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Clinical features and surgical outcomes in temporal lobe epilepsy with amygdala enlargement - a single tertiary center study

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Abstract

Objective: To analyze and summarize clinical features and surgical outcomes in temporal lobe epilepsy with amygdala enlargement (TLE-AE) in a single tertiary center. *Methods:* Patients with TLE-AE admitted to the Neurological Disease Center of Peking University International Hospital from January 2016 to September 2022 were continuously collected. The clinical data of TLE-AE patients were retrospectively analyzed. *Results:* A total of 19 patients with TLE-AE were included. The average age at onset was (29.0 ± 14.5) years and all patients had focal impairment awareness seizure (FIAS). Ten (52.6%) patients were in line with drug-resistant epilepsy and 8 cases received surgical treatment. Focal temporal interictal epileptiform discharges on scalp electroencephalography were exclusively present ipsilateral to AE in 15 (78.9%) patients. Stereo-electroencephalography analysis found the ictal onset zone involved not only the enlarged amygdala but also the hippocampus in 2 patients. Two patients who responded well to antiseizure medication exhibited AE remission on follow-up MRI. Histopathology of the amygdala showed focal cortical dysplasia (FCD) in 7 patients and ganglioglioma in 1 patient. The 8 surgical patients were followed up for 13-79 months after operation. Six (75.0%) patients achieved Engel class Ia or I outcome, whereas 2 cases did not fully respond to the surgery (Engel class II).
Conclusions: Patients with TLE-AE had a later age of seizure onset and FIAS was common. The epileptogenic zone in TLE-AE patients may be located in the enlarged amygdala and ipsilateral hippocampus. AE might be a secondary seizure-induced change in a subset of patients with favorable responses to drugs. As for drug-resistant patients, FCD may be the most common pathological change and surgical treatment could be taken into consideration.

Keywords: Amygdala enlargement, temporal lobe epilepsy, electroencephalography, focal cortical dysplasia

INTRODUCTION

Hippocampal sclerosis (HS) is recognized as the most common cause of temporal lobe epilepsy (TLE).[1] However, there is a significant portion of patients with TLE that do not have any lesions on magnetic resonance imaging (MRI), called "non-lesional" or "MRI-negative".[2] Significantly, the concept of amygdala enlargement (AE) has been highlighted in MRI-negative TLE, with a prevalence of AE ranging from 12% to 64%.[3-5] A considerable amount of literature on TLE with AE (TLE-AE) has been reported over the last twenty years, especially in Japan.[5-10] However, it remains unclear whether the enlarged amygdala should be considered an epileptogenic lesion similar to HS and whether there is a specific subtype of TLE. This study was designed to analyze the clinical features and surgical outcomes in TLE-AE patients. As we know, this is the first study to include both the medication and surgery cohorts of TLE-AE patients in China.

METHODS

Subjects

Patients with TLE-AE who were admitted to

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the Neurological Disease Center of Peking University International Hospital from January 2016 to September 2022 were continuously collected. Diagnosis of TLE was made based on semiology, electroencephalography (EEG) and MRI findings. AE was defined as a lesion with unilateral enlargement of the amygdala with or without increased signal intensity on fluid-attenuated inversion recovery and/or T2-weighed images. No patient had a significant past history of hypoxic encephalopathy, cerebral infarction, cerebral hemorrhage, brain trauma, intoxication, and encephalitis. Calcification, cysts, and enhanced lesions on MRI were also excluded. Baseline was defined as the first presentation at our center with a complete work-up including brain MRI, overnight video-EEG monitoring, neuropsychological assessment, and routine serum testing. At baseline, the amygdala volume of TLE-AE patients was compared against 20 sex- and age-matched healthy controls (HCs) without a history of neurological or psychiatric disease. The study was approved by the Medical Ethics Committee of Peking University International Hospital [No. 2021-053(BMR)].

