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Long term sequelae of amygdala enlargement in temporal lobe epilepsy

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ABSTRACT

Purpose: Amygdala enlargement (AE) has been reported in drug resistant lesional and non-lesional temporal lobe epilepsy (TLE). Its contribution to development of intractability of epilepsy is at best uncertain. Our aim was to study the natural course of AE in a heterogenous group of TLE patients with follow-up imaging and clinical outcomes.

Methods: A prospective observational study in patients with TLE with imaging features of AE recruited from epilepsy clinics between 1994 and 2018. Demographic data, details of epilepsy syndrome, outcomes and follow up neuroimaging were extracted.

Results: Forty-two patients were recruited including 19 males (45 %). Mean age at onset of epilepsy was 30.6 years and mean duration of epilepsy was 19.9 years. On MRI, 33 patients had isolated unilateral AE and eleven had AE with hippocampal enlargement (HE). Twenty (48 %) underwent temporal resections with most common histopathology being amygdalar gliosis (40 %). Engel Class IA outcome at last follow up (mean, 10 years) was 60 %.

Thirty-four patients had neuroimaging follow up of at least 1 year (mean, 5 years). AE resolved in 6, persisted in 25, evolved into bilateral HS in 1, bilateral mesial temporal atrophy in 1 and ipsilateral mesial temporal atrophy in 1. Resolution of AE was associated with better seizure free outcomes ($p = 0.013$).

Conclusions: TLE with AE is associated with favourable prognosis yet not benign. Over 50 % were drug resistant and surgical outcomes were similar to mTLE. Resolution of AE on follow up neuroimaging was associated with better seizure free outcomes.

1. Introduction

Mesial temporal lobe epilepsy (mTLE) is major contributor to the group of drug resistant epilepsies and is one of the leading indications for epilepsy surgery, the most common pathology being hippocampal sclerosis (HS) [1]. There is a significant group of patients with mTLE that do not have any lesions on MRI, called “non-lesional” or “MRI-negative [2]. These patients pose a challenge for treatment in terms of difficult presurgical work-up, frequently warranting intracranial EEG recordings. There is evidence that non-lesional patients fare worse in surgical outcomes in general as compared to lesional ones [3]. Interestingly, there is accumulating evidence that MRI-negative epilepsies are not necessarily non-lesional [4].

The amygdala, which is part of the limbic system, is known to be part of the epileptogenic network of patients with mTLE [5]. Intracranial EEG recordings have revealed interictal epileptiform discharges (IEDs) arising from the amygdala [6]. Structural abnormalities of the amygdala may be difficult to detect by conventional MR

Abbreviations: AE, amygdala enlargement; AED, antiepileptic drug; AH, amygdalohippocampectomy; ATL, anterior temporal lobectomy; CSF, cerebrospinal fluid; FCD, focal cortical dysplasia; HE, hippocampal enlargement; HS, hippocampal sclerosis; IED, interictal epileptiform discharge; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; MTLE, mesial temporal lobe epilepsy; TLE, temporal lobe epilepsy

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techniques [7], and thus may contribute to the so called non-lesional temporal lobe epilepsy (TLE-NL). Imaging studies of TLE-NL patients have identified amygdala enlargement (AE) as an increase in grey matter and amygdalar volume in 12 % of patients [8]. The same authors reported similar proportion (14 %) of AE in patients with mTLE and HS [9].

While the role of the amygdala is functionally defined and evidence of epileptogenicity in the amygdala exists, the significance of AE remains undefined. It has been hypothesized that AE represents a subtype of TLE without HS [10]. However, AE has also been reported in idiopathic generalised epilepsy and healthy controls at similar rates of 5.9 % and 6.4 % respectively raising questions whether it is a non-specific finding despite its higher occurrence in TLE-NL [11].

Most studies that have evaluated AE in TLE are retrospective cross-sectional studies comprising of a refractory presurgical cohort [12]. There is limited data on the clinical features, surgical outcomes, and pathological characteristics in patients with TLE with AE [12,13] and few on the long term surgical outcomes [14]. In this single centre study, we identified a heterogenous group with TLE with AE and report on their clinical, electroencephalographic, follow-up imaging and histopathological findings in operated cases in an attempt to study the natural course of this entity.

2. Methods

The study design was a prospective observational study comprising of TLE patients attending Epilepsy Clinics at the Calgary Epilepsy Programme. Informed consent for data utilization for research purposes was obtained from all patients and the study was approved by the Research Ethics Board. Patients with features of TLE clinically and MRI findings of AE (see criteria below) were prospectively recruited and followed. Diagnosis of TLE was made based on semiology, EEG data and MRI findings. Patients underwent detailed assessment, a pre-structured clinical proforma was filled, noting demographic details, epilepsy characteristics including age at onset, duration, frequency, seizure semiology, anti-epileptic drugs (AED) history, history of antecedents along with relevant medical and surgical history and detailed physical and neurological examination. Work-up of the epilepsy syndrome was carried out according to our centre's protocol, including routine and sleep deprived EEGs and MRI. Patients were prescribed AEDs according to the treating physician's discretion. Long term video-electroencephalography (VEEG) monitoring as part of presurgical work-up was done for all drug resistant cases. Further evaluation with nuclear imaging studies was done if required as per the discretion of the attending physician. Surgical candidacy was ascertained at the epilepsy surgical conference and surgeries were performed as per consensus. Histopathological data was available for all resected specimens. Clinical follow up data was retrieved from patient files.

