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Amygdala Volumetry in Patients with Temporal Lobe Epilepsy and Normal Magnetic Resonance Imaging

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Summary

Background: It has been suggested that the pathophysiology of temporal lobe epilepsy may relate to abnormalities in various brain structures, including the amygdala. Patients with mesial temporal lobe epilepsy (MTLE) without MRI abnormalities (MTLE-NMRI) represent a challenge for diagnosis of the underlying abnormality and for presurgical evaluation. To date, however, only few studies have used quantitative structural Magnetic Resonance Imaging-based techniques to examine amygdalar pathology in these patients.

Material/Methods: Based on clinical examination, 24-hour video EEG recordings and MRI findings, 50 patients with EEG lateralized TLE and normal structural Magnetic Resonance Imaging results were included in this study. Volumetric magnetic resonance imaging (MRI) studies of the amygdalas and hippocampi were conducted in 50 non-epileptic controls (age 7–79 years) and 50 patients with MTLE with normal MRI on a 1.5-Tesla scanner. Visual assessment and amygdalar volumetry were performed on oblique coronal T2W and T1W MP-RAGE images respectively. The T2 relaxation times were measured using the 16-echo Carr-Purcell-Meiboom-Gill sequence (TE, 22–352). Volumetric data were normalized for variation in head size between individuals. Results were assessed by SSPS statistic program.

Results: Individual manual volumetric analysis confirmed statistically significant amygdala enlargement (AE) in eight (16%) patients. Overall, among all patients with AE and a defined epileptic focus, 7 had predominant increased volume ipsilateral to the epileptic focus. The T2 relaxometry demonstrated no hyperintense signal of the amygdala in any patient with significant AE.

Conclusions: This paper presented AE in a few patients with TLE and normal MRI. These findings support the hypothesis that there might be a subgroup of patients with MTLE-NMRI in which the enlarged amygdala could be related to the epileptogenic process.

MeSH Keywords: Amygdala • Epilepsy, Temporal Lobe • Neuroimaging

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Background

Magnetic resonance imaging (MRI) has become the technique of choice for investigations of the macroscopic neuroanatomy *in vivo* due to high level of image resolution and excellent tissue contrast [1]. Dissimilar outcomes on antiepileptic drugs, surgical results, and evolution lead to a supposition that MTLE is not a single and uniform entity but instead a group of different diseases [2]. Mesial temporal lobe epilepsy (MTLE) is often associated with hippocampal

sclerosis (HS). Nevertheless, there is a considerable group of patients with MTLE that do not show any MRI signs of HS or any other abnormality on MRI visual analysis, these patients are known as "MRI-negative". "MRI-negative" TLE has been characterized by the lack of neocortical pathology, normal hippocampal volumetry, and no evidence of any increased signal in the mesial temporal lobe structures on routine visual assessment. Mesial temporal lobe epilepsy with normal MRI (MTLE-NMRI) is a very challenging condition as the underlying pathology is difficult to determine, particularly when patients are under assessment for epilepsy surgery [3,4]. In our routine practice, we have come across many cases of EEG-localized TLE where no lesion was detected on visual analysis even on retrospective review. For MTLE-NMRI patients it is little known whether the underlying pathology is a structural lesion in the temporal lobe or there is a covert cause that remains undiagnosed. In TLE related to HS, the amygdala is the main origin of seizures as depicted by invasive electrophysiological and pathological studies [4.5]. Although hippocampal volumetry is now an accepted method allowing discovery of mild degrees of hippocampal atrophy, there have been only few amygdala MR volumetric studies. The authors had previously conducted a study on intractable temporal lobe epilepsy in 30 patients and 50 controls and concluded that volumetric analysis and T2 relaxometry of the hippocampus detected mild abnormalities which were undetected on visual analysis [6]. The aim of the present study was to examine possible alterations in the brain amygdalar volume and signal intensity in patients with TLE-NMRI by means of quantitative MRI. As part of this study, the hippocampal volumes were also assessed in patients and controls.

