Approval

The study was approved by the Local Ethics Committee of the Medical School of Uludag University (date of approval: 09.05.2000, approval number: 2000-51).

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