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RESEARCH ARTICLE

Amygdala enlargement in temporal lobe epilepsy: Histopathology and surgical outcomes

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Abstract

Objectives: Amygdala enlargement is detected on magnetic resonance imaging (MRI) in some patients with drug-resistant temporal lobe epilepsy (TLE), but its clinical significance remains uncertain We aimed to assess if the presence of amygdala enlargement (1) predicted seizure outcome following anterior temporal lobectomy with amygdalohippocampectomy (ATL-AH) and (2) was associated with specific histopathological changes.

Methods: This was a case–control study. We included patients with drug-resistant TLE who underwent ATL-AH with and without amygdala enlargement detected on pre-operative MRI. Amygdala volumetry was done using FreeSurfer for patients who had high-resolution T1-weighted images. Mann–Whitney *U* test was used to compare pre-operative clinical characteristics between the two groups. The amygdala volume on the epileptogenic side was compared to the amygdala volume on the contralateral side among cases and controls. Then, we used a two-sample, independent *t* test to compare the means of amygdala volume differences between cases and controls. The chi-square test was used to assess the correlation of amygdala enlargement with (1) post-surgical seizure outcomes and (2) histopathological changes.

Results: Nineteen patients with and 19 patients without amygdala enlargement were studied. Their median age at surgery was 38 years for cases and 39 years for controls, and 52.6% were male. There were no statistically significant differences between the two groups in their pre-operative clinical characteristics. There were significant differences in the means of volume difference between cases and controls (Diff = 457.2 mm^3, 95% confidence interval [CI] 289.6–624.8; $p < .001$) and in the means of percentage difference ($p < .001$). However, there was no significant association between amygdala enlargement and surgical outcome ($p = .72$) or histopathological changes ($p = .63$).

Significance: The presence of amygdala enlargement on the pre-operative brain MRI in patients with TLE does not affect the surgical outcome following ATL-AH,

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and it does not necessarily suggest abnormal histopathology. These findings suggest that amygdala enlargement might reflect a secondary reactive process to seizures in the epileptogenic temporal lobe.

KEYWORDS
amygdala enlargement, histopathology, surgical outcome, temporal lobe epilepsy

1 | INTRODUCTION

Temporal lobe epilepsy (TLE) represents one-third of adults with focal epilepsy, with mesial TLE accounting for about 80% of TLE.[1] Drug-resistant TLE is a common indication for epilepsy surgery in adulthood, with hippocampal sclerosis (HS) being the most frequent histopathological finding.[2] About 70% of patients with drug-resistant TLE who undergo a temporal lobe resection achieve seizure freedom at least 1 year after surgery, and up to 60% are seizure-free 5 years post-surgery.[3–5]

The amygdala is part of the limbic system and plays a key role in the epileptogenic network in many patients with TLE.[6–8] Several studies have shown that in patients with TLE, seizures may arise from both the hippocampus and amygdala, either independently, simultaneously, or with fast propagation from one to the other structure.[8] In addition, anterior temporal lobectomy (ATL) achieves a better outcome when the amygdala is entirely resected.[9]

Amygdala enlargement has been reported on brain magnetic resonance imaging (MRI) in 4% of patients with drug-resistant TLE.[10] Several studies using amygdala volumetry concluded that amygdala enlargement could be a pathological epileptogenic substrate for otherwise "non-lesional" TLE.[11] Of interest, the resolution of amygdala enlargement on follow-up neuroimaging studies has been reported in some cases after better seizure control was attained on medical treatment.[12] In one study, up to 70% of TLE associated with amygdala enlargement achieved Engel class I following ATL.[13] However, the significance of amygdala enlargement in predicting seizure outcome after ATL remains uncertain.

A spectrum of histopathological findings has been reported in patients with amygdala enlargement. The most frequent finding was gliosis.[10,12] Focal cortical dysplasia (FCD), brain tumors, hamartoma-like lesions, and aggregated hypertrophic neurons not compatible with FCD have also been reported.[14–16] However, the association between amygdala enlargement and abnormal amygdala histopathology is still not well established.

We aimed in this study to investigate the following questions: (1) Does amygdala enlargement observed on preoperative MRI affect the seizure outcome post-epilepsy surgery in patients with drug-resistant TLE? (2) Is there a consistent histopathology underlying amygdala enlargement?