Material and Methods

Subject characteristics

This study included 50 patients with EEG-localized temporal lobe epilepsy with normal MRI on visual analysis and quantitative volumetric analysis. To acquire normal values, 50 non-epileptic control subjects were also recruited. Patients of all ages and both sexes were included in this study. The patient group included 50 patients (29 males, 21 females) with a mean age of 26.5±12.9 years (range, 9–56 years) who had clinical and electroencephalographic diagnosis of MTLE with normal MRI on visual analysis as well as quantitative volumetric analysis. The control group included 50 subjects (27 males, 23 females) with a mean age of 28.2±14.3 years (range, 7–79 years). A detailed history was taken from all patients. A positive and relevant past history was also recorded. All the patients were initially assessed clinically by a senior neurologist before referring them for MRI. All the MRI data were assessed by a senior radiologist. To increase the specificity of the visual MRI analysis and to exclude the patients with subtle HS signs, we also performed manual hippocampal volume measurements in all patients and in 50 healthy subjects. This project was reviewed and approved by the institutional review board and all procedures were in agreement with institutional guidelines. None of the patients with enlarged amygdala underwent surgery and hence histo-pathological evaluation was not possible.

Preparation of the patient

Before starting the MRI study, the procedure was explained to the patient in his/her vernacular language to allay the fear and anxiety. The length of the study in the magnet varied from 30 min to 45 min and was communicated to the patient before the start of the study. During the entire period of the procedure the patient was in contact with the technician/doctor by a two-way intercom system. To reduce the artifacts due to patient movement, sedation was given to patients of pediatric group and uncooperative patients.

MRI Assessment

Visual analysis of hippocampus and amygdala

MR imaging was performed on a 1.5-T MRI scanner (Magnetom Avanto, 18 channel, Siemens Medical Solutions, Erlangen, Germany) with a matrix head coil used as both transmitter and receiver. The T1-W, T2-W, Diffusion weighted and HEMO sequences were obtained in the axial plane with 5-mm slice thickness and 30% interslice gap. For dedicated hippocampal study, inversion recovery (IR) oblique coronal images (TE-51, TR-3500, FOV-250 mm, slice thickness 2 mm) and oblique coronal T2 W images (TR-4000, TE-101, FOV-230, Slice thickness – 2 mm) covering the whole brain were acquired. Oblique coronal plane was perpendicular to the long axis of the hippocampus and amygdala.

Volumetric analysis of hippocampus and amygadla

For Hippocampal volumetry we used the same method as described in our previously published study on intractable epilepsy patients and controls [6]. For Amygdala volumetry, we cited a former MRI-based study carried out by Watson et al. with minor modifications for anatomic boundaries [7,8]. Normal control values for the amygdala and hippocampus volumes were acquired from 50 control subjects using an identical protocol (Figures 1, 2). Abnormal hippocampal and amygdalar volume values were considered when these were both outside the range of all normal control values and more than two standard deviations outside the mean value of control hippocampal volumes. Volumetric data were normalized for variation in head size between individuals by Gullap's formula [6,9].

$$NV = \frac{(MMAG) \times (HV)}{(MAS)}$$

[NV – normalized volume; MMAG – mean mid-sagittal area of the group (controls or cases). HV – Absolute hippocampus volume; MAS – mid-sagittal area of the subject].