2.1. MRI assessment

As part of the routine interpretation of epilepsy MR scans, we relied on the visual inspection by our neuroradiologist (J.S) to determine whether lateralized AE was present. AE was identified as enlargement of amygdala with or without signal change on fluid attenuated inversion recovery (FLAIR) or T2-weighted sequences. In some cases, the AE was associated with subtle uniform decreased T1-weighted signal intensity, and increased T2-weighted and fluid attenuated inversion recovery (FLAIR) signal intensity that aided in its detection. Patients with suspicion of described lesions with cystic changes, calcifications or microhemorrhages, contrast enhancement, or tumour-like characteristics were excluded as per the discretion of a board-certified neuroradiologist (JS) with > 15 years of experience in epilepsy imaging. Patients who had clustering of seizures or status epilepticus within the two weeks prior to MR imaging were excluded in order to eliminate the possibility of peri-ictal imaging changes.

All patients underwent imaging using a conventional high-resolution epilepsy MRI protocol, although the MR vendors and specific parameters have varied during the 24 years of this study. However, our current 1.5 T and 3 T epilepsy MR protocols include axial 3-mm thick TSE T2 and FLAIR, axial 3-mm thick T2* GRE or 1-mm thick SWI, sagittal 1-mm thick 3D FLAIR with isotropic multiplanar reformats, axial 1-mm T1 MP-RAGE or FSPGR with isotropic multiplanar reformats, axial 3-mm DWI (b = 0 and 1000 mm/s^2, and oblique coronal 3-mm thick FLAIR and TSE T2-weighted images orthogonal to the long axis of the hippocampus. Magnetic resonance spectroscopy (MRS) was performed in a subset of cases using single voxel positioned over each amygdala and a short echo time (TE 30/35) was sampled.

2.2. Statistics

Statistical analyses was done using SPSS 23.0. For statistical comparisons, Fischer's exact test was used. A p-value < 0.05 was considered significant. For univariate analysis of continuous variables, analysis of variance (ANOVA) was used.

3. Results

3.1. Baseline demographic, clinical and imaging characteristics

We identified 42 patients with TLE with evidence of AE with or without HE on MRI brain [Table 1]. They included 23 females (55 %) with mean age at onset of epilepsy being 30.6 years (SD 17.6; range 0.5–72). Mean duration of epilepsy was 19.9 years (SD 9.5, range 4–40). Twenty- three had left AE and 19 had right AE. Eleven had additional HE (6 left, 5 right) [Fig. 1]. All AE were unilateral and the associated HE was ipsilateral. Thirty-four (81 %) had MRI follow up of at least one year (average,5 years; SD 3; range 1–11) [Table 2,3]. MR Spectroscopy (MRS) was available for four patients (Patients 15, 19, 24, 25) and showed lateralized increase in myoinositol (mI) peak (Fig. 2).

Twenty-five patients had focal aware seizures (FAS), 34 had focal impaired awareness seizures (FIAS) and 31 had bilateral tonic clonic seizures (BTCS). Twenty-seven patients had ictal onset with symptoms: deja vu [8], epigastric sensation [4], fear [3], vague cephalic sensation [3], olfactory hallucination [3], nausea [2], metallic taste [2] and autonomic [2]. Five (12 %) had antecedents for epilepsy; but none had febrile convulsions.

Focal temporal IEDs ipsilateral to side of AE exclusively were present in 26 patients and none had exclusive contralateral temporal IEDs. Five patients demonstrated bilateral temporal IEDs. Nine did not show IEDs and 2 showed non-specific abnormalities including diffuse and focal slowing. Twenty-seven patients (64 %) had drug refractory epilepsy and underwent presurgical evaluation. Twenty six patients had ictal recordings with 22 having ipsilateral temporal onset and 4 with bilateral independent temporal onsets. None had ictal onset from temporal lobe contralateral to AE. Three patients (Patients 26, 27, 40) had intracranial monitoring; two with depth electrodes (Patients 26, 27) with implantation involving amygdala and one with subdural grids (Patient 40). Both patients with coverage of amygdala had active IEDs and one had involvement of amygdala at ictal onset along with the hippocampus (Patient 27) [Fig. 3]. Both underwent surgical resection (Patient 26, left ATL; Patient 27, left SAH) with Engel I outcomes at last follow up. Histopathology showed amygdalar gliosis (Patient 27) and normal amygdala (Patient 26) respectively.

^{18} F Fluorodeoxyglucose positron emission tomography (FDG-PET) CT was performed for 7 patients with hypometabolism in the temporal lobe ipsilateral to AE. Three patients (Patients 34, 35, 37) in our series underwent ISSPECT with ipsilateral temporal hyperperfusion and additional contralateral posterior parietal hyperperfusion in one patient (Patient 37). Two patients (Patients 34, 35) underwent anterior temporal lobectomy (ATL) and are seizure free.

Table 1
Clinical and demographic features.