Key points

- In this case–control study, patients who underwent anterior temporal lobectomy with amygdalohippocampectomy (ATL-AH) showed comparable post-operative seizure outcomes post-operatively regardless of whether amygdala enlargement was detected on pre-operative magnetic resonance imaging (MRI).
- The resected amygdala was predominantly normal on histopathological examination, or showed reactive gliosis in a minority of patients.
- There was no correlation between amygdala enlargement on pre-operative MRI and the histopathological results in the resected amygdala.
- Amygdala enlargement might reflect a secondary reactive process to seizures in the epileptogenic temporal lobe.

2 | METHODS

2.1 | Study design and subjects

This was a case–control study. We retrospectively reviewed the pre-operative MRI brain reports of patients with drug-resistant TLE who underwent ATL with amygdalohippocampectomy (ATL-AH) at The Royal Melbourne Hospital, Australia, between March 2000 and November 2020. We defined as "cases" those patients whose pre-operative MRI brain was reported as showing unilateral amygdala enlargement. They were matched (1:1) by sex and age at surgery to patients with normal amygdala on MRI ("controls"). Both cases and controls were eligible for inclusion irrespective of the presence of hippocampal abnormalities such as HS or cystic lesion

(e.g., ganglioneurocytoma). We excluded patients who had less than 1 year of follow-up after surgery.

We collected the following clinical data for included patients: sex, age at epilepsy onset, age at epilepsy surgery, duration of epilepsy, history of febrile seizures, history of comorbid psychiatric disorders at the time of surgical evaluation, type of aura if present (psychic/experiential, somatosensory, cephalic, visceral-sensory, autonomic, vestibular, visual, auditory, olfactory, and gustatory), and frequency of convulsive (i.e., focal to bilateral tonic–clonic seizures) and non-convulsive seizures before surgery (Table S1).[17]

2.2 | Pre-surgical evaluation

All patients underwent standard pre-surgical evaluation, including neuroimaging studies (MRI brain, fluorodeoxyglucose–positron emission tomography [FDG-PET], single-photon emission computerized tomography [SPECT]), 5-day video-electroencephalography monitoring (VEM), visual field testing, and neuropsychological assessment. All patients were discussed in a multidisciplinary meeting to determine their eligibility for resective epilepsy surgery.

2.2.1 | Five-day VEM

All patients underwent 5-day VEM using the 10–20 international system with 10 additional sub-temporal electrodes as part of their pre-surgical evaluation. We reviewed the VEM reports and reported the presence or absence of interictal temporal epileptiform discharges (unilateral vs bilateral).

2.2.2 | MRI acquisition

Pre-operative MRI brain was reported by a neuroradiologist (E.L.) who was blinded to the patient's histopathology and post-surgical seizure outcome. All patients had an MRI brain with a spin-echo T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences. Axial and coronal sections were used to assess temporal mesial structures. Until 2005, MRI studies were carried out on a Genesis Signa 1.5 T (GE Medical Systems); thereafter the scans have been performed on a Magnetom Avanto 1.5 T and a Magnetom Trio Tim 3 T (Siemens Medical Solutions, Erlangen, Germany).[18]

2.2.3 | Amygdala volumetry

To validate the clinical reports of amygdala enlargement, amygdala volumes were quantified automatically for those cases and controls who had 1 mm three-dimensional (3D), T1-weighted image, magnetization-prepared rapid gradient echo (MPRAGE) as part of their MRI protocol. The hippocampal and amygdala subfields module (CITE)[19] in FreeSurfer (version 7.4.0) was used to segment the amygdala subregions, and whole amygdala volume was extracted. Amygdala segmentations were exported to nifti format and manually checked by a neurologist with 6 years of experience (L.S.) and with an epilepsy neuroradiologist with 16 years of experience (E.L.) using FSLeyes and corrected in ITKSNAP where Freesurfer had over- or under-segmented.

2.2.4 | FDG-PET acquisition

All patients had FDG-PET of the brain as part of their pre-surgical evaluation. FDG-PET scans were acquired on a GE Discovery 690 (GE Medical Systems, Milwaukee, WI) at the Peter MacCallum Cancer Centre, Melbourne, Australia, with a voxel size of $1.82 \times 1.82 \times 3.27$ mm, as described previously.[20]

2.3 | Neurosurgical procedure

Except for one patient who underwent amygdala lesionectomy, all patients underwent ATL, a technique developed by Spencer to preserve the function of the lateral temporal cortex.[21] The procedure begins with resecting the middle temporal gyrus and inferior temporal gyrus 3–3.5 cm from the tip of temporal pole, followed by resection of the mesial temporal structures (i.e., amygdala, hippocampus, and parahippocampal gyrus). A less-extensive neocortical resection, sparing the superior temporal gyrus, was considered in patients with left (i.e., language dominant) mesial TLE. One patient in the control group underwent repeat surgery with further resection of the inferior and middle temporal gyri, amygdala, and posterior hippocampus.