T2 relaxation time measurement

The T2 relaxation times were calculated using 16-echo Carr-Purcell-Meiboom-Gill sequence which is a multiple spin-echo sequence (TE: 22-352, TR-3000, slice thickness-5mm, FOV-230). Sixteen separate spin-echo images were acquired for each oblique coronal slice at echo times ranging from 22 ms to 352 ms. The T2 maps were acquired

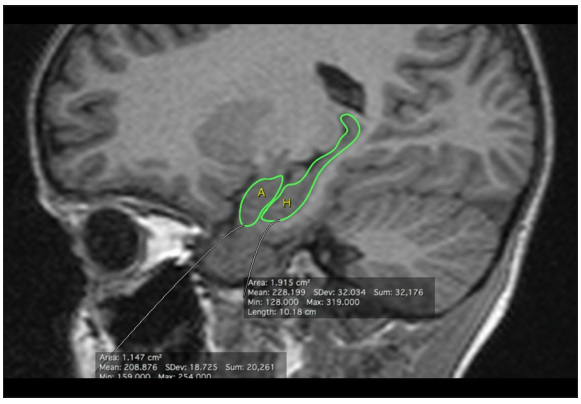


Figure 1. Sagittal T1-weighted MP-RAGE sequence on 1.5-T MR scan outlining the hippocampus (H) and amygdala (A) by manual volumetry.

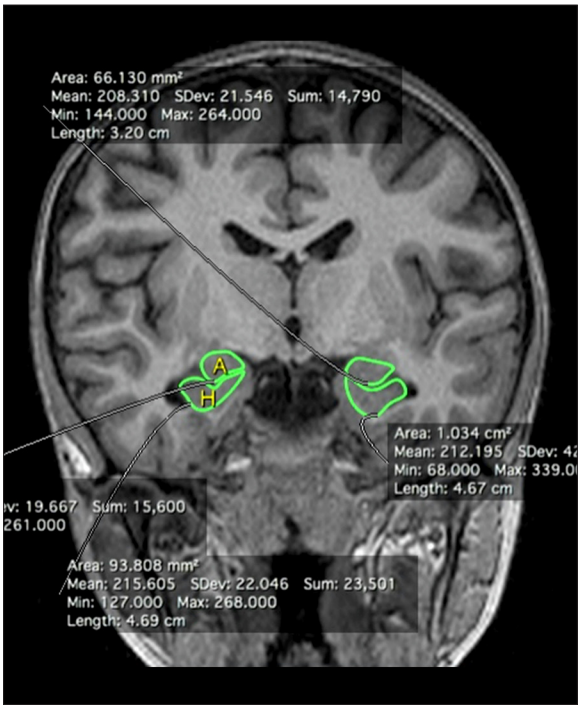


Figure 2. Coronal T1-weighted MP-RAGE sequence on 1.5-T MR scan outlining the hippocampus (H) and amygdala (A) by manual volumetry.

using a computer program that fitted a single exponential to the signal intensity data from corresponding pixels from all 16 echoes (Figure 3). The T2 relaxation time was then computed for each pixel and an image was constructed in which pixel intensity corresponded to the calculated T2 relaxation time. The mean hippocampal and amygdala T2 relaxation time was calculated by manually marking a region of interest (ROI) in the largest possible circular area within the three sections of the hippocampus and amygdala, while evading boundaries where partial volume effects with CSF might arise.

Normal control values for T2 relaxation time were acquired from control subjects using an identical protocol. Abnormal T2 values were considered when these were both outside the range of all normal control values and

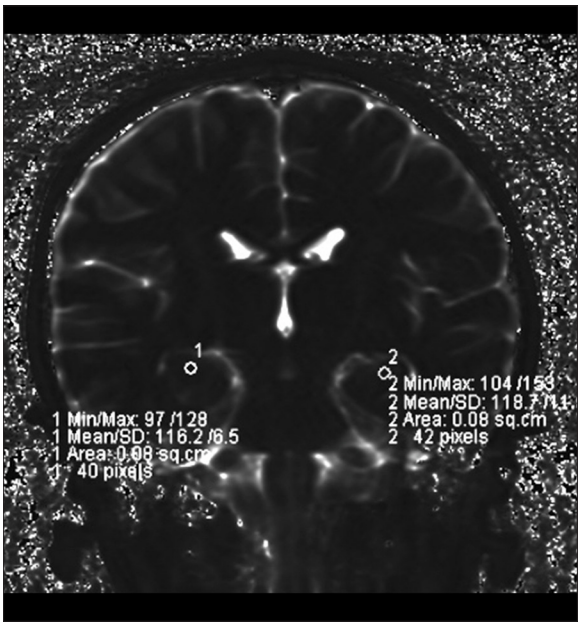


Figure 3. Image showing T2 relaxometry map with manually marked region of interest (ROI) in the hippocampus.

more than two standard deviations outside the mean value of control hippocampal T2 relaxation times.