The clinical characteristics including gender, age at onset, duration, seizure semiology, frequency, antiseizure medication (ASM) history, and past history were recorded. Drug-resistant epilepsy was referred to the International League Against Epilepsy (ILAE) criteria[11], and the seizure semiology was based on the latest ILAE consensus.[12]

MRI assessment

Brain MRI was performed in all patients and controls on a 3-Tesla MRI system (Siemens Verio-Dot, Erlangen, Germany), including 3-dimensional T1-weighted magnetization prepared rapid acquisition gradient echo (3D-MPRAGE) sequences. The sequences were listed as follows: repetition time 2300ms, echo time 3.2ms, time interval 900 ms, flip angle 8°, matrix 256 × 256, field of view 240 mm, voxel size 1.0 × 1.0 × 1.0 mm, slice thickness 1 mm, interslice gap 0 mm. Patients were excluded if they had clustered seizures or status epilepticus within 2 weeks prior to the MRI scan to preclude brain damage induced by seizure as far as possible.[13]

Amygdala volume was measured by manually tracing the anatomic borders on the 3D-MPRAGE image using Siemens-Viewing-Tool following a well-established protocol.[14] The volume of amygdala in each slice was calculated by multiplying the size within each trace by the slice thickness and then the total volume of amygdala complex was obtained.

EEG and nuclear imaging

All patients underwent long-term scalp EEG monitoring according to the 10-20 international system. Intracranial EEG was performed in selected cases for further location. Interictal fluorodeoxyglucose positron emission tomography (FDG-PET) or single photon emission computed tomography (SPECT) was performed to assist in localization.

Surgery and prognosis

All the surgical patients underwent standard anterior temporal lobectomy, including the hippocampus, amygdala, and anterior temporal lobe. Pathological diagnosis was made according to the ILAE classification.[15]

Patients were adopted with outpatient, inpatient or telephone visit and the latest follow-up was October 2023. Time from the first seizure to the present study and the postoperative survey duration were at least 1 year respectively. Seizure free was defined as no seizures for 1 year or for a minimum of three times the longest preintervention seizure interval, whichever was longer.[11] The prognosis of surgical patients referred to Engel classification.[16]

Statistical analysis

Statistical analysis was done using SPSS 23.0. Amygdala volume was analyzed between the affected and contralateral side for each patient by paired t-test. The amygdala volume of the affected side in patients was compared with that of the larger side in controls using a t-test. The lateral index (LI) of amygdala [(larger side - smaller side) × 2 / (larger side + smaller side)] was also compared between patients and controls to adjust the difference of individual intracranial volume.[9] Fisher exact test was used for the categorical variables. $P < 0.05$ was considered statistically significant.

RESULTS

Demographic and clinical features

A total of 19 patients with TLE-AE were included. The clinical features of TLE-AE patients are presented in Table 1. There were 8 males and the mean age at onset was 29.0 ± 14.5 years (range

Table 1: Demographic and clinical features of TLE-AE patients

Patient number	sex	Age at onset(yr)	Duration (yr)	Seizure type	FBTCS time	Neuropsychological assessment
1	M	38	18	FIAS, FBTCS	Sleep	
2	F	51	5	FIAS, FBTCS	Sleep	
3	M	24	7	FIAS, FBTCS	Sleep	
4	F	36	5	FIAS, FBTCS	Sleep	Anxiety
5	F	40	2	FIAS, FBTCS	Sleep	Anxiety, memory decline
6	M	59	4	FIAS		Depression
7	M	26	7	FIAS		
8	F	27	7	FIAS, FBTCS	Sleep	Anxiety, memory decline
9	F	33	2	FIAS		Depression, memory decline
10	F	39	2	FIAS, FBTCS	Sleep	Anxiety, memory decline
11	M	34	1	FIAS, FBTCS, SE	Sleep	
12	F	40	4	FIAS, FBTCS	Sleep	Anxiety, depression, memory decline
13	M	21	3	FIAS, FBTCS	Sleep	
14	F	22	1	FIAS		Anxiety, memory decline
15	F	5	3	FIAS		
16	F	1	13	FIAS, FBTCS	Awake	Memory decline
17	M	24	7	FIAS, FBTCS, SE	Sleep	
18	F	20	5	FAS, FIAS, FBTCS	Sleep	Anxiety, depression, memory decline
19	M	12	3	FIAS, FBTCS,		

Table 1 Continued

Patient number	AE on MRI	IEDs on scalp EEG	Follow-up (mth)	Outcome
1	R	R	48	Seizure free
2	R	B	50	Seizure free
3	R	R	72	Seizure free
4	R	R	35	Seizure free
5	R	R	33	Seizure free
6	R	R	51	Seizure free
7	L	L	70	Seizure free
8	R	R	46	Ongoing seizures
9	R	R	29	Seizure free
10	L	L	29	Ongoing seizures
11	R	R	21	Seizure free
12	L	B	78	Engel Ia
13	R	R	64	Engel III
14	L	L	79	Engel Ia
15	R	R	69	Engel Ia
16	L	B	62	Engel Ia
17	L	L	58	Engel I
18	L	L	58	Engel III
19	L	B	13	Engel I

