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De novo temporal intermittent rhythmic delta activity after laser interstitial thermal therapy for mesial temporal lobe epilepsy predicts poor seizure outcome

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HIGHLIGHTS

- Patients with mesial temporal sclerosis on pre-operative MRI have high chances to develop temporal intermittent rhythmic delta activity (TIRDA) on post-laser interstitial thermal therapy (LITT) EEG.
- TIRDA on post-LITT EEG can predict unsuccessful seizure outcomes.
- Most of the patients who underwent successful anterior temporal lobectomy after LITT had TIRDA on their post-LITT EEG.

ABSTRACT

Objective: To evaluate EEG abnormalities, particularly development of temporal intermittent rhythmic delta activity (TIRDA) after laser interstitial thermal therapy (LITT) and assess the role of further surgery after LITT.
Methods: We retrospectively identified consecutive cases of LITT for the prevalence of post-operative TIRDA. We assessed baseline demographics, clinical variables including age of seizure onset, age at surgery, pre-operative and post-operative EEG changes.
Results: 40 patients underwent LITT for drug-resistant temporal lobe epilepsy (TLE), 29 met inclusion criteria. Median duration of follow-up was 15 months. Ten patients had post-LITT ipsilateral TIRDA, another two demonstrated post-operative TIRDA but they occurred contralateral to the side of ablation. None of the patients with TIRDA on their post-LITT EEG became seizure-free. Six out of 29 patients (21%) eventually required anterior temporal lobectomy (ATL), and of those 6 patients 4 (66%) had evidence of TIRDA on their post-LITT follow up EEG. The sensitivity and specificity of post-LITT TIRDA in predicting surgical failure was 57.14% and 100% respectively.
Conclusions: Post-LITT TIRDA may serve as a biomarker to predict unsuccessful seizure outcome following LITT and be an early indicator for ATL.
Significance: The presence of TIRDA following LITT should prompt early consideration for reoperation.

1. Introduction

Temporal intermittent rhythmic delta activity (TIRDA) is an EEG pattern characterized by intermittent rhythmic sinusoidal bursts and trains of delta activity localized over the temporal regions (Cobb, 1945). Unlike other intermittent rhythmic delta activities such as occipital intermittent rhythmic delta activity (OIRDA) and frontal intermittent rhythmic delta activity (FIRDA), TIRDA

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represents a pre-operative EEG pattern that predicts focal seizures in patients with temporal lobe epilepsy (TLE) (Reiher et al., 1989). Of all EEG recordings obtained in a general clinical neurophysiology laboratory setting, TIRDA is identified in only 0.3% (Normand et al., 1995). In a surgical series, TIRDA was observed in 52 of 129 patients (40.3%) with drug-resistant focal epilepsy (Di Gennaro et al., 2003). The characteristic electrographic features of TIRDA include high-voltage, regional, temporal, monomorphic, rhythmical, 1–3.5 Hz slow waves. Bursts and trains of TIRDA may last up to 20 seconds in patients with TLE who are being evaluated for surgery (Geyer et al., 1999). Additionally, TIRDA is often associated with temporal epileptiform discharges with a high positive predictive value for TLE when it is present (Normand et al., 1995; Geyer et al., 1999).

Epilepsy surgery in the treatment of patients with drug-resistant temporal lobe epilepsy (TLE) has been validated in controlled clinical trials (Wiebe et al., 2001; Engel et al., 2012), and remains a standard of care (Engel et al., 2003) but has traditionally been performed with a craniotomy (Schaller and Cabrilo, 2016). The use of minimally invasive surgery is increasing as a surgical option (Ellis et al., 2016; Chang et al., 2015). Laser interstitial thermal therapy (LITT) has become a newer initial option in the surgical management of mesial TLE (mTLE) (Wicks et al., 2016; Petito et al., 2018). We observed TIRDA appearing do novo after LITT. Therefore, we sought to determine its clinical significance and to speculate on its origin in view of the super-selective neuroanatomic effects of amygdalohippocampotomy produced by LITT, without the confounding influence of neocorticectomy.