No	Sex	Age at Onset (yr)	Duration Of Epilepsy (yr)	Risk factors	Seizure types	Seizure onset	Interictal EEG	Ictal EEG	Ongoing seizures	AEDs no
1	F	0.5	40	Family history, SE	FAS, FIAS, BTCS	epigastric sensation	bitemporal spikes	bitemporal	yes	3
2	M	42	16	none	FAS	déjà vu	left temporal spikes	none	no	0
3	F	10	38	none	FAS, FIAS, BTCS	none	normal	none	no	0
4	F	30	18	none	FAS, FIAS, BTCS	nausea	bitemporal spikes	bitemporal	yes	1
5	M	50	27	none	FAS, FIAS	cephalic sensation	right temporal spikes	right temporal	yes	2
6	M	15	31	none	FAS,FIAS BTCS	Epigastric sensation	left temporal spikes	left temporal	no	0
7	F	37	19	none	FAS, BTCS	metallic taste	right temporal slowing	none	yes	1
8	F	34	22	none	FAS,BTCS	none	bitemporal slowing	none	no	0
9	F	30	29	none	FAS,FIAS BTCS	déjà vu	left temporal spikes	left temporal	yes	1
10	M	29	19	none	FIAS,BTCS	none	right temporal slowing	none	no	1
11	F	72	15	none	FIAS	none	right temporal spikes	none	no	1
12	F	50	17	none	FIAS,BTCS	nausea	right temporal spikes	right temporal	no	0
13	M	12	40	N/A	FAS, FIAS, BTCS	None	right temporal spikes	right temporal	no	0
14	F	65	17	none	FIAS, BTCS	None	left temporal slowing	left temporal	no	1
15	M	55	13	none	BTCS	None	right temporal spikes	none	yes	2
16	F	10	24	none	FAS, FIAS, BTCS	déjà vu	right temporal spikes	right temporal	no	0
17	M	23	30	unknown	FIAS, BTCS	anxiety	right temporal spikes	right temporal	yes	1
18	F	29	14	head injury	FIAS, BTCS	sweating	right temporal spikes	right temporal	yes	2
19	M	46	23	none	FAS, BTCS	epigastric sensation	right temporal	none	no	1
20	M	26	16	unknown	FIAS	None	right temporal spikes	none	no	0
21	F	45	14	unknown	FAS	None	normal	none	no	1
22	F	8	21	none	FAS	olfactory hallucination	normal	none	yes	1
23	M	2	39	unknown	FAS, FIAS	None	left temporal slowing	none	no	1
24	F	31	14	unknown	BTCS	None	left temporal spikes	none	no	0
25	F	26	20	unknown	FAS, FIAS	None	right temporal spikes	none	no	1
26	M	49	13	none	FAS, FIAS	olfactory hallucination	left temporal spikes	left temporal	no	1
27	F	37	11	none	FIAS, BTCS	epigastric sensation	left temporal spikes	left temporal	no	2
28	F	14	14	none	FAS, FIAS, BTCS	None	left temporal spikes	none	no	1
29	F	25	19	none	FAS, FIAS, BTCS	fear	right temporal spikes	right temporal	no	1
30	F	21	8	none	FAS, FIAS	déjà vu	left temporal spikes	none	yes	2
31	M	14	39	none	FIAS, FAS, BTCS	déjà vu	left temporal spikes	left temporal	yes	3
32	M	60	10	none	FIAS, BTCS	None	right temporal spikes	right temporal	yes	2
33	M	20	15	none	FIAS, BTCS	déjà vu	right temporal spikes	right temporal	no	2
34	M	28	18	family history	FIAS, BTCS	déjà vu	right temporal spikes	right temporal	yes	2
35	F	41	17	none	FIAS, BTCS	déjà vu	right temporal slowing and spikes	right temporal	no	2
36	F	62	5	none	FIAS	none	left temporal spikes	left temporal	yes	1
37	F	35	11	none	FAS, FIAS, BTCS	warmth	bitemporal spikes	Bilateral temporal	yes	1
38	M	6	33	family history, birth insult	FAS, FIAS BTCS	fear	left temporal spikes	left temporal	yes	2
39	M	23	21	none	FIAS, BTCS	Light headedness	none	left temporal	yes	2
40	F	28	12	status epilepticus	FAS, FIAS, BTCS	Chemical smell	bilateral temporal spikes	bilateral temporal	yes	3
41	M	16	7	none	FIAS, BTCS	Cephalic sensation	right temporal spikes	right temporal	yes	3
42	M	28	8	none	FAS, FIAS BTCS	metallic taste	bilateral temporal spikes	right temporal	yes	2

Abbreviations: AED, anti-epileptic medications; BTCS, bilateral tonic clonic seizures; FAS, focal aware seizures; FIAS, focal impaired awareness seizures; N/A, not available.

