

A simplified depth implantation approach in bitemporal lobe epilepsy

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Abstract

Background: Up to 73.0% of patients with bilateral temporal lobe epilepsy (BTLE) on scalp electroencephalogram (EEG) were found to have unilateral temporal seizure onset via invasive EEG monitoring (iEEG) and 58% of them achieved good surgical outcome. However, iEEG in resource-limited countries is limited by cost. We aimed to present the surgical outcome of a simplified and cost-effective 2-electrode bilateral hippocampal depth implantation strategy in 7 cases with bilateral temporal lobe epilepsy based on scalp EEG and unilateral mesial temporal sclerosis (MTS). **Methods:** Total 7 cases who underwent epilepsy surgery were reviewed. All patients underwent 2-stage evaluation of video-EEG monitoring followed by intracranial monitoring. A simplified 2-depth electrode implantation strategy was used, targeting the bilateral anterior hippocampus. **Results:** All 7 patients had interictal bilateral independent temporal epileptiform discharges. Four had bilateral temporal ictal onset on scalp EEG and 3 with ictal onset contralateral to the MTS. With iEEG, 4 patients (57.1%) were confirmed to be unilateral TLE, concordant with the MTS, and 3 patients (42.9%) had true BTLE. All 7 patients underwent anterior temporal lobectomy, ipsilateral to the side of MTS. Four patients (57.1%) achieved Engel I surgical outcome, of which 3/4 (75.0%) were patients with unilateral TLE. For those with true BTLE, 2/3 (66.7%) achieved favourable surgical outcome (Engel I and II).

Conclusions: This simplified two-electrode implantation strategy is effective in lateralization of TLE in patients with BTLE and more affordable to those in resource-limited countries.

Keywords: Bitemporal lobe epilepsy, depth implantation, cost, limited resources, epilepsy surgery

INTRODUCTION

Temporal lobe epilepsy (TLE) is the most common focal epilepsy, especially in the epilepsy surgery cohorts. There are up to 60.9% patients who underwent temporal lobectomy achieved seizure freedom.¹ However, in TLE especially those with mesial temporal sclerosis (MTS), bilateral or contralateral ictal or interictal activities are not uncommon. Questions remained as whether these patients with bitemporal activities are surgically remediable. A systematic review on those with bitemporal epileptiform discharges on scalp EEG found that 73.0% had unilateral temporal seizure onset on invasive electroencephalogram monitoring (iEEG), and 27.0% were true bitemporal epilepsy.² The overall surgical

outcome was better in patients with unilateral TLE (67%) compared to true BTLE (45%).² Therefore, patients with seemingly bilateral temporal epilepsy on scalp EEG would benefit from presurgical evaluation by iEEG. Despite the potential benefit of iEEG, this approach is limited by cost in most resource-limited countries, and consequently preventing many patients with bitemporal lobe epilepsy from receiving epilepsy surgery.

Bilaterality in TLE

Contralateral ictal scalp EEG onset in MTS is most probably due to burned-out hippocampus syndrome (BHS). This distinctive syndrome described a condition where the epileptic

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activities generated at the severely damaged hippocampus could not produce visible scalp discharges until its propagation to the contralateral temporal lobe.³ This propagation was thought to occur faster through the dorsal hippocampal commissural pathway in cases of severely damaged hippocampus.⁴

Damage to bilateral temporal lobe are common findings in autopsies of patients with TLE. When hippocampal sclerosis is present, it is bilateral in 86% of cases.⁵ This bilaterality of TLE and uncovering of the contralateral seizures from the less epileptogenic temporal lobe upon antiepileptic drugs (AEDs) withdrawal may contribute to the bilateral independent temporal discharges during video scalp EEG and intracranial monitoring.⁶ However, as distant hyperexcitability particularly in the temporal lobe contralateral to an epileptogenic lesion were commonly found, these contralateral seizures are often easily suppressed by AEDs.⁷

Another hypothesis for the mechanism of BTLE is kindling and secondary epileptogenesis. “Kindling” is a concept introduced by Goddard *et al.* in 1967 to describe the tendency of the brain to become progressively more epileptogenic when stimulated repeatedly at a stimulus intensity that initially may be sub-threshold for the generation of epileptic potentials.⁸ Secondary epileptogenesis is the tendency of an epileptogenic area to give rise to new epileptogenic areas separated by at least one synapse from the primary epileptogenic zone.⁹ Kindling of a unilateral TLE causes secondary epileptogenesis in the contralateral temporal lobe, leading to BTLE.

