

Case Report

Long-term seizure freedom following intracranial sEEG monitoring: Therapeutic benefit of a diagnostic technique

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ABSTRACT

Patients with treatment-resistant epilepsy often require surgery. It is very rare that patients with TRE can have sustained seizure freedom spontaneously, without undergoing further resection or neuro-modulation after invasive monitoring with sEEG. Of the 78 TRE cases monitored over last 5 years, we identified three patients who became seizure-free following sEEG monitoring without undergoing further resection or neuro-modulation. Seizure-freedom after sEEG is possible even without further intervention. In cases where seizures after the completion of the invasive monitoring are not observed, a longer observation period following electrode explantation prior to planned neuro-modulation or resection is warranted. This could be due to the disruption of the cortical–subcortical epileptogenic network due to focal area of tissue damage along and around the electrode tract.

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1. Introduction

It is infrequent that treatment-resistant epilepsy (TRE) remits spontaneously. Chances of remission with each trial of currently available anti-seizure drugs (ASDs) in patients with TRE are low, likely less than 10% after trying more than 2 ASDs [1–4]. In patients who are determined to have treatment-resistant focal epilepsy, resective surgery is typically considered [4]. Often, in MRI negative TRE, anterior-medial temporal lobe and limbic networks, and other deep structures are monitored for localization of the seizure-onset zone for possible surgical resection. Invasive monitoring with stereoelectroencephalogram (sEEG) has been widely utilized to identify the area of epileptogenesis in focal TRE. Contemporary sEEG typically utilizes the placement of multiple intracortical depth electrodes in the targeted cortical and subcortical regions after defining potential anatomical obstacles, including blood vessels. Limited reports exist to indicate the possibility of seizure freedom after a diagnostic intracranial EEG electrode implantation [5,6]. Here we report and analyze in detail three cases of focal TRE who were observed, in subsequent and prolonged follow-up, to be seizure-free after invasive electrode explantation. This series suggests that the micro-lesions caused by sEEG electrode implantation and explantation

may alter the epileptogenic network and, thus, result in sustained seizure freedom.

2. Methods

Between January 2014 and May 2019, we have monitored 78 patients with TRE with sEEG of whom three became seizure-free following invasive monitoring without undergoing further resection or neuro-modulation and without ASD adjustment for a year following explantation. In two of these patients, seizure freedom was sustained for 2–5 years, and one patient was seizure-free for 12 months with later recurrence of seizure at a lower than pre-implantation frequency. Data of three patients were analyzed retrospectively and are reported (Table 1).

3. Case reports

3.1. Case 1

This is a 30-year-old right-handed Caucasian female with a history of anxiety, ADHD and focal onset with impaired awareness epileptic seizures at the age of 24 years. Her semiology consisted of an aura of lightheadedness, déjà-vu, with subsequent behavioral arrest. Despite treatment with three concurrent ASDs, she continued to have 2–3 seizures per week. The patient was on levetiracetam (LEV) 1500 mg twice a day, carbamazepine (CBZ) 400 mg twice a day and valproic acid (VPA) 1500 mg daily at the time of sEEG

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Table 1
Patient Demographics.

Patient number	1	2	3
Age (years)	30	45	34
Age at sEEG (years)	28	39	30
Gender	F	M	F
Handedness	RH	RH	RH
Epilepsy duration (years)	8	27	18
Number of seizures	2–3/day	6–20/month	1–8/month
Type of seizures	Focal with impaired awareness	Focal with hyperkinetic motor features	Focal with impaired awareness, focal to bilateral GTC
Current AEDs	LEV, CBZ, VPA	LTG, TPM, OXC	LEV, OXC
Prior AED	TPM, ZNS, LCM	ZNS, CBZ, PHE, LEV, LCM	CBZ, VPA, PB, TPM, LCM, ZNS
Scalp inter-ictal EEG	left temporal	None	left frontal, fronto-temporal, posterior temporal
Scalp ictal EEG	Left temporal	Obscured by artifact	Poorly localized to the left fronto-temporal region
sEEG inter-ictal	Left hippocampus and temporal pole	Right and left orbitofrontal and medial frontal	Amygdala, hippocampus and superior temporal gyrus
sEEG ictal pattern	Left hippocampus onset	Variable onset between right orbitofrontal and left orbitofrontal	Independent focus in superior temporal gyrus and anterior hippocampus
Number of sEEG electrodes	11 left hemisphere	7 left and 7 right hemisphere	9 left hemisphere
MRI	Normal	Normal	Normal
PET	Left temporal hypometabolism	Normal	left temporo-parietal hypometabolism
MEG	Left temporal pole, mesial basal temporal and left posterior temporal region	Not obtained as no interictals	Left infra-sylvian and basal temporal, temporo-parietal
SPECT	Not performed	Right > left mesial frontal, right insula and right orbitofrontal	Inconclusive
Seizure-free duration (months)	24	60	12 and then seizure recurrence at a lower rate