3.2. Outcomes

AE persisted in 25 (73 %), resolved in 6 (18 %) [Fig. 2] evolved into bilateral HS in 1, bilateral mesial temporal atrophy in 1 and ipsilateral mesial temporal atrophy in 1 [Table 2 and 3]. Patients with resolution of AE had better seizure free outcomes compared to those with stable MRI findings at last clinical follow up. Five (83 %) of 6 with resolution were seizure free compared to 6 (24 %) of 25 with persistent AE ($p = 0.013$)

3.3. Surgery and post-surgical follow up

Twenty-one patients were considered for epilepsy surgery of which 20 (48 %) underwent epilepsy surgery and 1 declined. Twelve underwent ATL and 8 underwent selective amygdalohippocampectomies (AH). Histopathology was available for all surgical specimens and included amygdalar gliosis in 8 (40 %) [Fig. 4], amygdalar sclerosis and HS in 4 (20 %), DNET in 1 (5 %), cortical dysplasia in 1 (5 %), non-specific changes in 4 (20 %) and normal in 2 (10 %). Average surgical follow up was 10 years (SD 5; range 1–18) with Engel Class IA outcome

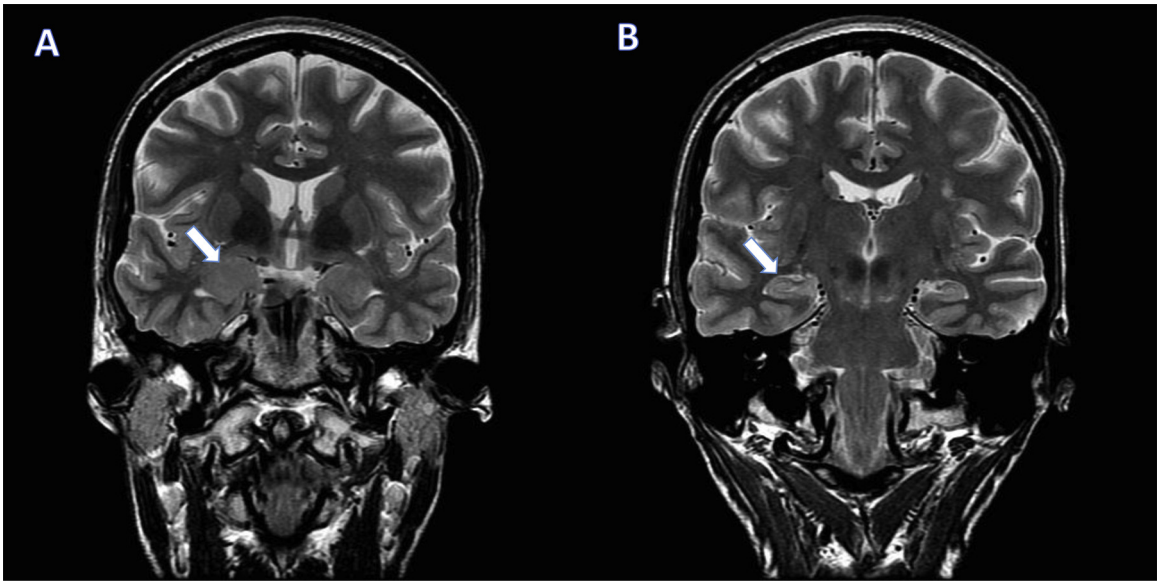

Fig. 1. AE and HE in Patient 27. Images: A) Coronal T2W image showing right AE. B) Coronal T2W image showing right HE.

Table 2
Imaging and medical follow up.

No	Sex	Initial MRI	Follow-up MRI	MRI follow up Duration (yr)	Clinical Follow-up duration (yr)
1	F	LAE	Bilateral HS	7	18
2	M	LAE	LAE	8	17
7	F	RAE	RAE	8	17
9	F	LAE + LHE	LAE + LHE	7	17
10	M	RAE	normal	10	13
11	F	RAE	normal	3	8
14	F	LAE + LHE	bilateral mesial temporal atrophy	11	12
15	M	RAE	RAE	4	4
19	M	RAE	normal	7	12
20	M	RAE	right mesial temporal atrophy	8	3
21	F	RAE + RHE	RAE + RHE	1	5
22	F	LAE	LAE	1	7
23	M	LAE + LHE	LAE + LHE	3	11
24	F	LAE	normal	3	10
25	F	RAE	RAE	N/A	3
28	F	LAE	normal	2	8
30	F	LAE	resolved	8	10
35	F	RAE	RAE	3	4
36	F	LAE	LAE	2	6
39	M	LAE	LAE	7	11
41	M	RAE	RAE	8	6
42	M	LAE	LAE	8	8

Abbreviations: AE, amygdala enlargement; HE, hippocampal enlargement.

in 12 (60 %), Engel Class II outcome in 6 (30 %) and Engel Class III outcome in 2 (10 %). Six surgical patients were seizure free off AEDs at last follow up [Table 3].

3.4. Long-term follow up

Clinical follow up of at least one year was available for all patients with an average of 9.8 years (SD 4.8; range, 1–18). AED treatment was continued in 33 patients at last follow up with 17 on polytherapy. None of the patients received immunotherapy.Twenty-two patients were seizure free at last follow up; 11 on monotherapy, 2 on polytherapy and nine off AEDs. Of the 9 patients (21 %) who were seizure free off AEDs; 6 were surgical patients. Of the 3 non-surgical patients; AE resolved in 1, persisted in 1 and became atrophic in the other. Eleven patients (50 %) in the non-surgical group remained seizure free at last follow up. Three patients deceased; one following septic shock and multiorgan failure (Patient 12), 1 with metastatic ovarian carcinoma (Patient 29) and in the other (Patient 4) the cause was uncertain.