AE, amygdala enlargement; IEDs, interictal epileptiform discharges; EEG, electroencephalography; M, male; F, female; FIAS, focal impairment awareness seizure; FBTCS, focal to bilateral tonic-clonic seizure; FAS, focal aware seizurs; SE, status epilepticus; R, right; L, left; B, bilateral

1-59). The mean duration of epilepsy was 5.2 ± 4.2 years (range 1-18). All patients had focal impairment awareness seizure (FIAS). Fourteen (73.7%) patients had focal to bilateral tonic-clonic seizure (FBTCS), which often happened during sleep in 12 patients. Nine (47.4%) patients were complicated with anxiety or depression disorder. Eight (42.1%) patients showed cognitive impairment based on the Montreal Cognitive Assessment. None had a history of febrile convulsions, and 2 patients (Cases 5 and12) had a family history of epilepsy. Seven patients (Cases 1, 2, 9, 11, 14, 15, 17) underwent lumbar puncture with negative paraneoplastic and autoimmune encephalitis antibodies in both blood and cerebrospinal fluid. Antibodies against Titin, Recoverin, PKCγ, GAD65, Zic4, Tr, SOX1, Ma1, Ma2, Amphiphysin, CV2, Hu, Yo, Ri, NMDAR, AMPA1R, AMPA2R, LGI-1, $GABA_AR$, $GABA_BR$, CASPR2, DPPX, IgLON5, mGluR5, GlyRα1, D2R, and Neurexin3α were test.

At baseline, 8 patients (Cases 12-19) were labeled as drug-resistant according to the ILAE definition and received surgical treatment. At the latest follow-up, another 2 (Cases 8,10) patients were in line with refractory epilepsy. In total, 10 (52.6%) patients were drug-resistant.

Brain MRI and amygdala volume at baseline

Eight (42.1%) patients with left AE and 11 with right AE were present on MRI by vision (Figure 1, Table 1). In TLE-AE, the mean amygdala volume on the affected side was 1898.6 ± 405.2 mm^3 (range 1121-2516), and the mean volume on the contralateral side was 1113.6 ± 176.7 mm^3 (range 824-1463). The amygdala volume of the affected side was larger than that of the contralateral side at both individual level and group level ($p < 0.01$, paired t-test).

In HCs, the mean amygdala volume on the larger side was 1178.5 ± 136.0 mm^3 (range 1004-1493) and the mean volume on the smaller side of was 1012.5 ± 121.5 mm^3 (range 839-1330). There was significant difference between the two sides ($p < 0.01$, paired t test). When they were grouped into left and right sides, the amygdala volume ranged from 839 mm^3 to 1493 mm^3 on the left side, with a mean volume of 1124.5 ± 139.4 mm^3, and the right side ranged from 893 mm^3 to 1416 mm^3, with a mean volume of 1066.6 ± 163.0 mm^3. There was no significant difference between the two sides ($p > 0.05$, paired t-test).

The TLE-AE and HCs were matched in sex ($p > 0.05$, Fisher exact test) and age at scan ($p > 0.05$, t test). The amygdala volume of the affected side in TLE-AE was significantly greater than that of the larger side in HCs ($p < 0.01$, t-test), while there was no significant difference between the amygdala volume of the contralateral side in TLE-AE and that of the smaller side in HCs ($p > 0.05$, t test). The LI of amygdala in TLE-AE was significantly higher than that in HCs ($p < 0.05$, t-test) (Table 2).

EEG and nuclear imaging

Focal temporal interictal epileptiform discharges (IEDs) on scalp EEG were exclusively present ipsilateral to AE in 15 (78.9%) patients and 4