electrode implantation. She failed treatment with ASDs (due to lack of efficacy) with topiramate (TPM), zonisamide (ZNS), and lacosamide (LCM). Scalp video-EEG monitoring showed frequent left temporal epileptiform discharges and seizures arising from the left temporal region (FT9 > FT7, F3) with theta activity in the left temporal region and quick involvement of the frontal area within 1 s of onset. In some of the seizures, the ictal EEG change was delayed from the clinical onset by up to 10 s. 3 T MRI of the brain with epilepsy protocol was non-lesional and did not show any hippocampal pathology (Fig. 1B). FDG-PET documented mild left temporal lobe hypo-metabolism. Functional brain MRI showed left language dominance. MEG localized dipoles to the left temporal pole, mesial basal temporal region and in the left posterior temporal region. Neuropsychological testing showed overall normal performance with areas of mild difficulty across aspects of expressive language, episodic memory, and psychomotor processing speed that are commonly seen in patients with dominant temporal lobe epilepsy. Considering the non-lesional MRI, delayed EEG onset from the clinical onset, and with the rapid frontal involvement at the ictal onset, the patient underwent sEEG evaluation. sEEG electrodes targeted the left amygdala, hippocampus, temporal pole, orbitofrontal, insular, anterior and mid-cingulate, and posterior temporal regions (Fig. 1A). Inter-ictal epileptiform discharges were recorded from the left hippocampus and temporal pole. Seven stereotypical seizures were recorded with left hippocampal onset. The seizure onset pattern for one of the seven stereotypical seizures is shown in Fig. 1C. Immediately post-explantation the brain CT showed left frontal and temporal hypo-attenuation in the region of electrode trajectories, indicating possible vasogenic edema. Intra-carotid amobarbital procedure (IAP) was performed in anticipation of a left medial temporal resection. It showed left language lateralization and memory score of 100% on the left hemisphere testing and 75% on the right hemisphere testing. Surgical resection was not pursued due to the cognitive risks of such an approach [7], but left hippocampal responsive neuro-stimulation was considered. However, following sEEG implantation, the patient went into remission and has been seizure-free for 28 months. ASDs were then decreased with maintenance on LEV 1500 mg twice daily and lamotrigine (LTG) 300 mg twice daily after being weaned off CBZ and VPA at 6 months post-explantation, considering her childbearing potential. She continues to be seizure-free, including freedom of auras. Follow-

up MRI at one year (Fig. 1D–G) showed multiple small superficial areas of cortical encephalomalacia and deep white matter lesions in the area of previous sEEG electrode implantation.

3.2. Case 2

This is a 45-year-old right-handed male with a history of paranoid delusions and seizures since the age of 12 who reported 6–20 seizures per month. Seizures consisted of an aura of dizziness and chest tightness followed by an odd facial expression, hand fumbling, and loss of awareness, as well as hyperkinetic motor seizures. He was managed with LTG 100 mg twice a day, TPM 100 mg twice a day, oxcarbazepine (OXC) 300 mg twice a day during the surgical evaluation and had failed LCM, ZNS, LEV, CBZ, and phenytoin (PHT). Interictal scalp video-EEG monitoring was normal with ictal events obscured by movement artifact. However, the events were clinically suggestive of medial frontal onset, given their stereotypic nature. 3 T brain MRI (Fig. 2A) and FDG-PET were normal. MEG was not performed due to the absence of inter-ictal abnormalities. Ictal SPECT showed hyperperfusion in the right frontal, insular, and orbitofrontal regions. Neuropsychological testing showed areas of cognitive difficulty across aspects of expressive language and episodic memory, which were felt to be related to his antiseizure medication regimen; full-scale IQ was estimated at 119 with verbal IQ at 121 and performance IQ at 112. The patient underwent sEEG evaluation considering his non-lesional MRI and frontal lobe semiology that was non-lateralizing. sEEG electrodes targeted frontal, anterior frontal, posterior fronto-lateral, posterior fronto-mesial, anterior orbitofrontal, and posterior orbitofrontal regions bilaterally. Twenty-eight events were captured, 15 had EEG correlates and 13 had no EEG correlates. Both the auras and typical hypermotor seizures had variable onset between the right orbito-frontal and left orbito-frontal regions and some had no clear onset pattern and unclear laterality. The hyperkinetic motor seizure (Fig. 2D and E) has an evolving pattern in the right frontal leads with simultaneous rhythmic activity in the left frontal leads. He also had his similar typical auras and hypermotor seizures that were electrographically negative. It was hypothesized that the patient either had an independent seizure focus in the right and the left frontal region or that the ictal onset zone was not explored during the invasive evaluation and what was visualized on the sEEG ictally was a variable