Video-EEG monitoring

A 24-hour Video-EEG monitoring was carried out in every patient before MRI by the standard protocol. The electrodes were glued to the scalp of the patients. A camera was used to visually record the patient activity continuously while at the same time the EEG was recording the brain activity. We used a TV monitor with a split screen in the room of the patient; the screen showed EEG on one side and the video recording of the patient on the other side. EEG was analyzed for temporal or extratemporal localization of epilepsy.

Statistical analysis

The MRI findings were correlated with clinical data and 24-hour video EEG findings. Comparison of values obtained from the patient and control groups were made. The Pearson's correlation coefficient and t-test were used wherever indicated. Results were evaluated by SSPS version 16.0 for windows (SSPS Inc., Chicago, IL). P-value <0.05 was considered to be significant.

Results

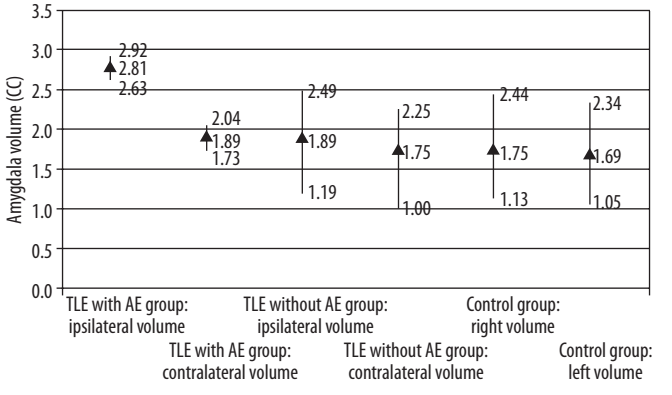
Normative data in controls (n=50)

Volumes of right and left amygdala were measured and T2 relaxometry values were calculated from MRI images in 50 control subjects. Volumetric data were normalized for variation in head size between individuals by Gullap's formula. The mean mid-sagittal head circumference in 50 control subjects was 168 cm^2 (138.7–199.8 cm^2). There was a positive correlation ($r=0.77$, $p<0.05$) between mid-sagittal head circumference and absolute amygdala volumes,

Table 1. Clinical data and MR evaluation of the 8 temporal lobe epilepsy patients with significant ipsilateral amygdala enlargement (AE) examined by 1.5-T MRI.

Patient No.	Age/sex (years)	Onset (years)	Seizure type	Abnormal EEG side	AE side	AV R (cc)	AV L (cc)	HV R (cc)	HV L (cc)
1	35/M	18	GTC	R	R	2.84	1.83	3.50	3.46
2	55/M	40	CPS	R	R	2.77	1.87	3.70	3.65
3	39/M	24	CPS	L	L	2.00	2.63	3.77	3.71
4	17/F	9	GTC	R	R	2.92	2.04	3.86	3.79
5	51/M	41	CPS	R	R	2.73	1.81	3.79	3.77
6	56/F	30	CPS	L	L	1.73	2.90	3.75	3.60
7	9/M	4	GTC	L	L	1.94	2.91	3.72	3.67
8	44/F	35	CPS	R	L	2.10	2.65	3.76	3.63

R – right; L – left; CPS – complex partial seizure; GTC – generalized tonic – clonic seizure; AE – amygdala enlargement; AV – amygdala volume; HV – hippocampal volume.