2.4 | Post-operative seizure outcomes

Post-operative seizure outcomes were assessed at last follow-up and categorized using Engel's classification.[22] The duration of follow-up varied between patients (Table 1), although all were followed for at least 1 year following epilepsy surgery.

We categorized post-operative seizure outcomes into either "favorable" or "unfavorable." The former included outcomes consistent with Engel class I; Engel class II–IV were regarded as "unfavorable." Seizures occurring within the first week were disregarded in the categorization of seizure outcomes.[23]

TABLE 1 Clinical, MRI, and VEM data for included patients.

Clinical and VEM data	Cases ($n = 19$)	Controls ($n = 19$)
Male sex (n, %)	10 (52.6%)	10 (52.6%)
Median age at seizure onset in years (IQR)	23.0 (15.0–31.5)	17.0 (9.0–26.0)
Median age at surgery in years (IQR)	38.0 (34.5–48.5)	39.0 (32.5–53.5)
History of febrile convulsions (yes)	6 (31.6%)	5 (26.3%)
Type of aura (n, %)	None (5, 26.3%) Visceral-sensory (3, 15.8%) Psychic/experiential (6, 31.6%) Autonomic (2, 10.5%) Cephalic (1, 5.3%) Auditory (1, 5.3%) Vestibular (1, 5.3%)	None (8, 42.1%) Visceral-sensory (3, 15.8%) Psychic/experiential (2, 10.5%) Autonomic (2, 10.5%) Cephalic (1, 5.3%) Auditory (1, 5.3%) Somatosensory (1, 5.3%) Gustatory (1, 5.3%)
Median number of ASMs used pre-surgery (IQR)	3 (2.0–3.0)	2 (2.0–3.0)
Median pre-surgical convulsive seizure frequency score (IQR)[a]	2.0 (1.0–5.0)	2.0 (0)
Median pre-surgical non-convulsive seizure frequency score (IQR)	8 (7.0–8.5)	7 (7.0–8.0)
Pre-surgical comorbid psychiatric history (n, %)	9 (47.4%)	8 (42.1%)[b]
Laterality (right: left)	12:7	7:12
Bilateral temporal interictal discharges (n, %)	0 (0%)[c]	3 (15.8%)
Pre-operative MRI findings (n, %)	Amygdala enlargement on R (12, 63.2%) and L (7, 36.8%) HS (9, 47.4%) Hippocampal cyst (1, 5.3%)	Normal (4, 21.1%) HS (14, 73.7%)[d]

Abbreviations: ASMs, anti-seizure medications; HS, hippocampal sclerosis; IQR, interquartile range; L, left; MRI, magnetic resonance imaging; N, number of patients; R, right; VEM, video-EEG monitoring.

[a]Convulsive seizures: focal to bilateral tonic–clonic seizures.

[b]One patient had one episode of psychosis in the context of non-compliance on ASMs.

[c]One patient had independent right frontocentral discharges (suspected autoimmune encephalitis and positive GAD antibodies with titer >2000 U/mL).

[d]Expected post-operative appearance following left anterior temporal lobectomy was demonstrated on the pre-operative MRI for one control.

2.5 | Histopathology

Amygdala slides were stained with hematoxylin and eosin (H&E) and immunostained with antibodies directed against neuronal nuclei antigen (NeuN) and glial fibrillary acidic protein (GFAP). Slides stained with additional immunoperoxidase (e.g., neurofilament, CD34 antibodies, isocitrate dehydrogenase 1 [IDH1] antibodies, and Luxol Fast blue stain for myelin) were available for some cases. Histopathological diagnosis was made by a neuropathologist (C.M.) blinded to the clinical and MRI findings.