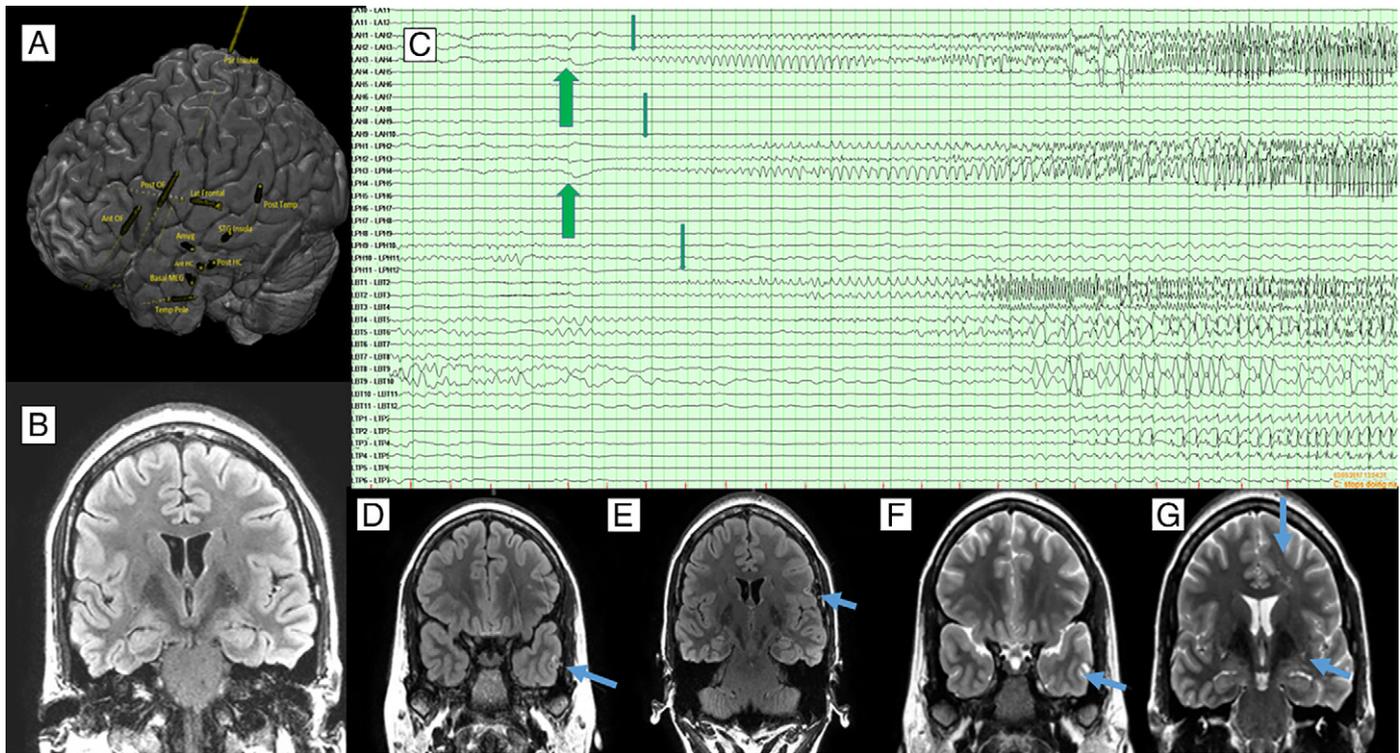


Fig. 1. A – Surface overlay of the implanted sEEG electrodes showing left hemisphere implant covering anterior orbitofrontal (Ant OF), posterior orbitofrontal (Post OF), lateral frontal (Lat Frontal), amygdala (Amyg), anterior hippocampus (Ant HC), posterior hippocampus (Post HC), basal temporal (Basal MEG), temporal pole (Temp Pole), superior temporal gyrus (STG insula), posterior temporal (Post Temp) and parietal insular (Par Insular) electrode. B – Normal pre-surgical MRI-FLAIR sequence in coronal section. C – Seizure onset pattern recorded from the implanted sEEG electrodes showing electrodecrement response (green thick arrow) at LAH 1–4 and LPH 1–4 electrodes followed by the onset of low amplitude fast activity (green thin arrow) at LAH 1–4 contacts followed by LPH 1–3 followed by LBT 1–3 contacts which then transitions to ictal pattern. D, E – MRI brain (1-year post-explantation) with FLAIR sequence and F, G – with T2 sequence showing the lesions (blue arrows) at the site of prior sEEG electrode trajectory. Left anterior hippocampus (LAH), left posterior hippocampus (LPH), left basal temporal (LBT) and left temporal pole (LTP) are shown.

spread pattern. He was not offered surgical intervention. His immediate post-explantation CT scan showed few micro-hemorrhages and pneumocephalus along the electrode tracts – this was not associated with any immediately apparent clinical sequela. However, following the sEEG implantation, he went into seizure remission. No ASD changes were made within the first year. He has been maintained on LTG monotherapy 100 mg twice a day after transitioning from TPM 100 mg twice a day and OXC 300 mg twice a day. One year post-explantation, an MRI (Fig. 2B and C) showed nodular foci and thin lines of hemosiderin along the electrode tracks. The patient has been seizure-free for over 5 years on monotherapy.

3.3. Case 3