3.5. Medical versus surgical group

The medical and surgical groups did not differ in terms of gender ($p = 0.76$), age at epilepsy onset ($p = 0.42$), duration of epilepsy ($p = 0.16$), laterality of AE ($p = 0.99$) and duration of clinical follow up ($p = 0.64$).

3.6. Associated hippocampal enlargement

Of the eleven patients who had associated HE; seven underwent epilepsy surgery with Engel class I outcome in six (86 %). Pathology showed HS [2], gliosis [2], FCD [1], non-specific changes [1] and normal [1]. Engel Class I outcomes in AE alone group was 46 % (6/13). However, this difference did not reach statistical significance ($p = 0.16$).

4. Discussion

The role of amygdala as an integral part of the TLE syndrome was elegantly outlined in Gloor's sentinel paper in 1982 [15]. Several authors since then implicated the amygdala and emphasized its contribution to the group of refractory TLE [16,17]. It should be noted that the majority of previous studies relating to AE with TLE are cross-sectional or with short follow ups and did not look into long-term outcomes. To the best of our knowledge, this is the largest and the longest prospective study investigating natural course of AE.

AE has been reported in TLE-NL ranging between 12 % and 63 % [8,13,18]. Most studies have reported AE ipsilateral to ictal onset or bilateral AE with rare studies [8] reporting ictal onset contralateral to AE. Variable rates of bilateral AE in TLE have been reported in studies using volumetric analysis between 6–35 % [10,11,19]. None of our patients had AE contralateral to ictal onset or bilateral AE; latter of which could suggest autoimmune etiology [20]. Eleven patients (26 %) had additional ipsilateral HE. A neuroimaging study with voxel based relaxometry (VBM) [21] demonstrated that patients with TLE-AE have isolated enlargement in the dorsomedial part of the amygdala with no significant volume change in the hippocampus. This morphologic pattern was considered distinct from mTLE-HS, in which hippocampal

Table 3
Imaging and surgical follow up.

No	Sex	Initial MRI	Follow-up MRI	MRI follow up Duration (yr)	Type of surgery	Pathology	Post surgical Outcome	Clinical Follow-up duration (yr)
3	F	LAE + LHE	post surgical changes	N/A	Left SAH 2003	HS	Engel I	15
4	F	LAE	post surgical changes	7	Left SAH 2001 Left ATL 2006	non specific	Engel III	15
5	M	RAE + RHE	post surgical changes	5	Right SAH 2003	cortical dysplasia	Engel II	15
6	M	LAE + LHE	post surgical changes	3	Left SAH 2004	HS	Engel I	5
8	F	LAE	LAE	N/A	Left SAH 2002	gliosis	Engel I	9
12	F	RAE + RHE	post surgical changes	N/A	Right ATL 2003	normal	Engel I	13
13	M	RAE	post surgical changes	N/A	Right ATL 2001	DNET	Engel I	18
16	F	RAE	post surgical changes	7	Right ATL 2010	gliosis	Engel I	15
17	M	RAE	post surgical changes	1	Right SAH 2005	gliosis	Engel II	15
18	F	RAE	post surgical changes	1	Right ATL 2010	non specific	Engel II	6
26	M	LAE	post surgical changes	2	Left ATL 2007	normal	Engel I	13
27	F	LAE + LHE	post surgical changes	6	Left AH 2016	gliosis	Engel I	9
29	F	RAE + RHE	post surgical changes	N/A	Right ATL 2009	gliosis	Engel I	6
31	M	LAE	post surgical changes	4	Left SAH 2013	gliosis	Engel II	5
32	M	RAE	RAE	1	Right ATL 2012	HS	Engel I	8
33	M	RAE	RAE	6	Right ATL 2017	non specific	Engel I	4
34	M	RAE + RHE	RAE + RHE	2	Right ATL 2016	non specific	Engel I	1
37	F	LAE	LAE	10	Left ATL 2017	HS	Engel III	4
38	M	LAE	LAE	N/A	Left SAH 2007	gliosis	Engel II	13
40	F	LAE	LAE	3	Right ATL 2016	gliosis	Engel II	16

Abbreviations: AE, amygdalar enlargement; ATL, anterior temporal lobectomy; HE, hippocampal enlargement, SAH, selective amygdalohippocampectomy.

atrophy is the most prominent finding [22]. Another MRI volumetric study showed no significant difference in bilateral hippocampal volumes in TLE-AE; but surprisingly showed significant increases in gray matter volumes in the ipsilateral temporal pole in half of the patients [14]. AE associated with HE is a novel finding in this study. However, whether HE is an isolated pathology or part of AE pathology is uncertain and needs larger studies. Presence of associated HE did not influence surgical outcomes in our study.