2.6 | Statistical analysis

Descriptive statistics were used to summarize the clinical and radiological features of individual patient data. Continuous variables were expressed as mean and standard deviation (SD) if they followed approximately normal distributions; otherwise the medians and interquartile range (IQRs) were reported. Categorical variables were reported as frequency counts and percentages. Mann–Whitney U test was used to assess differences in clinical and VEM characteristics between cases and controls. The amygdala volumes were compared between the ipsilateral (to the epileptogenic

temporal lobe) and contralateral sides among cases and controls who had high-resolution T1-weighted images. Then, we used the two-sample, independent *t* test to compare the means of amygdala volume differences between cases and controls. The chi-square test was used to evaluate the association of presence of amygdala enlargement on preoperative MRI brain with (1) post-operative seizure outcomes and (2) histopathological findings in the amygdala.

The significance level was set at $p = .05$. All statistical analyses were performed using SPSS (version 29.0).

3 | RESULTS

3.1 | Pre-operative clinical characteristics

During the study period, one patient underwent amygdala lesionectomy following the detection of an amygdala enlargement only on pre-operative MRI. Among 121 patients with drug-resistant TLE who underwent ATL-AH, an additional 18 (14.9%) were found to have amygdala enlargement on pre-operative MRI brain. Thus there was a total of 19 cases with MRI evidence of amygdala enlargement. These were matched by sex and age at surgery to 19 controls who underwent ATL-AH for drug-resistant TLE without amygdala enlargement. Table 1 shows the clinical characteristics and VEM findings of the cases and controls. The median age at epilepsy surgery was 38.0 years (IQR 34.5–48.5) for cases and 39.0 years (IQR 32.5–53.5) for controls, and 52.6% were male in both groups.

Cases tended to have an older age at epilepsy onset than controls (median 23.0 years vs 17.0 years), more frequent non-convulsive seizures (median 8.0 vs 7.0), a higher proportion of individuals with psychiatric comorbidities on presurgical assessment (47.4% vs 42.1%), a higher proportion of antecedent febrile seizures (31.6% vs 26.3%), and a lack of bilateral temporal interictal epileptiform discharges (0% vs 15.8%). However, none of these differences reached statistical significance (Table S2). In cases, unilateral temporal interictal discharges were ipsilateral to the side of amygdala enlargement.

3.2 | Pre-operative brain MRI

Among the cases, the median duration between pre-operative MRI and surgery was 1.1 years (IQR 0.6–2.5). Unilateral amygdala enlargement was detected on the right in 12 patients (63.2%) and on the left in 7 patients (36.8%) (Figure 1). Eighteen patients (94.7%) had increased T2/ FLAIR signal intensity of the enlarged amygdala; nine (50%) had mild signal changes. Ten patients (52.6%) had a concomitant hippocampal abnormality (nine HS and one hippocampal ganglioneurocytoma). Nine patients (47.4%) had no other MRI findings (Table 1).

Among the controls, the median duration between the pre-operative MRI and surgery was 0.8 years (IQR 0.5–1.5). Fourteen patients (73.7%) had unilateral HS, whereas four patients (21.1%) had no epileptogenic lesion demonstrated on their pre-operative brain MRI (Table 1).

3.3 | Amygdala volumetry

Fifteen cases and 17 controls had a 1 mm 3D, T1-weighted image and MPRAGE as part of their MRI protocol. One case and one control were excluded due to motion artifact affecting the clarity of amygdala margins and, thus, the reliability of volumetry. Most cases had larger amygdala volumes on the ipsilateral side than on the contralateral side (Figure 2A). On the other hand, most controls had smaller amygdala volumes on the ipsilateral side compared to the contralateral side (Figure 2B). The mean percentage of the amygdala volume differences (relative to the ipsilateral side) was 13.2% (SD 11.1) for cases ($n = 14$) and −11.4% (SD 10.6) for controls ($n = 16$) (Figure 2C). Independent-sample *t* tests revealed statistically significant differences in the means of volume difference between cases and controls (Diff = 457.2 mm^3, 95% CI 289.6–624.8; $p < .001$) and in the means of percentage difference ($p < .001$).

3.4 | Pre-operative FDG-PET scan

All cases and controls had ipsilateral temporal hypometabolism on pre-operative FDG-PET, except for one case with isolated amygdala enlargement on MRI who did not exhibit any focal hypometabolism.

3.5 | Post-operative seizure outcomes

Median post-operative follow-up period was 4.6 years (IQR 2.1–7.1) among cases and 3.8 years (IQR 2.2–5.8) among controls. Fourteen cases (73.7%) and 13 controls (68.4%) achieved favorable surgical outcomes at the last follow-up (Table 2). There was no association between amygdala enlargement and post-operative seizure outcome ($p = .72$).