This is a 34-year-old right-handed female with a history of TRE since the age of 12 years with seizures described as clonic activity of the right shoulder, arm and face. She had failed several different anticonvulsants (CBZ, VPA, PB, TPM, PHT, LCM, ZNS, LTG, CZP) with seizure frequency of 1–2 seizures/month while on LEV 2000 mg twice a day and OXC 600 mg in the morning and 900 mg at night. Scalp video-EEG revealed left temporal discharges with broad and varying fields (frontal, fronto-temporal and posterior temporal). Multiple seizures were recorded that were poorly localized on scalp video-EEG, but had left hemispheric lateralization with several involving the left temporal electrodes maximally. Epilepsy-protocol 3 T MRI of the brain was negative (Fig. 3A), and an FDG-PET scan showed decreased uptake in the left temporal and parietal regions. MEG showed left intra-sylvian and basal temporal and temporo-parietal spikes. Ictal SPECT was inconclusive. IAP showed strong left hemisphere dominance for speech/language and relatively symmetrical support for memory (75% with left injection and 63% with

the right injection). The neuropsychological performance showed a full-scale IQ of 90, verbal IQ of 85, and performance IQ of 99. She underwent sEEG placement for seizure localization targeting the following left hemispheric amygdala, anterior hippocampus, posterior hippocampus, posterior temporal, insula (from parietal approach), superior temporal gyrus, anterior supra-sylvian, posterior supra-sylvian, and orbitofrontal regions. Eight typical seizures were captured. It was noted that the patient had independent seizure foci in the superior temporal gyrus and the anterior hippocampus (Fig. 3D). Immediate post-explantation CT scan showed a small left frontal extra-axial hemorrhage and edema at the site of implantation, which was clinically silent (Fig. 3B and C). She was considered for responsive neurostimulation (RNS) device placement in the left hippocampus and left superior temporal gyrus. However, she was seizure-free for 12 months after sEEG, hence, RNS was deferred. Seizures recurred after 12 months, but were clinically mild, far less frequent, and occurring in clusters of 2–3 seizures every 4–6 months. No ASD changes were made within the first year.

4. Discussion

This series describes three patients who had variable periods of seizure freedom, ranging from 12 to 76 months, following sEEG implantation. Two of them continue to be seizure-free and one patient (case 3) had seizure recurrence at a much lower frequency (reduced by at least 50%) and severity.