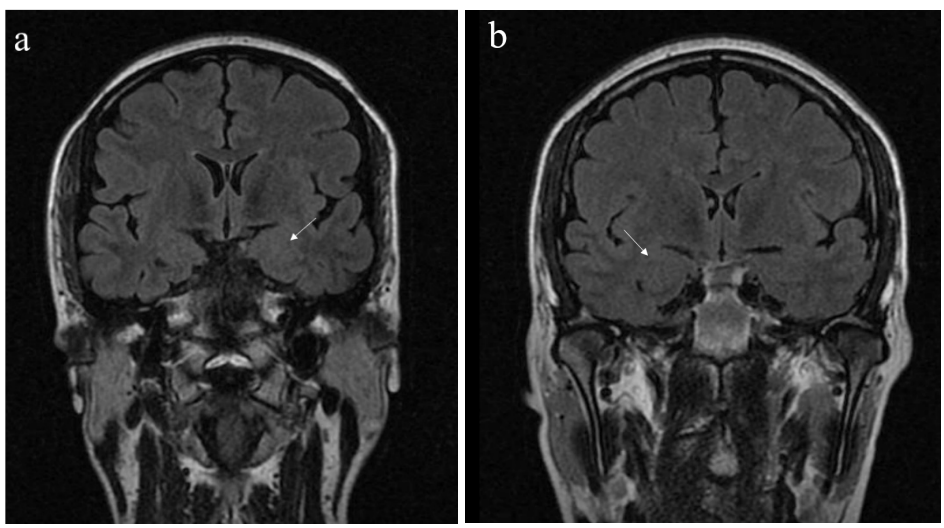

Figure 1. Coronal Flair MRI images in TLE-AE patients. (a) The arrow indicates a representative image of left AE in Case 12. (b) The arrow indicates a representative image of right AE in Case 5.

Table 2: Comparison of amygdala volume between two groups

	TLE-AE (n = 19)	HC (n = 20)	*p*
Male/female	8/11	13/7	0.748
Age at scan (yr)	34.2 ± 14.7	36.4 ± 10.0	0.578
Affected side (mm^3)	1898.6 ± 405.2	Larger side (mm3) 1178.5 ± 136.0	0.000
Contralateral side (mm^3)	1113.6 ± 176.7	Smaller side (mm3) 1012.5 ± 121.5	0.062
LI of amygdala	0.506 ± 0.175	0.152 ± 0.069	0.000

TLE-AE, temporal lobe epilepsy with amygdala enlargement; HC, healthy controls; LI, lateral index

demonstrated bilateral temporal IEDs (Table 1). Eight surgical patients had ictal EEG recordings with temporal onset ipsilateral to AE in 6 patients and with bilateral independent temporal onsets in two (Case 16, 19). Four patients had intracranial EEG monitoring, three with depth electrodes (Cases 13, 18, 19) and one with subdural electrodes (Case 16). Long-term EEG monitoring was initiated and continued until at least three habitual seizures were captured. The average recording time was 9.5 days (range 5 to 14 days). IEDs were demonstrated on both the amygdala and hippocampus in Case 13, 18, 19, and stereo-electroencephalography (SEEG) found the ictal onset zone involved not only the enlarged amygdala but also the hippocampus in case 13 and 18 (Figure 2). In case 19, the ictal