Limitations of non-invasive investigations in BTLE

BTLE is commonly diagnosed based on the electro-clinical manifestation during scalp video-EEG monitoring. However, when seizures originated in one temporal lobe and propagated rapidly to the contralateral side, it is difficult to lateralize the onset. Ictal patterns may include (1) non-lateralizing bitemporal seizures with simultaneous bitemporal EEG ictal onset or (2) independent bilateral temporal onset. Therefore, scalp video-EEG is a weak predictor of true BTLE.^{10,11}

The usefulness of other non-invasive tests such as brain MRI, WADA test and positron emission tomography (PET) in lateralization of TLE with bilateral independent epileptiform discharges on scalp EEG were studied previously. The results were contradicting, of which some reported MRI and WADA test were useful predictors in

lateralization and associated with seizure freedom post-surgery,¹² but the other studies showed the contrary.¹³ Similarly, PET imaging were also found to be not useful in lateralization of BTLE.^{13,14}

Accessibility of iEEG in resource limited countries

In countries with limited resources such as Southeast Asia, iEEG services such as subdural grid electrodes or depth electrodes monitoring are either inaccessible or unaffordable.¹⁵ The limited access to iEEG can result in difficult decision for epilepsy surgery in cases with possible BTLE.

Comparison of iEEG approaches for BTLE

The standard iEEG approach for BTLE is a six-depth electrode implantation approach which targets the amygdala, anterior and posterior hippocampus bilaterally.¹⁶ Another approach used to assess the mesial temporal lobe is the occipito-temporal approach where the trajectory targets the hippocampus along its longitudinal axis, to the amygdala from an occipital entry point.¹⁷ This approach is technically more difficult and was shown to result in longer operation time with otherwise no difference in monitoring, complications and outcome compared to the standard transtemporal approach in patients with TLE.¹⁷ In order to improve the affordability of iEEG, we designed a simplified approach using only two depth electrodes implanted at the anterior hippocampus bilaterally. This approach aims to determine the seizure laterality in patients with bitemporal ictal onset from scalp EEG, with the hypothesis that the seizures are originated from the hippocampus and not from other regions in the brain. (Figure 1)

This study aimed to present the surgical outcome of this simplified bilateral hippocampal depth implantation strategy in 7 cases with BTLE and unilateral MTS.

METHODS

This study included 7 cases with unilateral MTS with bilateral independent/discordant temporal interictal discharges or ictal onsets on scalp EEG or discordant seizure semiology. All patients underwent bitemporal depth electrode implantation followed by temporal lobe resective surgery between 2015 and 2019 at University of Malaya Medical Centre (UMMC). Clinical and demographic information, including imaging and EEG findings, surgery, postoperative follow-up and outcome were included for analysis.