3.6 | Histopathology results

Among cases, the primary histopathological finding was HS in 10 patients (52.6%), FCD in 7 patients (36.8%), normal in 1 patient (5.3%), and hippocampal gangliocytoma in

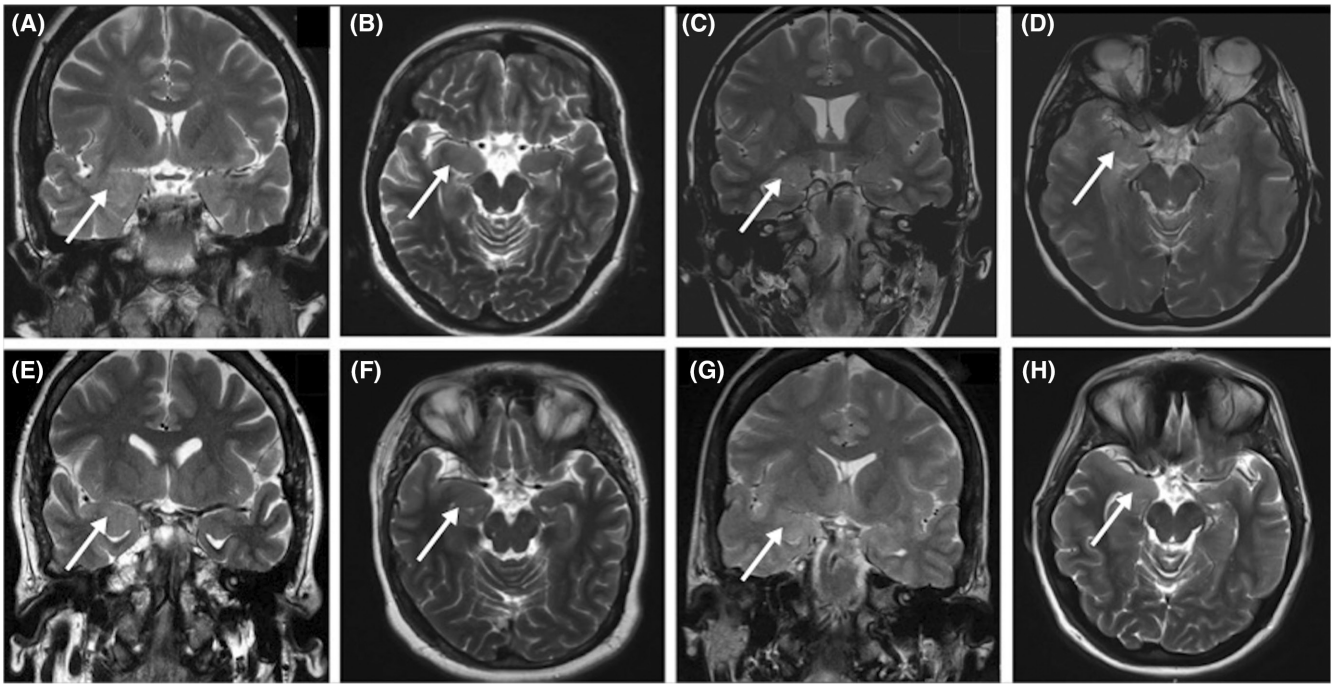

FIGURE 1 Enlarged right amygdala with increased T2 intensity on coronal and axial magnetic resonance imaging (MRI) sections (arrows) for case 7 (A, B), case 3 (C, D), case 20 (E, F), and case 19 (G, H).