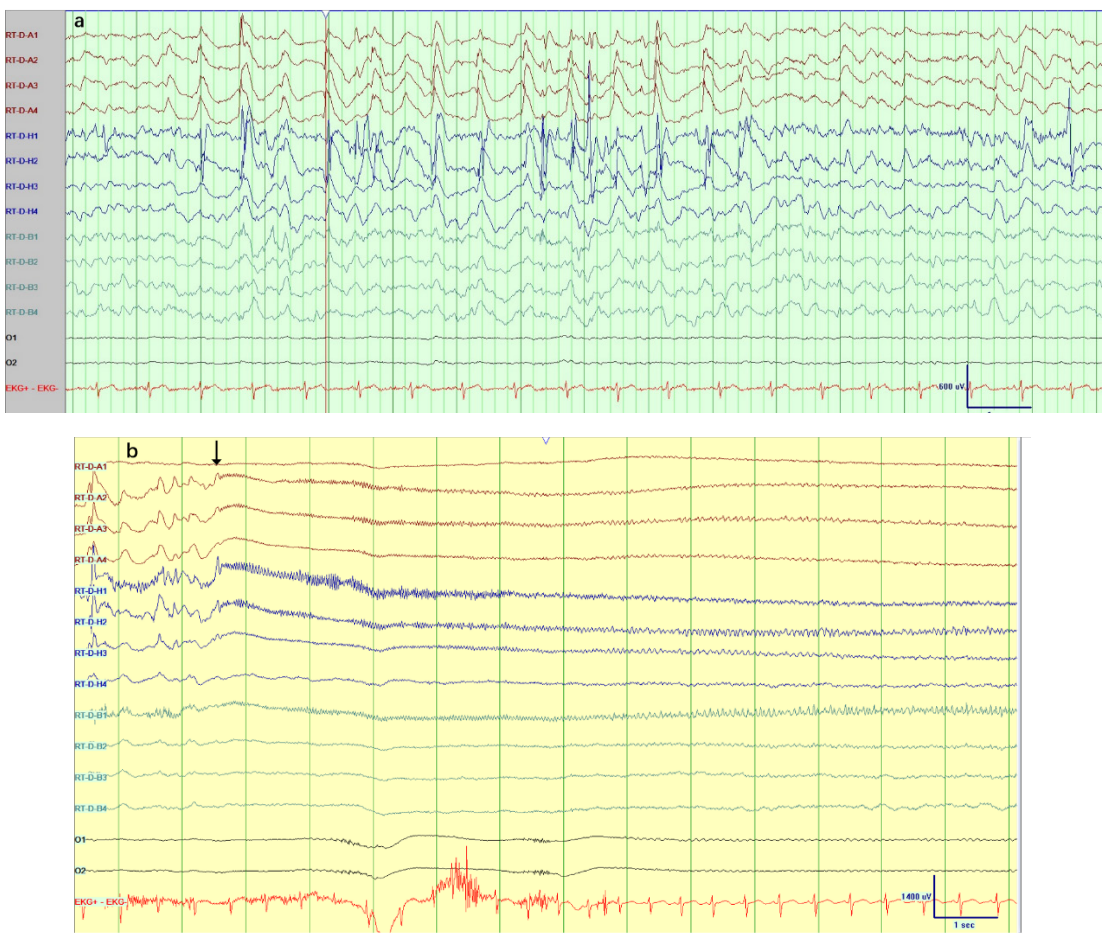

Figure 2. Intracranial SEEG recording in Case 13. (a) Interictal epileptiform discharges in deep contacts of right amygdala and hippocampus. (b) Ictal onset (black arrow) involves deep contacts of amygdala (A), head of hippocampus (H) and body of hippocampus (B).

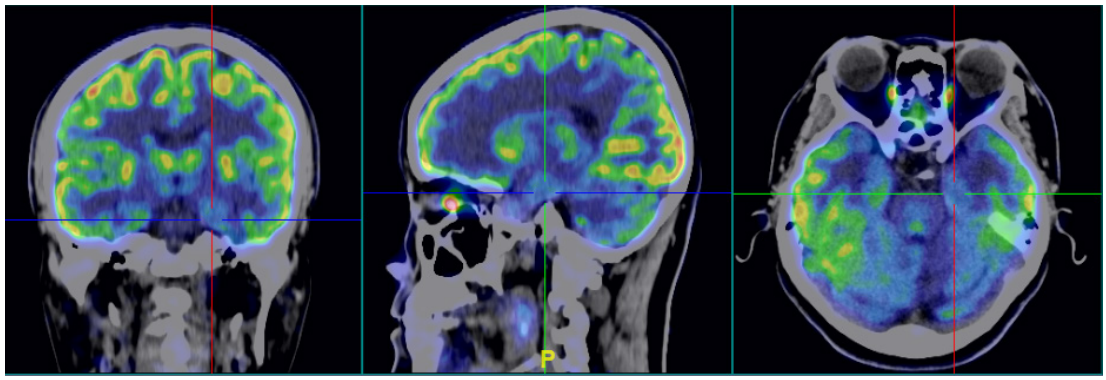

Figure 3. Interictal FDG-PET scan in case 12. The patient shows left AE on MRI and FDG-PET demonstrates ipsilateral hypometabolism in the enlarged amygdala and mesial temporal lobe.

onset zone was located in the head and body of the hippocampus, ipsilateral to AE. The ictal onset zone was located in the anterior temporal lobe ipsilateral to AE in Case 16. The intracranial EEG seizure onset patterns were identified according to Lagarde's research[17]. Three patients (Cases 13, 18, 19) presented with low voltage fast activity (LVFA) pattern and one (Case 16) with preictal spiking followed by LVFA pattern. Intraoperative electrocorticography was performed on temporal lobe before resection and IEDs was present in anterior and middle temporal lobe in all of the surgical patients.

Five patients (Cases 12, 13, 14, 17, 18) finished interictal FDG-PET with hypometabolism in the temporal lobe ipsilateral to AE in 4 patients (Cases 12, 14, 17, 18). Illustrated case was demonstrated in Figure 3. Interictal SPECT was performed in 11 patients (Cases 1, 2, 6, 7, 9, 13, 14, 16-19), with hypoperfusion in the temporal lobe ipsilateral to AE in 7 patients (Cases 1, 2, 9, 14, 17-19) and bilateral temporal lobe hypoperfusion in one (Case 16).