TLE – temporal lobe epilepsy; AE – amygdala enlargement. Ipsilateral and contralateral volume represents volume of amygdala ipsilateral and contralateral to seizure focus on EEG respectively

Figure 4. Chart showing range and mean values (depicted by triangles) of controls, in patients with amygdala enlargement and patients without amygdala enlargement.

that is, absolute volumes of amygdala increased proportionately with head size. Right and left amygdala volumes in controls were found to be positively correlated (r=0.97, p<0.01). Right amygdala volume was larger than left by a statistically non-significant amount (p=0.41). The mean normalized volume of the amygdala in controls on the right side was 1.79±0.35 (range, 1.13–2.44 cc) and on the left 1.69±0.31 (range, 1.05–2.34 cc), respectively. The mean amygdala volume was slightly higher in males (1.9 cc) than females (1.8 cc) but no significant difference was found between them (P=0.25).

Visual analysis

No case of amygdala enlargement or T2 hyperintense signal was identified on visual analysis in controls or in patients.

Amygdala volumetry in cases (n=50)

Individual volumetric evaluation confirmed significantly increased amygdala volumes in eight (16%) MTLE-NMRI patients with values outside the range of all normal control values as well as more than two standard deviations outside the mean value of control s. Table 1 depicts the amygdalar volumes of eight patients in the AE group determined manually by 1.5 T MRI. In patients with AE and ipsilateral seizure focus on EEG, amygdalar volume ranged from 2.63 cc to 2.92 cc (mean 2.81 [SD 0.109] cc). On the contralateral side, amygdalar volume was lower and ranged from 1.73 cc to 2.04 cc (mean 1.89 [SD 0.11] cc). There was a significant difference between the two sides (p<0.05). One patient had AE contralateral to seizure focus, therefore 7 out of 8 (87.5%) of the patients had concordance of MRI findings with the side of EEG localization of the seizure focus. In the "TLE without AE" group (42 patients), amygdalar volume on the ipsilateral side to the seizure focus on EEG ranged from 1.89±0.39 cc (range; 1.19–2.49) and that on the contralateral side ranged from 1.75±0.37 (1.00–2.25 cc) (Figure 4). There was no significant difference between the two sides (p=0.20), with the volume being slightly higher on the EEG focus side. On comparison of all cases (n=50) and controls (n=50), the former had higher amygdalar volumes. However, no significant difference was seen (Table 2). There was a statistically significant difference of amygdalar volumes between controls and "TLE

Table 2. Comparison of the amygdala volumes of controls (n=50) and all cases (n=50).

Amygdala	Controls (n=50)	Cases (n=50)	p-value
	A. Volume (cc)		
Right			
Mean	1.79	1.88	0.10
SD (standard deviation)	0.35	0.40	
Range	1.13–2.44	1.22–2.92	
Left			
Mean	1.69	1.76	0.15
SD (standard deviation)	0.31	0.39	
Range	1.05–2.34	1.19–2.94	

Table 3. Table showing amygdala volumes in controls (n=50), in patients with amygdala enlargement (n=8) and patients without amygdala enlargement (n=42).

Amygdala	1. Controls (n=50)	2. TLE without AE (n=42)	3. TLE with AE (n=8)	p values*
		A. Volume (cc)		
Right				0.12 (1,2), 0.01 (1,3), 0.02(2,3)
Mean	1.79	1.83	2.38	
SD	0.35	0.37	0.48	
Range	1.13–2.44	1.16–2.48	1.73–2.92	
Left				0.14 (1,2), 0.03 (1,3), 0.01 (2,3)
Mean	1.69	1.72	2.44	
SD	0.31	0.34	0.51	
Range	1.05–2.34	1.08–2.37	1.81–2.94	

* The three groups were numbered as 1, 2 and 3. The p value between these groups was written as the "p value (group numbers)". The Bracket contains the group numbers and the p value between these groups was written outside the bracket.

with AE" group, and also between "TLE without AE" and "TLE with AE" groups on the side of seizure focus ($p<0.05$). However, no significant difference of amygdalar volumes was seen between controls and patients of "TLE without AE" group both ipsilateral and contralateral to the seizure focus ($p>0.05$). There was also no significant difference between the unaffected side of the AE group and either left or right side in normal subjects. However, a significant difference was seen between the affected side of the AE group and both the left and right sides in normal subjects (Table 3).