The literature on seizure remission after intracranial electrode implantation is very limited [5,6,8] and the pathophysiology of seizure remission following such intervention is unknown. Past studies included both subdural grid placement and/or depth electrode placement for invasive investigation. In those reported cases, there was evidence

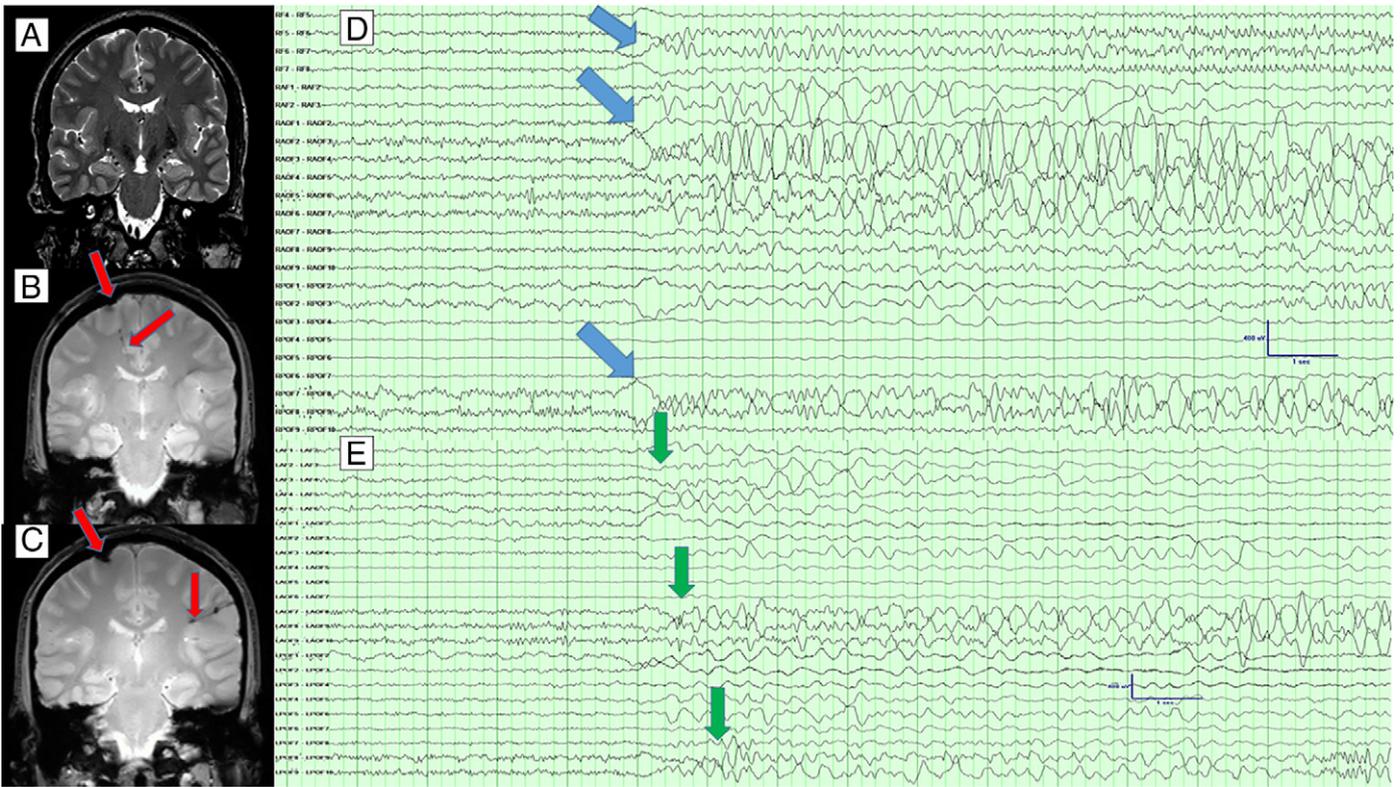


Fig. 2. A – Pre-surgical MRI brain shown in coronal section, with no pathology. B and C – MRI post-explantation—Coronal GRE sequences showing electrode tract (linear) and superficial (nodular) hemisiderin deposit (red arrows). D – Seizure onset pattern recorded from the implanted sEEG electrodes showing transition from inter ictal to ictal activity (blue arrow) at RF 5–7, RAOF 2–7 and RPOF 7–9 electrodes. E – Left side shows rhythmic delta activity (green arrow – LAF 1–6, LAOF 7–10 and LPOF 8–10) at the same time, but no definitive ictal pattern, showing that the seizure onset lateralizes to the right side. Right frontal (RF) right anterior frontal (RAF), right anterior orbitofrontal (RAOF), right posterior orbitofrontal (RPOF), left anterior frontal (LAF), left anterior orbitofrontal (LAOF) and left posterior orbitofrontal (LPOF) are shown.