AE has been observed to remain stable, remit or rarely progress. In our study, AE persisted in 25 (73 %), resolved in 6 (18 %), evolved into bilateral HS in 1, bilateral mesial temporal atrophy in 1 and ipsilateral mesial temporal atrophy in 1.Coan et al. [9] proposed that AE may be the result of hypertrophy secondary to hypoxic insult and could progress to atrophy and HS later as was seen with Patient 1. Our findings showing progression to bilateral HS reiterate bilaterality of mTLE [23] and that these changes could represent a continuum to HS [24]. The same patient had history of status epilepticus. None with bilateral changes on follow up had history of encephalitis or febrile convulsions. Previous studies have reported higher rates of remission over a shorter follow up [10,25]. Lv et al. [10] demonstrated decrease in the volume of the amygdala in 22 of 33 patients (67 %) on MRI volumetry on follow up between 6 months to 1 year. Malter et al. [25] reported on 40 patients with new onset TLE-AE who were followed up for a median duration of 25 months. AE remained stable in 40 %, partial remission occurred in 30 % and full remission in 30 % at last follow up. Higher remission rates compared to our study despite having a shorter follow up is probably due to use of volumetric methods which are more accurate in detecting AE than visual inspection. This could also suggest remitting relapsing course; however none of our patients who had multiple interval scans suggested this. However, they [25] demonstrated better seizure-free outcomes in the remittent group compared to stable group as did our study. In a smaller study with 5 patients [19]; after a follow up between 2–5 years, 2 remained stable and 3 showed mild resolution in AE.

The mean age at onset of epilepsy was similar to previous studies [12,13,18] and suggests later onset compared to TLE-HS and TLE without AE [26]. Five patients (12 %) had antecedents for epilepsy including family history [3] status epilepticus [2], perinatal insult [1]

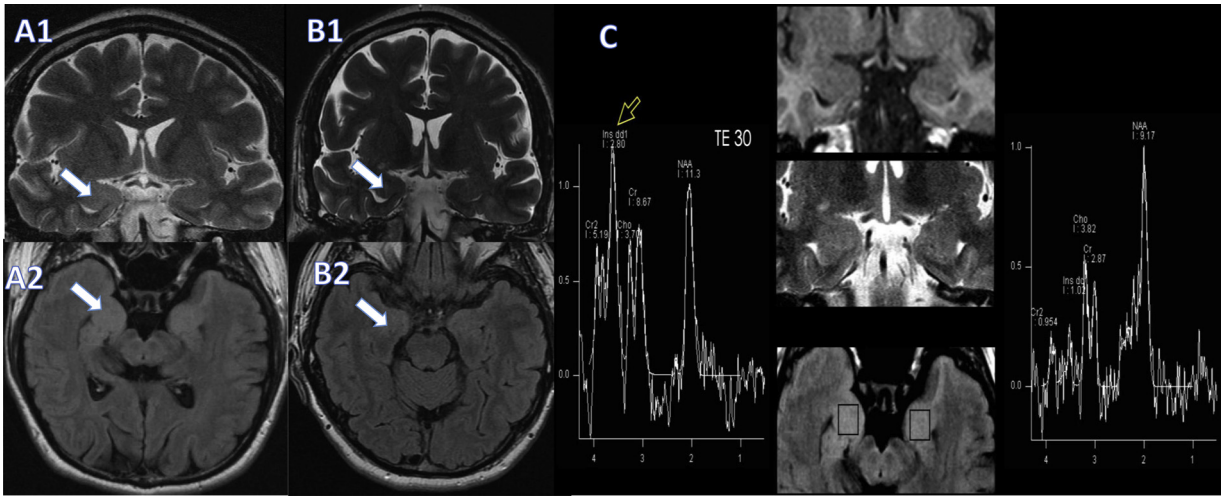

Fig. 2. Resolution of Right AE after 7 years of imaging follow up in Patient 19. The patient is seizure free on single AED at 12 years of clinical follow up. **A1**) Right AE on coronal T2W image **A2**) Right AE on axial FLAIR image. Follow up imaging after 7 years shows **B1**) Resolution of AE on coronal T2W and **B2**) Resolution of AE on axial FLAIR images. **C**) Lateralized increased myoinositol peak (3.6 ppm) in the enlarged right amygdala.