Pathological changes

Histopathology (Figure 4) showed FCD in the amygdala and anterior temporal lobe in 7 patients (Cases 12-14,16-19) along with HS in 3 patients (Cases 12, 16, 17). One patient (Case 15) demonstrated ganglioglioma in AE with FCD in the anterior temporal lobe.

Follow-up and prognosis

Four patients performed longitudinal brain MRI in our center and illustrative cases are demonstrated in Figure 5. Two patients (Cases 1 and 4) who responded well to ASM showed AE remission both on visual inspection and volumetric measurement. In case 1, the volume of the right enlarged amygdala decreased from 1761 mm^3 at baseline to 1287 mm^3 after a follow-up of 16 months. In case 4, the volume of the right amygdala decreased from 2516 mm^3 at baseline to 1857 mm^3 after a follow-up of 17 months. Two drug-resistant patients (Cases 8, 10) showed stable AE on visual

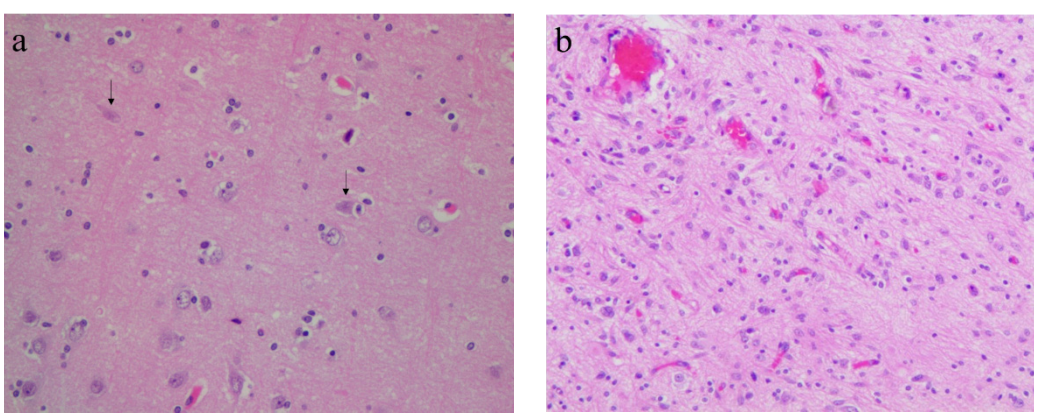

Figure 4. Histopathology of amygdala specimens. (a) Balloon neurons (arrow) indicate FCD IIb in Case 13 (H-E staining, ×400). (B) Ganglioglioma in Case 15 (H-E staining, ×200).