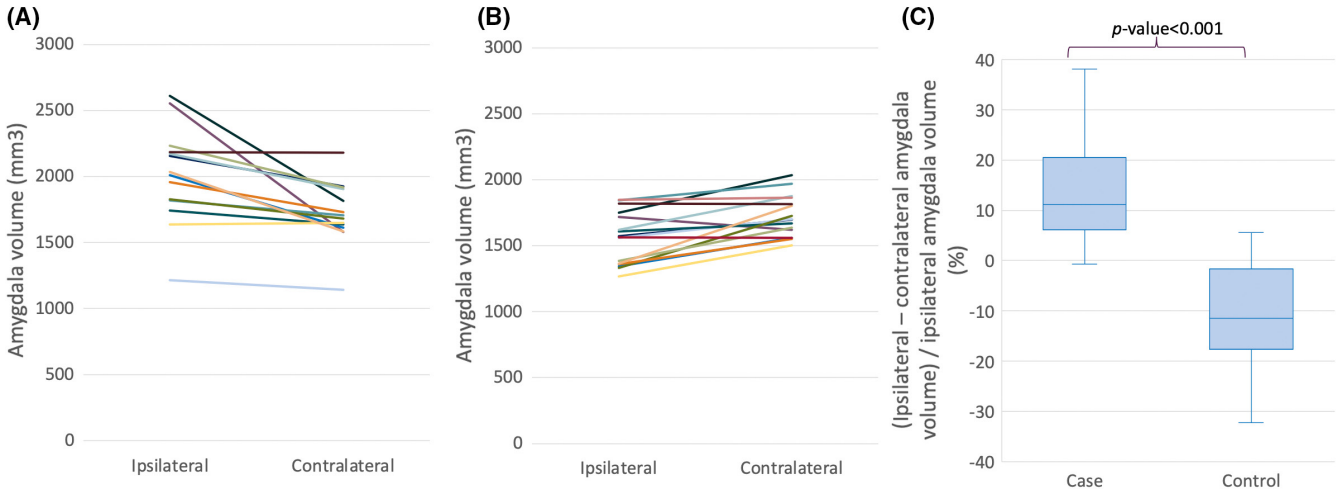

FIGURE 2 (A) A slope graph represents the difference in amygdala volume on the ipsilateral side and amygdala volume on the contralateral side among cases. (B) A slope graph represents the difference in amygdala volume on the ipsilateral side and amygdala volume on the contralateral side among controls. (C) A parallel box-plot illustrates the distribution of percentage difference in amygdala volume on epileptogenic and contralateral sides among cases and controls. The line in the box represents the mean percentage difference, whereas the whiskers indicate the minimum and maximum percentages.

1 patient (5.3%) (Table 2). Histopathology of the resected amygdala was normal in 16 patients (84.2%), whereas 3 patients (15.8%) had reactive gliosis (Figure 3). Notably, there was no histological evidence of inflammation in the examined tissues.

Among controls, the primary histopathological finding was HS in 16 patients (84.2%), normal in 2 patients (10.5%), and FCD in 1 patient (5.3%) (Table 2). Histopathology of the resected amygdala was normal in 17 patients (89.5%), whereas 2 patients (10.5%) had mild reactive gliosis.

There was no correlation between amygdala enlargement on pre-operative MRI and histopathological findings in the resected amygdala ($p = .63$).

3.7 | Isolated amygdala enlargement

Nine cases with amygdala enlargement had no concomitant hippocampal or temporal neocortical pathology on pre-operative MRI; 44.4% were male. The median age at epilepsy

surgery was 37.0 years (IQR 30.0–52.5), whereas the median age of epilepsy onset was 18.0 years (IQR 16.5–34.5). Two cases with isolated amygdala enlargement (22.2%) had antecedent febrile seizures. The median convulsive seizure frequency was 2 (IQR 1–6), whereas the median non-convulsive seizure frequency was 8 (IQR 8–10). Four cases (44.4%) had psychiatric comorbidities on presurgical assessment. Only one case was tested for suspected autoimmune encephalitis and was found to have positive serum glutamic acid decarboxylase (GAD) antibodies (titer >2000 U/mL); the same case had right temporal interictal discharges and occasional independent right frontocentral discharges on EEG.

All cases with isolated amygdala enlargement had normal histopathology of the resected amygdala, except one, who had reactive gliosis (11.1%). Six of the nine cases (66.7%) had favorable seizure outcomes.

4 | DISCUSSION

In this case–control study, we compared the clinical characteristics, post-operative seizure outcomes and histopathological findings between a group of patients who had epilepsy surgery for drug-resistant TLE with amygdala enlargement, and a control group of patients with normal amygdala on pre-operative MRI brain. There were some differences in the clinical and EEG characteristics between cases and controls, which were not statistically significant. Furthermore, we found no significant association between amygdala enlargement and post-surgical seizure outcome or histopathological findings. Thus the presence of amygdala enlargement on pre-operative MRI does not appear to affect the surgical outcome and does not necessarily suggest the presence of an underlying pathological abnormality.