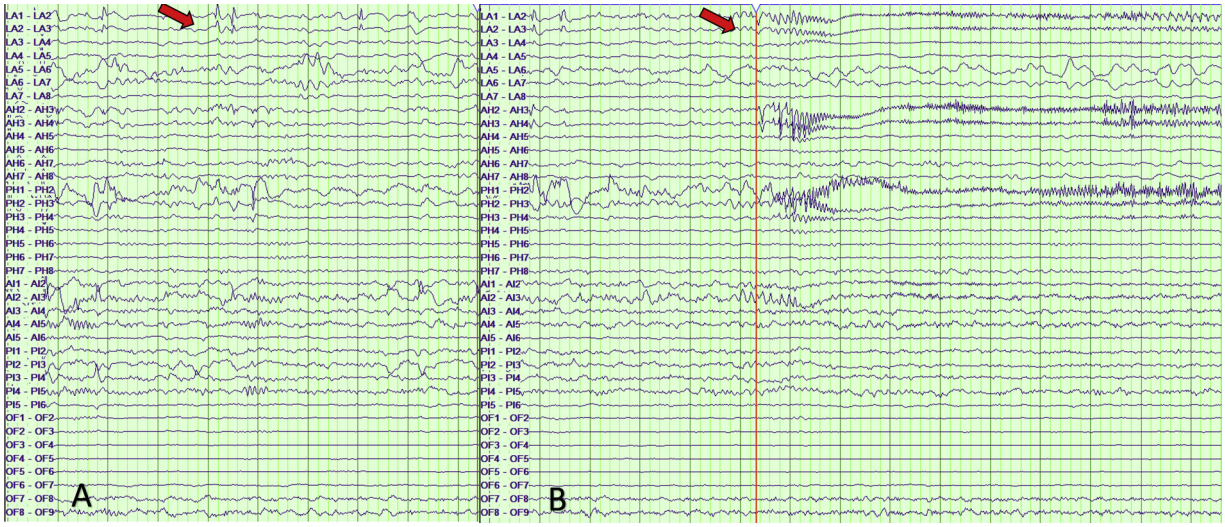

Fig. 3. Intracranial EEG recording using depth electrodes in amygdala in Patient 27. Patient underwent left AH with histopathology showing amygdalar gliosis and Engel IA outcome at last follow up.
A) Interictal spikes in deep contacts of left amygdala (LA electrode).
B) Ictal onset involving deep contacts of anterior hippocampus (AH), posterior hippocampus (PH) and amygdala (LA).

and head injury [1]. None had history of febrile convulsions. Most previous studies have reported lower incidence of febrile convulsions in TLE-AE [10] as compared to TLE-HS [18]. Gloor et al. [15] demonstrated experiential symptoms with amygdalar stimulation in refractory TLE. Lower amygdalar volumes were found to be associated with ictal fear [27]. Deja vu was the most common symptom at ictal onset followed by epigastric sensation, fear, vague cephalic sensation, olfactory hallucination, nausea, metallic taste and autonomic features which have been described in previous studies on “amygdalar epilepsy”(6). Twenty five (60 %) patients had focal aware seizures, 34 (80 %) had focal impaired awareness seizures and 31(74 %) had bilateral tonic clonic seizures (BTCS). The occurrence of BTCS was higher in our series compared to those reported previously [12,26] in TLE-AE.

The role of AE in epileptogenicity has always been a matter of debate. Studies have shown spontaneous interictal like discharges contributing to seizures from lateral nucleus of amygdala in patients with epilepsy with abnormal patterns of receptor densities and synaptic function [28]. There have been previous reports of “amygdalar epilepsy” with ictal onset proven with intracranial recordings [6,29,30]. Our study provides evidence for epileptogenicity in AE with notable concordance of IEDs and ictal onset to the side of AE. Majority of previous studies have shown high IED concordance to AE ranging between 89–100 % [10,19]. Most previous studies have shown ictal onset ipsilateral to AE [18]. There are contrasting previous studies which demonstrated ictal onset contralateral to AE in up to 45 % [8,11]. King et al. [31] published one of the earliest reports with depth electrodes showing amygdala involvement at ictal onset.

Many authors [25] have suggested autoimmune etiology for AE especially due to its remitting nature. In our series, one patient (Patient 22) underwent cerebrospinal fluid (NMDA, LGI1, CASPR, AMPA, GAD65) and another (Patient 36) had serum (NMDA, LGI1, CASPR) antibody testing with negative results and ongoing seizures with persistent AE. In a series of patients with new onset TLE-AE [25], all received some form of immunotherapy but none of the serum testing for antibodies for limbic encephalitis (LE) was positive. That the higher rate of remission in their series was a result of immunotherapy is difficult to correlate in the light of negative antibody results and spontaneous remission in those not treated with immunotherapy. Lv et al. [10] also reported low yield with autoantibody testing in TLE-AE with a single patient testing positive for LGI1 in both CSF and serum on testing 21 patients with 12 having both CSF and serum tested and the remaining having serum testing only. None of our patients had AE contralateral to ictal onset or bilateral AE which could suggest autoimmune etiology [20].

FDG-PET CT showed hypometabolism of mesial temporal structures concordant to the AE as shown in previous studies [10,14,19]. Takaya et al. [21] demonstrated significant glucose hypometabolism on FDG-PET CT in affected amygdala in TLE-AE without hypometabolism in the hippocampus which is commonly involved in TLE-HS; concluding that amygdala per se is an epileptogenic focus. In addition, glucose

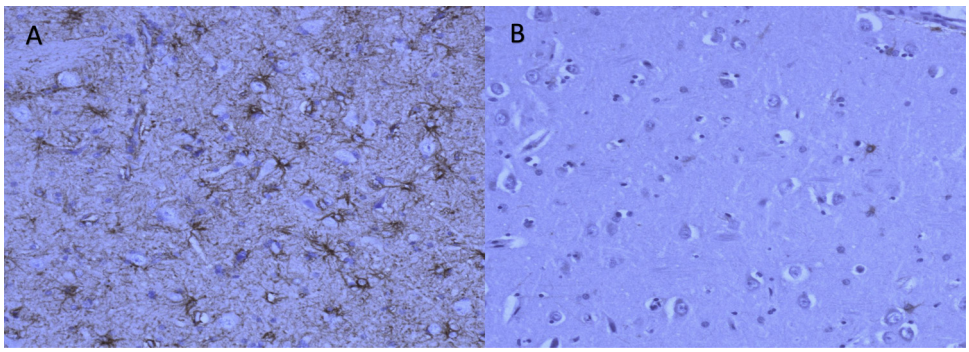

Fig. 4. (A) Histopathology specimen showing amygdala gliosis with GFAP positivity in Patient 31 who underwent left AH with Engel Class II outcome (B) Control specimen of normal amygdala stained with GFAP GFAP: Glial fibrillary acidic protein.