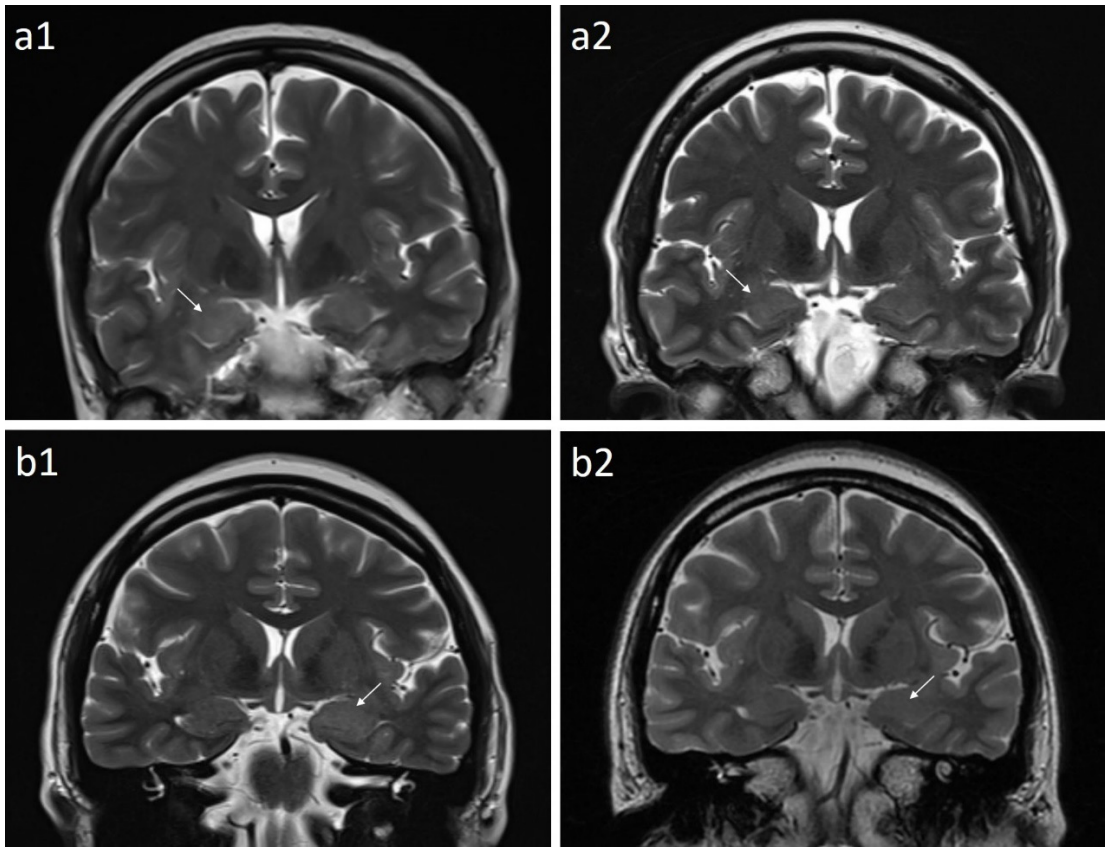

Figure 5. Coronal T2-weighted MRI images of illustrated cases with remittent (a1, a2) and stable (b1, b2) AE. (a) Case 4 was treated with levetiracetam and lacosamide. MRI shows right AE at baseline (a1), which is gradually resolved after a follow-up of 17 months (a2). (b) Case 10 was treated with levetiracetam and perampanel. MRI shows left AE at baseline (b1), which appears to be unchanged after a follow-up of 10 months (b2).

inspection. The 8 surgical patients were followed up for 60.1 ± 20.7 months (range 13-79) after operation. Six (75.0%) patients achieved Engel class Ia or I outcome, whereas 2 cases did not fully respond to the surgery (Table 1).

DISCUSSION

In 1999, Tebartz *et al*.[18] first reported AE as a special sign on MRI in patients with TLE and dysthymia. Subsequently, clinical studies of TLE-AE have gradually increased, and a concept linking AE with epileptogenesis has emerged.

The onset age of TLE-AE was often older than that of TLE with HS (TLE-HS) and TLE without AE, with an average of 16-44 years.[3-6,8-10,13,19-25] FIAS was the most common seizure type, ranging between 62%-100%.[5-7,9-10,13,19-20,22,24,26] The incidence of FBTCS was 7%-82%.[3-10,13,19-20,22-24,26] In this study, thirteen (72.2%) patients developed FBTCS, especially with a high incidence at night. To our knowledge, only Lv *et al*.[24] have reported similar finding and there was no plausible explanation currently for it. Lv *et al*.[24] found that 90% of patients were accompanied by anxiety or depression. In this study, half of the patients presented with anxiety or depression, suggesting more attention should be paid to epilepsy comorbidities in TLE-AE. By contrast with TLE-HS, the history of febrile convulsion[3-6,8-9,13,19,21,23-24,26] and family history[4,13,23,26] in TLE-AE are rare, suggesting that there may be a relatively specific pathogenesis in TLE-AE.

At present, there are three main methods for quantitative determination of amygdala volume, including manual outline of amygdala, voxel-based morphological studies, and measurement software such as Free-surfer.[27-28] In this study, visual inspection was used to determine the AE side firstly, and then the amygdala volume was calculated by manually tracing the amygdale

complex. It was found that the quantitative measurement confirmed the amygdala of the affected side was larger than the contralateral side, which was completely consistent with the visual interpretation. The amygdala volume on the affected side in TLE-AE patients ranges from 1162.4 to 3179 mm^3, and the amygdala volume in normal controls ranges from 783 to 2046 mm^3 in literatures.[27] Due to the complex anatomical boundary and different research methods, the amygdala volume measurements are highly variable.[27] The volume of amygdala in this study agreed with literature approximately. The LI of the amygdala in TLE-AE was significantly higher than in controls, which is in keeping with previous reports.[9,25]