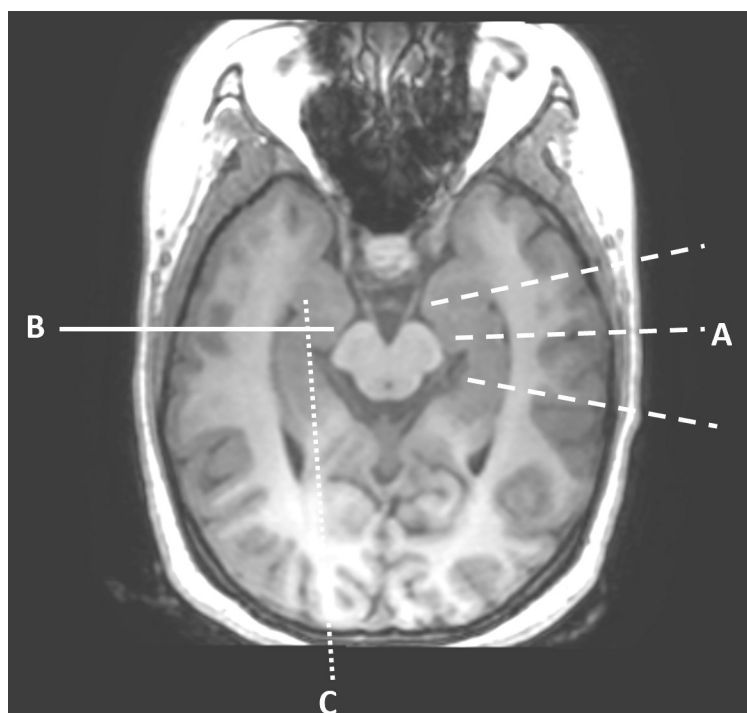


Figure 1. T1-weighted MRI brain with different approaches used in temporal lobe epilepsy. Approach A (dash line) showed the standard 6-electrode transtemporal depth electrode trajectories, targeting the amygdala, anterior and posterior hippocampus via middle temporal gyrus. Approach B (solid line) showed the simplified 2-electrode transtemporal depth electrode trajectories used in our study. Approach C (dotted line) showed the 2-electrode occipito-temporal lobe approach targeting the hippocampus along its longitudinal axis, to the amygdala from an occipital entry point.

Case identification

Cases of refractory TLE with unilateral MTS diagnosed based on clinical and drug history, routine scalp EEG and MRI brain findings were identified by an epileptologist and counselled for comprehensive epilepsy surgery evaluation at UMMC. MRI brain was performed using dedicated epilepsy protocol developed in house¹⁸ and the diagnosis of MTS was made based on visual screening of the MRI brain with hippocampal atrophy on coronal T1-weighted images and signal hyperintensity on T2-weighted or fluid-attenuated inversion-recovery (FLAIR) images.

Stage 1 evaluation: Video EEG monitoring

Stage 1 evaluation included a 3-to-4-day video-EEG monitoring. The clinical history, neuroimaging and EEG findings were reviewed and discussed in a multidisciplinary team (MDT) which includes neurologists, neurosurgeon and neuroradiologists, neuropsychologist, neurophysiology technologists and epilepsy

specialist nurses.¹⁹ The decision for stage 2 evaluation with intracranial monitoring was based on bilateral nature of the seizures semiology or EEG data, as below: (1) Bilateral independent temporal interictal discharges, without a clear unilateral predominance; (2) Discordant ictal EEG onset, contralateral to the side of MTS in MRI brain; (3) Discordant seizure semiology, suggesting contralateral ictal onset.

Surgical procedure for intracranial electrode implantation

All the procedures were performed under general anesthesia. The trajectories of the 6-contact hippocampal depth electrodes were planned on MRI fast spoiled gradient echo (FSPGR) T1-weighted images using the Brainlab IPLAN® Stereotactic planning software. All the trajectories were planned with an entry point at the middle temporal gyrus and a target point at the anterior hippocampus. A preoperative volumetric Computed Tomography (CT) scan was obtained after the stereotactic frame (CRW Integra

Radionics, Burlington, USA) was positioned, and merged with the MRI. The Ad-Tech 6-Contact, 5mm depth electrodes were implanted along the stereotactic coordinates via single burr holes bilaterally. The electrode position was determined using an immediate intraoperative volumetric CT scan. (Figure 2)

Stage 2 evaluation: Intracranial video-EEG monitoring

Stage 2 evaluation included one-week video-EEG monitoring with bilateral hippocampal depth electrodes and concurrent scalp video-EEG. (Figure 3) The outcome of intracranial monitoring was discussed again in an MDT conference to draw an appropriate surgical plan.

RESULTS

The demography and clinical characteristic of the 7 cases were shown in Table 1. Mean age of onset was 10.5 years old and the mean duration of epilepsy at the time of surgery was 28.4 years. All cases had unilateral MTS on MRI. One patient (case 5) had ipsilateral hemispheric atrophy in addition to MTS. All 7 cases had interictal

bilateral independent temporal epileptiform discharges. Four cases (case 1, 2, 4 and 7) had bilateral temporal (sequential or simultaneous) ictal onset on scalp EEG. Another 3 cases (case 3, 5 and 6) had ictal EEG onset contralateral to the MTS. Total 4 patients (57.1%) were confirmed to be unilateral TLE with the ictal EEG onset concordant with the side of MTS. Three cases (42.9%, case 2, 6 and 7) were found to be true BTLE from intracranial monitoring.