hypometabolism on FDG-PET images in TLE-AE was relatively restricted to the affected amygdala, with greater hypometabolism ipsilateral to the AE. In contrast, significant glucose hypometabolism in the hippocampus, which is a defining feature of MTLE- HS, [32] was not observed in TLE-AE patients. Our patients did not have focal hypometabolism restricted to amygdala. A study [26] using ^{11} C- methionine PET suggested that it could help differentiate neoplastic from non-neoplastic pathology in AE and contribute to clinical decision making. Previous studies have shown concordance to AE and hypoperfusion in ipsilateral temporal lobe with interictal SPECT [19]. There are no reports of ISSPECT in TLE-AE to the best of our knowledge. All three patients in our series who underwent ISSPECT had findings concordant to AE.

Previous studies in drug refractory mTLE have shown better outcomes with inclusion of amygdala in the resection [33]. There have been reports of hippocampal sparing tailored resection with AE with good outcomes (66 %) at short term follow up [12]. The most common histopathology of AE in our series was amygdalar gliosis (40 %). This is in keeping with previous study by Bower et al., [18] who demonstrated amygdalar gliosis in all but one patient among 16 cases of HS. Hudson et al. [16] proposed the concept of abnormal pathology in amygdala in TLE in the absence of HS. He described isolated amygdaloid sclerosis in patients without HS which was as severe as seen in HS. Kim et al. [12] found that the main etiology of AE was FCD followed by brain tumours. However, 5 out of the 8 patients with FCD had additional HS, even though there was no radiological evidence. None in their series of 12 patients had amygdala gliosis. In the series by Mitsueda-Ono et al. [19], 2 patients had refractory epilepsy and subsequently underwent AH, with pathology showing gliosis and cortical dysplasia in the amygdala. Minami et al. [13] reported aggregated hypertrophic neurons without gliosis which were not compatible with FCD as the pathological characteristic of AE. These findings are completely different from our study even though mild gliosis was found in 9 out of the 11 specimens.

In our study, half of the patients became drug refractory. This higher rate may be due to longer follow up and chronicity of epilepsy with associated extended networks. Majority of studies have demonstrated lower rates of drug refractoriness [26] and favourable response to AEDs [10]. Average follow up of surgical patients in our study was 10 years with seizure free outcomes in 12 (60 %) which is comparable with TLE. Kim et al. [12] retrospectively studied 12 patients who had undergone surgical treatment for refractory epilepsy with radiological evidence of AE, and 11 became seizure free at follow up of more than a year. Minami et al. [13] reported seizure freedom at 1 year follow up in 10 of 11 patients who underwent surgery for AE. Amongst 22 patients who were followed up on medical management, half were seizure free at last clinical follow up and 3 were seizure free off medications.

This is the only study to the best of our knowledge that has MRS done in AE causing epilepsy. All four patients who had MRS showed mI as the dominant peak with increased myoinositol/creatinine (mI/Cr) ratio. Increased mI is thought to result from induction of Na^+/mI co-transporter (SMIT) resulting in glial proliferation [34]. mI is considered to be an astrocyte marker and correlates with increased population of glial cells. Its elevations are described with low grade gliomas [35] and reduced levels with AEDs like valproic acid and carbamazepine [36]. The increased mI levels in our patients could be consistent with the most common pathology of amygdala gliosis and could be a potential biomarker. It could represent some form of tissue reaction in AE. It is noteworthy that in one patient (Patient 24), the lateralised increased mI/Cr ratio persisted on follow up imaging despite resolution of AE suggesting that microscopic pathology could be persisting despite radiological resolution. Despite this patient became seizure free and is off AED at clinical follow up at 10 years. There was also decrease in N-acetyl aspartate/creatinine (NAA/Cr) ratio which is a marker of neuronal injury. Decrease in NAA with presence of lactate is considered to be a marker of epileptogenic zone in TLE [37]. Decreased NAA and increased mI has been described in ipsilateral temporal lobe in TLE-HS [36]. Given the occurrence of AE in normal asymptomatic population and concerns of it being a non-specific finding [11]; single voxel based MRS could prove to be a tool to identify “epileptogenic” AE in the future. Larger studies with pathology are required to ascertain this.

4.1. Limitations

Volumetric analysis was not performed in our study and may be considered a limitation. Given presumed etiology of autoimmune encephalitis in AE, investigation with autoimmune markers would have been ideal especially for cases with inconclusive pathology.

4.2. Conclusions

AE is a distinct form of TLE with most common pathology being gliosis and may be associated with HE. Whether AE progresses to or is a risk factor for HS needs to be ascertained with larger studies. Serial neuroimaging may help identify patients with resolution of AE which is associated with better prognosis and to detect neoplastic change. With high proportion of drug refractoriness, surgery is a good option with reasonable outcomes. Further studies are required to assess the role of mI peak on MRS in identifying “epileptogenic” AE. Presence of coexistent HE did not influence surgical outcomes in our study.

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Declaration of Competing Interest

None.

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