A later age at seizure onset, before the third decade, was reported previously in patients with amygdala enlargement.[24,25] Psychiatric comorbidities have also been reported to be more common in TLE associated with amygdala enlargement, possibly related to the amygdala playing a crucial role in influencing and activating our emotions. The amygdala also regulates emotional behavior and adaptive stress responses to external stimuli.[26,27] Furthermore, increased dysthymia, affective aggression, depression and psychosis have been reported to be associated with amygdala enlargement in patients with TLE.[27–31] Previous studies reported more frequent seizures in patients with TLE and amygdala enlargement with focal impaired awareness seizures more than focal to bilateral tonic–clonic seizures.[13] Psychic aura (e.g., anxiety and anger) and déjà vu were the most frequent auras in patients with amygdala enlargement.[8,12,14,25,32,33] Furthermore, ictal psychosis

TABLE 2 Histopathological findings and surgical outcomes.

Surgical outcomes		
	Cases ($n=19$)	**Controls ($n=19$)**
Favorable		
Engel class I	14 (73.7%)	13 (68.4%)
Unfavorable	5	6
Engel class II	2 (10.5%)	3 (15.8%)
Engel class III	2 (10.5%)	2 (10.5%)
Engel class IV	1 (5.3%)	1 (5.3%)
Histopathological findings		
Hippocampus	Cases ($n=19$)[a] HS (13, 68.4%)[b] Normal (2, 10.5%) FCD (2, 10.5%)[c] Gangliocytoma (1, 5.3%)	Controls ($n=19$) HS (16, 84.2%) Normal (2, 10.5%) Reactive gliosis (1, 5.3%)
Amygdala	Normal (16, 84.2%) Reactive gliosis (3, 15.8%)	Normal (17, 89.5%) Reactive gliosis (2, 10.5%)
Temporal neocortex	Normal (9, 47.4%) FCD (5, 26.3%)[d] Chaslin's sclerosis (4, 21.1%)	Normal (11, 57.9%) Chaslin's sclerosis (7, 36.8%) FCD (1, 5.3%)

Abbreviations: FCD, focal cortical dysplasia; HS, hippocampal sclerosis.

[a]One patient had amygdala lesionectomy.

[b]Ten patients had HS only and three patients had concurrent neocortical FCD (FCD type IIIa).

[c]FCD was confined to the hippocampus only.

[d]Two patients had neocortical FCD only and three had concurrent HS.

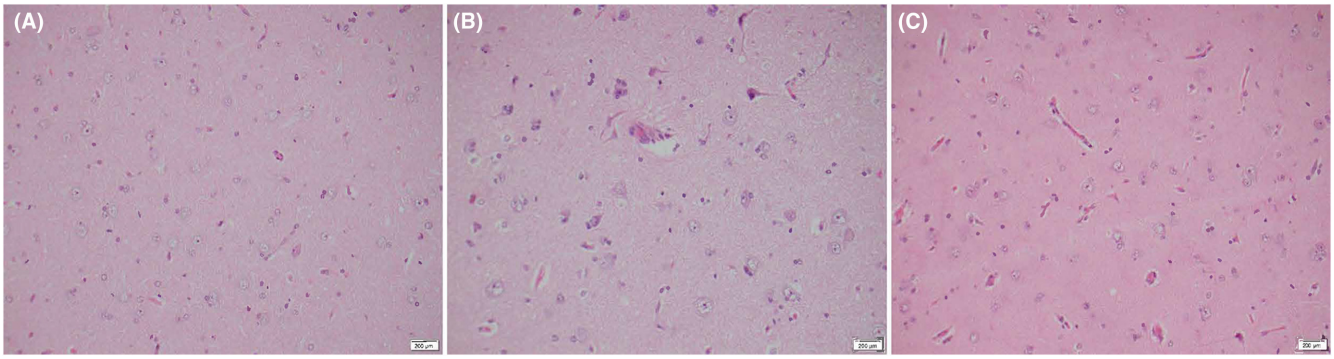

FIGURE 3 (A) Mild reactive gliosis on H&E stain (Case 14). (B, C) Moderate reactive gliosis (Cases 16 and 17).

was reported previously in TLE patients with amygdala enlargement.[31] Bilateral temporal interictal epileptiform discharges were not detected in our cases, which is consistent with most previous studies.[8,10,11,14,25,34,35] Unilateral temporal epileptiform discharges are usually ipsilateral to the side of amygdala enlargement.[8,10,11,14,25,34,35]