T2 relaxometry

T2 relaxometry revealed no hyperintense signal in the amygdala in any patient with significant AE.

Discussion

This study revealed that patients with EEG-localized TLE with AE had isolated enlargement of the amygdala with no significant volume alteration of the hippocampi. There have been only a couple of preceding papers calculating amygdala volumes in "imaging-negative" TLE [10–14]. We discovered eight patients with unanticipated amygdala enlargement among 50 "imaging-negative" patients. AE was identified in none of those cases on visual inspection and no patient had isolated amygdala atrophy or increase in T2 signal on T2 relaxometry. This structural pattern is different from MTLE with HS, in which hippocampal atrophy is the most striking finding. This further fortifies the notion that TLE with AE might be a subtype of MTLE [13]. To date, there have been very few amygdala volumetric studies, partially because of the amygdala's poorly defined anatomical outlines. Nevertheless, the technique of amygdala volume measurement utilized in this study is presently well accepted. Our normal ranges and amygdala volume ratios are agreeable with lately reported data [7,8]. The amygdala volumetry was done in both patients and controls by the same radiologist (PDS), thus there was no inter-rater difference or bias. "Imaging-negative" TLE is

a tough group to diagnose and without intracranial electrode studies or surgical data, we cannot be definite that all cases had TLE. Even though patients with occipital, parietal, and orbitofrontal origin can resemble the clinical findings of TLE, given that the ictal EEG was well lateralized in patients of the present study and the clinical features were agreeable with TLE, we were quite confident of the diagnosis of TLE.

In the patients incorporated in this study, structural pathology was restricted to the amygdala without any hippocampal volume alterations. As per previous neuropathological and imaging studies, pathology in the amygdala can coexist with HS in patients with MTLE with HS. Nevertheless, the existence of histopathological HS can be very well foreseen by volumetric MRI [15–20]. Thus, accompanying HS is rather improbable in the patients of present study who had TLE with AE. In this paper we exhibited an increase of the amygdala volume in 16% of patients with MTLE with normal MRI on visual analysis. The amygdala plays a key role in emotional behavior as well as epilepsy and epileptogenesis. The participation of the amygdala in MTLE has been investigated for the most part; yet, its complete involvement in MTLE is still not completely known. Previous studies have shown that stimulation of the amygdala can cause experimental symptoms and epileptiform discharges arising from the amygdala in intracranial EEG recordings which support the evidence of the significance of this structure in MTLE. Reduced volume of the amygadla ipsilateral to the HS has been consistently documented. On the contrary, few papers have depicted amygdala enlargement in MTLE with HS. Even though the enlarged amygdala in MRI-negative MTLE has already been documented and investigated as the possible localization of seizure onset in previous studies, no consistent pattern can be observed in these studies, which might be due to heterogeneous clinical and imaging characteristics of TLE patients and small number of patients in past studies [12–23].

The underlying pathophysiology leading to amygdala enlargement in TLE is a topic of debate. One probable cause of AE is a mild form of a neuroinflammatory disorder causing mild gliosis which has been described to be one of the underlying reasons of adult-onset TLE. Another potential reason of AE may be disorders such as hamartoma, focal cortical dysplasia or low-grade tumors, as described in the past studies [24–29]. It is possible that acute seizure activity might lead to brain oedema and amygdala enlargement, yet none of the patients in the present study underwent MRI within 48 hours of seizures. Notwithstanding, it must be stressed that these explanations are very notional and at present, there are no specifically accepted models that can confirm the underlying pathophysiology leading to the phenomena of enlarged amygdala. Further studies are needed to ascertain the underlying cause. Hence, we feel that the AE patients in our study could have a multifactorial etiology.