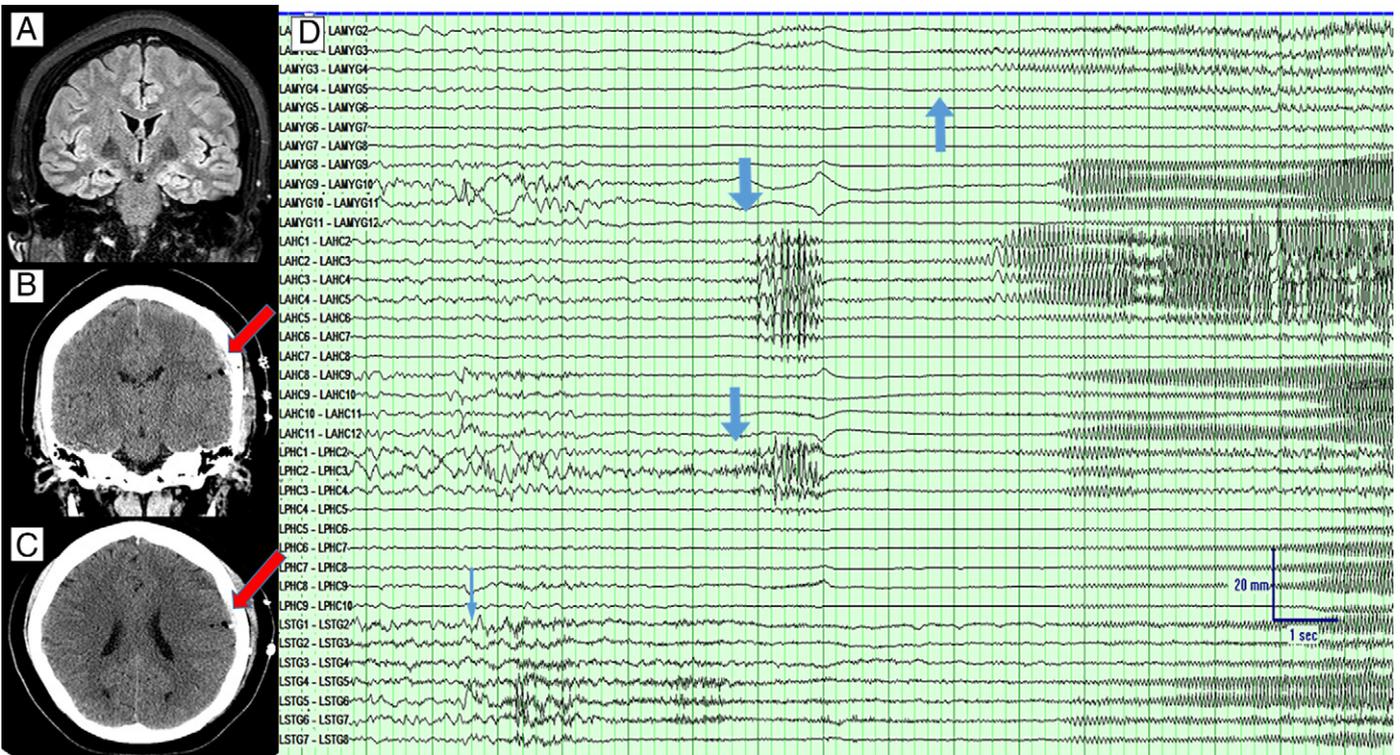


Fig. 3. A – Pre-surgical MRI of the brain shown in coronal section, with no pathology. B and C – Immediate post-explantation CT scan showed a small left parietal extra-axial hemorrhage and edema at the site of implantation (red arrows) in coronal section (B) and axial section (C). D – Seizure onset pattern recorded from the implanted sEEG electrodes showing brief low amplitude fast activity in LSTG electrodes (thin blue arrow), which then stopped, followed by the development of a clear ictal pattern in LAHC and LPHC followed by LAMYG (thick blue arrows). Left amygdala (LAMYG), left anterior hippocampus (LAHC), left posterior hippocampus (LPHC) and left superior temporal gyrus (LSTG).