The normal histological appearance of the amygdala is composed of irregularly arranged globular, medium-sized neurons. Mixed features of gliosis and dysplasia were the most frequent histopathological findings reported in a recent systematic review of reported cases of TLE with amygdala enlargement.[13] Of interest, amygdala hamartoma-like lesion (AHL) was also recently reported in patients with amygdala enlargement.[16] The histological appearance of AHL was described as an intermediate entity in the spectrum from the normal tissue to FCD and benign tumor such as ganglioglioma, composed of prominent neuronal polymorphisms not typical of dysmorphic neurons observed in FCDs with a back-to-back position of the neurons.[16] AHL was not observed in our cases. Furthermore, amygdala enlargement in TLE related to autoimmune encephalitis had been reported previously.[12,35–37] Autoimmune encephalitis typically occurs in middle-aged patients with TLE, with some patients observed to have a self-limited course.[38–40] More prominent amygdalar volume changes have been demonstrated in the acute stage of voltage-gated potassium channel (VGKC) complex–associated limbic encephalitis compared to GAD-associated limbic encephalitis, reflecting the more severe initial clinical presentation.[37] The likelihood of underlying autoimmune etiology does increase in amygdala enlargement–associated hippocampal swelling and bilateral amygdala enlargement.[12,35,36]

Most of our cases had a normal amygdala histopathology. This discrepancy with previous reported series might be related to the fact that only 86 of the 361 patients (23.8%) reported in the systematic review underwent surgery.[13] Furthermore, 118 of the 361 patients (32.7%) had a decrease in the amygdala volume in subsequent scans, mostly related to a reduction in seizure frequency.[13] Accordingly, the reversible changes in the amygdala volume may suggest a transient reactive process secondary to seizures in the epileptogenic temporal lobe.[8,11]

Engel class I outcomes post-surgery were achieved in 70% of the amygdala enlargement group following ATL-AH, consistent with the existing literature.[13] We could not find an association between amygdala enlargement and seizure outcomes post-surgery, suggesting that detecting an enlarged amygdala on pre-operative MRI does not affect post-operative seizure outcome. The absence of an association between amygdala enlargement and seizure outcomes further supports the likelihood of a transient reactive process accounting for the appearance of amygdala enlargement on MRI.

This study has limitations. First, MRI images were performed using three different machines, two of which were 1.5 T and one was 3 T. Second, in two cases, amygdala volumetry did not demonstrate a significant difference between the ipsilateral and contralateral sides. This inconsistency between volumetric measurements and visual inspection of amygdala enlargement may be attributed to various factors influencing the accuracy of amygdala volumetry, such as the precise definition of the amygdala anatomic landmarks and image quality in terms of resolution, contrast, and slice thickness. Third, a small sample size could not rule out associations that may have a small effect size. In addition, due to the small sample, we could not clarify if the presence of hippocampal pathology could influence the surgical outcome in amygdala enlargement because we could not perform subgroup analysis (amygdala enlargement with hippocampal pathology vs isolated amygdala enlargement). Fourth, except for one patient, the cases were not investigated for a possible underlying autoimmune process (e.g., paraneoplastic and autoimmune antibodies). Fifth, none of the cases had pre-operative invasive EEG monitoring to clarify the potential role of amygdala in the epileptogenic network.

5 | CONCLUSION

Our study revealed no association between amygdala enlargement and surgical outcome in patients with drug-resistant TLE who underwent ATL, and no characteristic histopathological changes associated with the enlarged amygdala. Careful pre-operative evaluation, including potentially invasive EEG monitoring, is warranted in patients with TLE associated with amygdala enlargement if there is no other epileptogenic pathology identified on MRI. Further studies are required to clarify factors affecting the association between amygdala enlargement and surgical outcome and the amygdala's role in the epileptogenic network of patients with TLE and amygdala enlargement.

AUTHOR CONTRIBUTIONS

Lubna Shakhatreh: conceptualization (equal); methodology (equal); data curation (lead); investigation – data collection (lead); formal analysis (lead); writing – original draft (lead); writing – review and editing (equal). **Ben Sinclair:** software (lead); conceptualization (supporting); investigation- data collection (supporting); writing – review and editing (supporting). **Catriona McLean:** conceptualization (supporting); investigation – data collection (supporting); writing – review and editing (supporting). **Elaine Lui:** conceptualization (supporting); investigation – data collection (supporting); writing – review and editing (supporting). **Andrew P. Morokoff:** writing – review and editing (supporting). **James A. King:** writing – review and editing (supporting). **Zhibin Chen:** formal analysis (supporting). **Piero Perucca:** conceptualization (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Terence J. O'Brien:** conceptualization (equal); methodology (equal); supervision (equal); writing – review and editing (equal). **Patrick Kwan:** conceptualization (equal); methodology (equal); supervision (lead); writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

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ETHICS STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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