Surgical planning

Patients with unilateral seizure onset from depth electrode monitoring ipsilateral to the MTS (case 1, 3, 4 and 5) underwent anterior temporal lobectomy (ATL). The decision for surgery for 3 cases (case 2, 6 and 7) with true BTLE were made based on side of MTS and the proportion of seizures from each temporal lobe during intracranial monitoring. Case 2 had 83.0% seizures from the right temporal lobe, concordant with right MTS, therefore, a right ATL was performed. Case 6 and 7 had almost equal proportion of clinical seizures from each temporal lobe. As 100% of the electrographic seizures were ipsilateral to the

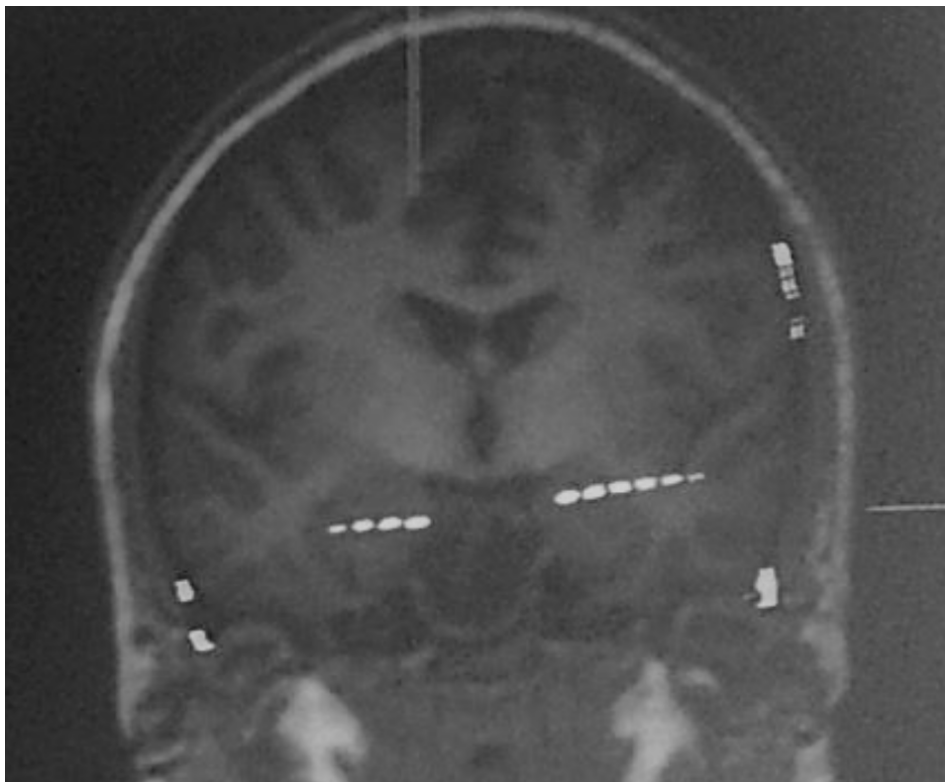


Figure 2. Post-operative co-registered CT and MRI FSPGR T1-weighted image of case 1 with 2 depth electrodes targeted at both anterior hippocampi via middle temporal gyrus.