The role of AE in epileptogenesis remains somewhat controversial. The majority of studies have shown high IEDs concordance to AE ranging between 62%-100%[7,9,13,20-21,24] along with ictal onset ipsilateral to AE in 83% to 100%.[13,21] However, there are contrasting studies that demonstrated ictal onset contralateral to AE in up to 45%-52%.[4,29] Our study also provides evidence for epileptogenicity in AE with notable concordance of IEDs and ictal onset to the side of AE. Suzuki *et al*.[10] first demonstrated the seizure onset zone involved both the enlarged amygdala and hippocampus in 87.5% of TLE-AE using intracranial EEG. We found ictal onset signals simultaneously in the enlarged amygdala and hippocampus in 2 patients using SEEG. Laboratory animal studies demonstrated that the amygdala tended to acquire the kindling phenomenon more easily than hippocampus, and electrical discharge from the amygdala was usually synchronised with that from hippocampus.[30,31] It was suggested that the amygdala was one of the core epileptogenic structures within the distributed epileptogenic network in drug-resistant TLE-AE.[32] Intracranial EEG features of TLE-AE are seldom discussed. Our study demonstrated two different seizure onset patterns owing to the limited cases. LVFA was found in all etiologies of epilepsy but with an overrepresentation in malformation of cortical development[17], which was consistent with the pathological findings in our study.

FDG-PET has demonstrated high sensitivity in detecting the epileptic focus even in patients with MRI-negative TLE.[33,34] Studies that included FDG-PET in presurgical evaluation reported hypometabolism in mesial temporal lobe including the amygdala ipsilateral to AE in 62%–100%.[27] Interictal SPECT was found to be concordant to FDG-PET results in 77.8% cases.[7]

The pathomechanism underlying AE is still controversial. Autoimmune and neurodevelopmental abnormalities are the two mainstream hypotheses at present.[22,25,27] Malter *et al*.[21] suspected that even autoantibody-negative TLE-AE could have an autoimmune etiology based on the finding that seizure controlled and AE improved after immunotherapy. Another finding pointed out by Peedicail *et al*.[13] and Malter *et al*.[21] that may argue for an autoimmune cause was bilateral AE or hippocampal swelling involvement. However, Na *et al*.[23] and Lv *et al*.[24] found seizure was also well controlled and AE was reversible after receiving ASM alone. Two patients who responded well to ASM exhibited AE remission in our study. The reversible change in amygdala indicates that AE may be a secondary phenomenon rather than actual neuronal damage.[10,24] However, not all patients in our study received autoantibody testing. Nevertheless, none showed ictal onset contralateral to AE or bilateral AE which could suggest autoimmune etiology.[35]

Chakravarty *et al*.[27] reported a mixed feature of gliosis with dysplasia was the most common histological finding noted in 29% of amygdala specimens, followed by isolated gliosis in eighteen (20.9%) and dysplasia in sixteen (18.6%). About 7% revealed a tumor. However, the pathological findings from refractory patients cannot be directly extrapolated to cases that respond well to ASM.[23] Besides, Capizzano *et al*.[22] found apart from the amygdala, the adjacent anterior hippocampus, temporal uncus, temporal pole, and lateral temporal cortex were also involved with dysplasia, and 2 patients had pathologic HS. Our study demonstrated similar findings. The pathological changes support the concept that AE is the tip of iceberg of a more extensive abnormality in temporal lobe.[22] AE should be regarded as a marker of the extensive epileptogenic network rather than a specific epileptogenic lesion.[32]

In terms of prognosis, 67%-91% of TLE-AE responded well to ASM[7,9,23-24], in comparison with drug-resistant epilepsy ranging from 43%-62%.[8,13,21] Resolution of AE and rapid volume reduction rate were predictors of favorable prognosis.[13,23] Surgical treatment was recommended for drug-refractory TLE-AE and anterior temporal lobectomy was the usual surgical procedure. It was reported that 69.8% of surgical TLE-AE had Engel class I outcome[5,10,19,22,25], being similar to our study.

The limitation of our study are, firstly, this is a retrospective study based on a relatively small patient group in a single center, comprising

all known limitations of such a study setting. Secondly, the average duration of epilepsy at baseline was relatively long and some patients had received ASM in other hospitals. This might represent a relevant selection bias. Thirdly, not all of the patients received autoantibody testing, so it was not able to exclude paraneoplastic syndrome and autoimmune encephalitis completely. Finally, longitudinal MRI was not available in all patients. The detailed pathophysiological mechanism of AE deserves further in-depth study.

In conclusion, this study found that TLE-AE patients had a later age of seizure onset and the frequency of FIAS was pretty common. The epileptogenic zone may be located in the enlarged amygdala and ipsilateral hippocampus. AE might be a secondary seizure-induced change in a subset of patients with favorable responses to drugs. As for drug-refractory TLE-AE, FCD may be the most common pathological change, and surgical treatment could be taken into consideration.

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DISCLOSURE

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Conflict of interest: None

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