Quantitative T2 relaxometry of the amygdala has been projected as a more systematic technique than volumetry in observing amygdaloid lesions. Van Paesschen et al. [30] presented findings in patients with intractable TLE and found an abnormally high hippocampal T2 signal in 52% of patients with unilateral HS. Two of those patients with a high amygdala T2 signal had amygdala sclerosis which was validated by histopathological examination. Of 31 patients with normal quantitative hippocampal values, same to our "imaging-negative" patients, 15 had an isolated abnormal amygdala T2 signal. Pathological specimens which were accessible in two cases revealed amygdala gliosis in one and microdysgenesis in another case. The authors asserted that atrophy in all probability is not an attribute of the majority of epileptogenic lesions of the amygdala, and that T2 mapping might be a finer method than amygdala volumetry to discover these lesions. On the contrary, we did not find any increased T2 signal on visual analysis or on T2 relaxometry in any of the patients which is similar to recently published MRI studies on patients with TLE and normal MRI [12,14,24]. This difference, as compared to the study carried out by Van Paesschen et al., might be due to the small sample size, heterogeneous clinical and imaging characteristics of TLE patients and difference in T2 relaxometry technique.

In the present study, the amygdala appeared uniformly enlarged accounting for the measured asymmetry. Based on our amygdala volumetric analysis of 50 patients without HS, amygdala enlargement was comparatively infrequent (16%), seven patients had ipsilateral enlargement and one patient had contralateral enlargement. In keeping with previous pathological studies it is probable that amygdala gliosis does not usually lead to volume loss detectable by MR imaging. Astrocytes at sites of axonal degeneration are known to go through morphological alterations comprising hypertrophy and hence it has been documented that gliosis does not always lead to volume loss [31]. It has been suggested that a previous insult might cause hypertrophy of the mesial temporal structures due to the proliferation of astrocytes, which are well known to be susceptible to hypoxic injuries. These patients could then subsequently develop progressive atrophy of one of the mesial structures with perseverance of the volume of the mesial structures of an opposite temporal lobe [35,36]. Therefore, it has been suggested that the amygdala hypertrophy seen in patients with MTLE is part of a constant process that sooner or later will evolve as atrophy. More research comprising histopathological evaluation and prospective amygdala measurements is needed to substantiate these findings and to improve understanding of the underlying pathological processes causing amygdala enlargement in MTLE.

The results of this study point towards the possible role of a structural pathology in the amygdala which might be implicated in some patients with MRI-negative MTLE. The enlargement of the amygdala could be the source of the pathology of these patients. In a group of 100 MTLE patients referred for temporal lobectomy with amygdalectomy and negligible hippocampal resection exhibited analogous outcomes as compared to a series of 100 MTLE patients who underwent temporal lobectomy with major hippocampectomy in the same center and therefore reinforced the opinion that some patients with MTLE may have a primary amygdalar seizure focus and may not need resection of the hippocampus [33,34]. Based on a review of literature and our findings in the present study of MRI-negative TLE patients, we feel that there is indeed nonuniformity of epileptic pathologies in these patients and TLE with AE

may be defined as a subgroup of "imaging-negative" TLE patients that are distinct from those with HS [13,36].

The primary limitation of the present study is that we did not have ictal intracranial EEG recordings of the cases, nor surgical management outcomes with pathological samples. Nevertheless, this exploratory finding may give assistance for further research, and thus will aid to define such patients who would gain from amygdala removal only, leaving the hippocampus and parahippocampus. In forthcoming studies, the amygdala volume must be analyzed in the preoperative MRI of patients with MTLE-NL referred for anterior temporal lobe resection and particular attention should be paid to the pathology of the amygdala in these patients. The preliminary findings of present study could be of great value not only in the understanding of imaging-negative TLE but also in the surgical management of this condition.

Conclusions

A subgroup of patients with MTLE and normal MRI have enlarged amygdala which is the likely cause of epilepsy in these patients.

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