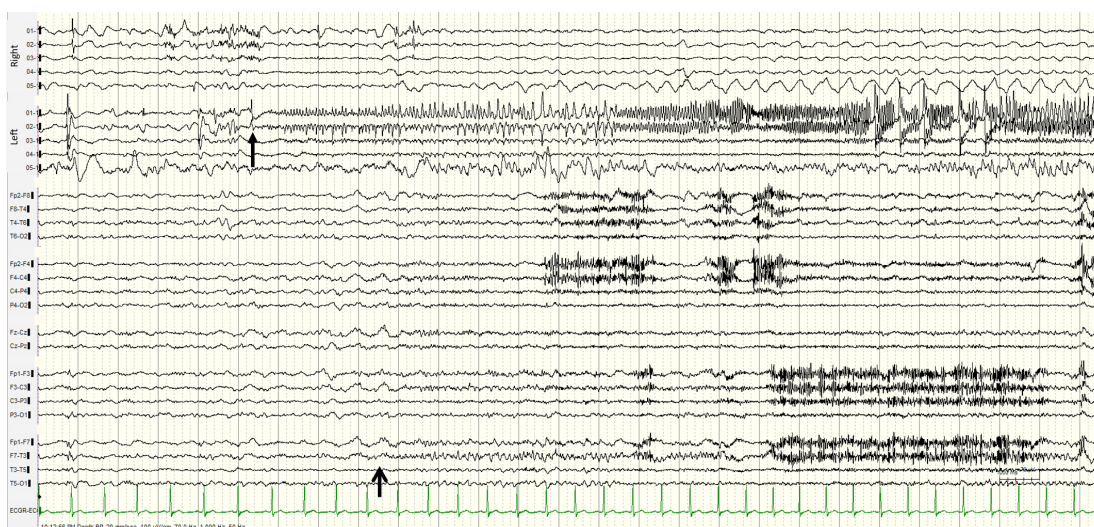


Figure 3. Concurrent iEEG and scalp EEG of case 7 showed a seizure with ictal onset at the left anterior hippocampus. Depth electrode EEG were shown in top 2 panel in bipolar montage and concurrent scalp EEG were shown in bottom panel in longitudinal bipolar montage. Ictal onset was marked (block arrow) by low amplitude fast activities at the left anterior hippocampus depth electrode (Left contact 02). Scalp EEG showed ictal onset (line arrow) as left anterior temporal recruiting rhythm, 3 seconds after the ictal onset recorded in depth electrode.

MTS in case 6, a left ATL was performed. The left sided seizures in case 7 were recorded at the initial period when AEDs were withdrawn, and right sided seizures emerged after the re-initiation of AEDs during the monitoring. Therefore, a right ATL was performed.

Surgical outcome

Three patients (75%) (case 1, 3 and 5) with unilateral TLE achieved Engel I surgical outcome. Of the 3 cases with true BTLE, 2 cases (66.7%, case 6 and 7) achieved favourable surgical outcome (Engel I and II) and another case (case 2) had poor surgical outcome (Engel IIIa). Case 3, 6 and 7 were maintained with single anti-epileptic drug (AED). Case 5 was still on triple AEDs as the patient developed withdrawal seizures upon reduction of topiramate from 100mg to 50mg daily. None of the patients had post-surgical complications.

DISCUSSION

This case series showed that this simplified depth implantation approach is effective to lateralize the seizures and was associated with good seizure outcome in BTLE cases. We found 4 patients (57.1%) were unilateral TLE and 3 (42.9%) were true BTLE in our case series. Overall, 4 cases (57.1%) achieved Engel I surgical outcome. These

findings were compatible to the systematic review which found that 73% of BTLE on scalp EEG were proven to be unilateral on iEEG, and 58% achieved good surgical outcome.²

The controversy for the need of iEEG monitoring in patients with BHS remained. As patients with BHS and classic MTS had similar surgical outcomes, one could possibly avoid invasive intracranial monitoring in patients with BHS despite of discordant semiology or interictal/ ictal EEG findings.²⁰ In our series, BHS would explain the findings of case 1, 3, 4 and 5, in which iEEG revealed exclusively unilateral ictal onset ipsilateral to the MTS. This raised the question on the possibility of making a surgical decision based on the MRI findings. However, without iEEG, we will not be able to differentiate unilateral TLE from true BTLE.