of tissue damage due to hemorrhage and edema following explantation of invasive electrodes [5,6]. Similarly, our patients monitored with sEEG had MRI changes after explantation. Patient 1 had cortical and sub-cortical electrode track hyper-intensities that were evident in MRI images one year post-explantation (Fig. 1D–G). Patient 2 had linear (electrode tract) and nodular (superficial) micro-hemorrhages visible on susceptibility-weighted imaging sequences (Fig. 2B and C). Patient 3 had a post-explantation brain CT that showed asymptomatic superficial frontal hemorrhage (Fig. 3B and C).

The effectiveness of symptomatic microlesions secondary to implanted deep brain stimulation depth electrodes is a well-documented phenomenon in patients with Parkinson's disease [9]. Similarly, long-term data from the anterior nucleus of thalamus (ANT) DBS electrodes also demonstrated a reduction in seizure rate during the first three months post-implantation prior to initiation of therapy. The beneficial response in seizure control could be primarily related to the micro-thalamotomy caused by electrode insertion, but the study design could not assess the long-term effects of micro-thalamotomy in isolation [10]. However, one has to account for the differences in the electrode size between sEEG (0.8 mm) vs DBS (1.27 mm).

A typical sEEG investigation involves implantation of 10–15 penetrating depth electrodes targeting potential seizure onset and propagation sites distributed within the cortico-subcortical regions. It is possible that these depth electrodes during implantation or explantation inadvertently disrupted the cortical laminar organization or transected the long cortico-subcortical axons [11]. Acute contusions, infarction, and chronic inflammation around the electrode track have been documented in histopathology of the resected brain following invasive EEG monitoring for epilepsy surgery [12]. Any of these pathological changes can contribute to an altered network associated with seizure remission. One study reported that multiple hippocampal transections could improve seizure control [13]. It is possible that intracranial electrode implantation could similarly disrupt the ictal network resulting in transient or sustained seizure cessation.

Patient 1 had also undergone extra-operative direct cortical stimulation of the hippocampal electrode for functional mapping of the memory with sustained stimulation [14,15]. It is unclear if this approach had any contribution to seizure remission [16]. Seizure remission after mild or clinically unapparent injury from intracranial electrode placement may suggest that the epileptogenic zone can be altered by small lesions which is similar to the radiofrequency ablation techniques and MRI-guided laser interstitial thermo-ablation techniques that have been adapted at some centers with clinical success [17]. Finally, the presence of sEEG-induced lesions in regions outside the seizure foci may have contributed to the disruption of the epileptogenic network and contributed to sustained seizure remission as the epileptic network is complex and involves interactions between primary focus and other cortical-subcortical areas.

5. Conclusion

We report seizure remission in 3 patients with TRE following sEEG evaluation and the potential role of a localized cortical injury, in the area of epileptogenesis to result in seizure cessation. This series highlights the potential need for monitoring patients longer following intracranial electrode explantation prior to a planned neuro-modulation or a resective surgery.

Abbreviations

sEEG	stereotactic electroencephalogram
MRI	magnetic resonance imaging
FDG-PET	5-fluorodeoxyglucose positron emission tomography
MEG	magnetoencephalogram
SPECT	Single photon emission computed tomography

ASD	anti-seizure drug
IAP	intra-carotid amobarbital procedure
IQ	intelligence quotient
RNS	responsive neuro-stimulation
ANT	anterior nucleus of thalamus
DBS	deep brain stimulation
TPM	topiramate
ZNS	zonisamide
LCM	lacosamide
LEV	levetiracetam
CBZ	carbamazepine
VPA	valproic acid
PHT	phenytoin
PB	phenobarbital
LTG	lamotrigine
CZP	clonazepam

Ethics

This case series involves 3 subjects who have undergone sEEG (intracranial monitoring) and post-explant follow-up as per standard of care and treatment. Informed written consent was obtained from the patient before the surgical procedure as part of standard of care. Our IRB waived the need of a separate IRB for publishing a case series. The privacy right of the subject's was observed.

Declaration of competing interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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