There were three cases with true BTLE in our series (case 2, 6 and 7), of which 66.7% achieved favourable surgical outcome. This is also consistent with the systematic review which reported good surgical outcome in 45.0% patients with true BTLE.² It was previously thought that seizure freedom or >75% seizures reduction would occur when one of these factors: (1) > 75% preponderance of interictal scalp EEG discharges to one temporal lobe, (2) unilateral temporal lesion on MRI and (3) lateralising verbal/ visual reproduction memory deficits on

Table 1: Demographic and clinical characteristics, scalp and intracranial EEG findings, side of surgery, histopathology and surgical outcome of all 7 cases

Case	Gender	Age of onset (years)	Duration of epilepsy (years)	Semiology	MRI (MTS)	Scalp EEG		Depth electrode		Surgery (ATL)	Histopathology	Engel surgical outcome at 2 years
						IEDs (%)	Number of IEDs (%)	IEDs (%)	Number of seizures, ictal onset, lateral			
1	F	16	11	Aura of fear, blank stare, oral automatism, left hand dystonia, bilateral hand automatism.	Right	50R:50L	2R:2L	50R:50L	3R, > 100 (ES) R	Right	MTS	Ib
2	F	16	16	Asymmetric tonic right version, postictal dysphasia	Right	5R:95L	2R:2L	60R:40L	5R:1L	Right	MTS	IIla
3	M	5	34	Oral automatism left hand dystonia	Right	60R:40L	3L	100R	8R	Right	MTS	Ia
4	M	3	30	Blinking, oral automatism, right sided tonic clonic	Left	50R:50L	7R:5Bi	30R:70L	4L	Left ^a	MTS	IIb
5	M	1	45	Blank stare, left hand automatism, left head and eye version, oral automatism.	Left ^b	20R:80L	5R	100L	2L	Left	MTS, FCD I at lateral temporal, AVM at parahippo-campus and amygdala	Id
6	F	8	25	Seizure type 1: Blank stare, left hand and oral automatism, right RINCH ^c , left version followed by right dystonia, Seizure type 2: Blank stare, bilateral automatism, right RINCH, late left version, left asymmetric tonic, generalised tonic clonic.	Left	40R:60L	3R	70R:30L	3R: 3L, 17(ES) L	Left	MTS	Ia
7	M	25	38	Seizure type 1: Facial grimacing, left hand dystonia, oral automatism Seizure type 2: Oral automatism	Right	80R:20L	2R:8L	80R:20L	17R:13L	Right	MTS	IIa

Bi: Bilateral; M: Male; F: Female; IEDs: Interictal epileptiform discharges; MTS: mesial temporal sclerosis; FCD: focal cortical dysplasia; AVM: arteriovenous malformation; R: right; L: left; ATL: anterior temporal lobectomy; a: A repeated and more extensive surgery was performed because of incomplete resection; b: with left hemispheric atrophy; c: rhythmic ictal non-clonic hand motions.

neuropsychological evaluation, were concordant with the side of surgery.²¹ However, recent systematic review found that the lateralization of iEEG findings has poor correlation with surgical outcome.² This poor correlation could explain the poor outcome in case 2. Whereas in case 6 and 7, seizures from the contralateral lobe only appeared after AEDs withdrawal, suggesting that they were less epileptogenic and can be suppressed by AEDs.

When cost remained as a limitation for epilepsy surgery in resource limited countries, our simplified intracranial implantation strategy would reduce the cost of procedure significantly, compared to the 6-electrode implantation strategy. As a reference, a depth electrode costs about USD1,000, which is a higher price compared to developed countries due to low utility. Six electrodes will cost up to USD6,000, which is 1.5 to 1.7 times higher than the annual GDP per capita in Vietnam (USD 3,000) and Indonesia (USD 4,000).

Our simplified approach utilises 2 electrodes only targeting the anterior hippocampi, and we could possibly miss an epileptogenic zone outside the anterior hippocampus mimicking BTLE.⁹ Diligent selection of cases with temporal lobe semiology or MRI lesion in the hippocampus will minimise such risk. We used six-contact electrode our series due to its availability, which recorded activities in the hippocampi only. Ten-contact electrode would be a better choice as it allows recording of both lateral and medial temporal lobe, and the cost between a 6-contact and 10-contact electrode does not differ much.

In conclusion, this simplified two-electrode implantation approach is effective in lateralization of TLE in patients with BTLE and more affordable to those in resource-limited countries.

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DISCLOSURE

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Conflict of interest: None

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