2. Methods

After approval by the institutional review board established at the Mayo Clinic, we performed a chart review of all patients who underwent LITT. The study involved patients with drug-resistant focal epilepsy operated at the Mayo Clinic in Florida between March 2013 and May 2017. All patients underwent pre-operative scalp-based video-EEG monitoring during a standard presurgical evaluation (Rosenow and Luders, 2001; Ryvlin and Rheims, 2008; Petito et al., 2018) prior to undergoing LITT and anterior temporal lobectomy (ATL). All patients underwent pre-operative scalp video-EEG monitoring during pre-surgical evaluation and invasive EEG in selected cases to confirm localization of the seizure-onset zone. Standard EEG was performed in each case prior to video-EEG monitoring and post-operatively according to an institutional protocol following the acute effects of surgery. Preoperative and postoperative standard EEG after LITT was compared in the analysis. Post-operative EEG following LITT was interpreted by two board-certified clinical neurophysiologists-epileptologists (AMF and WOT) unblinded to the history of LITT, but blind relative to outcome. Video-EEG monitoring was repeated when LITT was unsuccessful and re-operation was considered. For the purposes of study, we assessed baseline demographics (age, gender) and clinical variables including age of seizure onset, age at surgery obtained from charted information during the pre-surgical evaluation. Patients were included in the study if they were localized to the temporal lobe, were drug-resistant and disabled by their seizures, underwent surgery at our center, obtained pre- and post-operative EEG, and were motivated to undergo surgery and able to sign informed consent. They were excluded from analysis when post-ablation EEG changes were unable to be documented following LITT, when prior temporal lobe epilepsy surgery had been performed prior to LITT, when extratemporal surgery with LITT was performed, if severe cardiopulmonary or system disease contraindicated surgery, and when injury to the temporal lobes was in question from another structural-metabolic cause (e.g., traumatic contusion, brain tumor, stroke, etc.) aside from hippocampal sclerosis.

2.1. Statistical analysis

Fischer's exact test assessed the categorical outcome for patients before and after LITT comparing seizure-free vs non-seizure-free results. The same test was used to compare presence and absence of TIRDA with pre and post-LITT. A p- value of 0.05% or less reflects clinical significance.

3. Results

3.1. Demographics

During the study period, a total of 40 patients (55.2% male) underwent LITT for drug-resistant epilepsy. The breakdown is listed in Fig. 1**.** Clinical seizures were diagnosed in all patients and focal impaired awareness seizures and/or focal to bilateral generalized tonic-clonic seizures was well documented in all cases undergoing LITT. The median age at the time of surgery was 48 years old. Of the 40 patients, 11 patients were excluded from the study. Reasons for exclusion were due to the lack of available post-surgical EEG. There were no differences in the demographic or clinical characteristics between the 2 groups.

3.2. MRIs

All 40 patients underwent high-resolution 1.5 T (if a vagus nerve stimulator was present) or 3.0 T brain MRI utilizing an epilepsy protocol. Mesial temporal sclerosis (MTS) was identified in 23/29 (79.3%) of patients before LITT. Other pre-LITT MRIs included normal (n = 2), Type II focal cortical dysplasia (n = 2), and non-specific gliosis (n = 2). The patients who did not have MTS on the pre-LITT MRI also did not develop post-LITT TIRDA. The mean ablation volume was 2618.7 cubic centimeters and the percent ablation of the amygdala was 41.6% and the hippocampus 53.3%. Fig. 2 is a representative MRI brain without contrast pre-LITT (panels A) demonstrating right MTS and a representative image of gliosis involving the medial temporal lobe following LITT.

3.3. EEGs

Twenty-nine patients had pre-LITT and post-LITT EEG available for analysis. We compared pre- and post-LITT standard EEG. Video-EEG monitoring was used separately for surgical decision-making. Fig. 1 is a flow chart demonstrating the breakdown of patients with TIRDA. Two patients with left MRI – PET + TLE had a normal MRI and underwent intracranial EEG following scalp-based video-EEG monitoring to confirm the site of seizure onset. Invasive monitoring demonstrated left hippocampal onset in both cases (seizure free following LITT). Four of 29 patients undergoing LITT demonstrated recurrent bursts of TIRDA on pre-operative EEG obtained during video-EEG monitoring (Table 1). Of these four patients with TIRDA, one remained ipsilateral (not seizure free) and 1 appeared contralateral (seizure free) following LITT. The other two patients had TIRDA eliminated post-LITT, one was seizure free and the other one was not. Fig. 3 is a representative epoch of the post-LITT EEG demonstrating right TIRDA. TIRDA was always ipsilateral to the side of the lesion and surgery judged by pre-operative video-EEG monitoring performed during pre-LITT evaluation. Overall, 12/29 (41%) had a post-LITT EEG that contained TIRDA compared with 4/29 (10.3%) on pre-operative evaluation. The post-operative delta frequency often slowed to 1–2 Hz **(**Fig. 4**).**

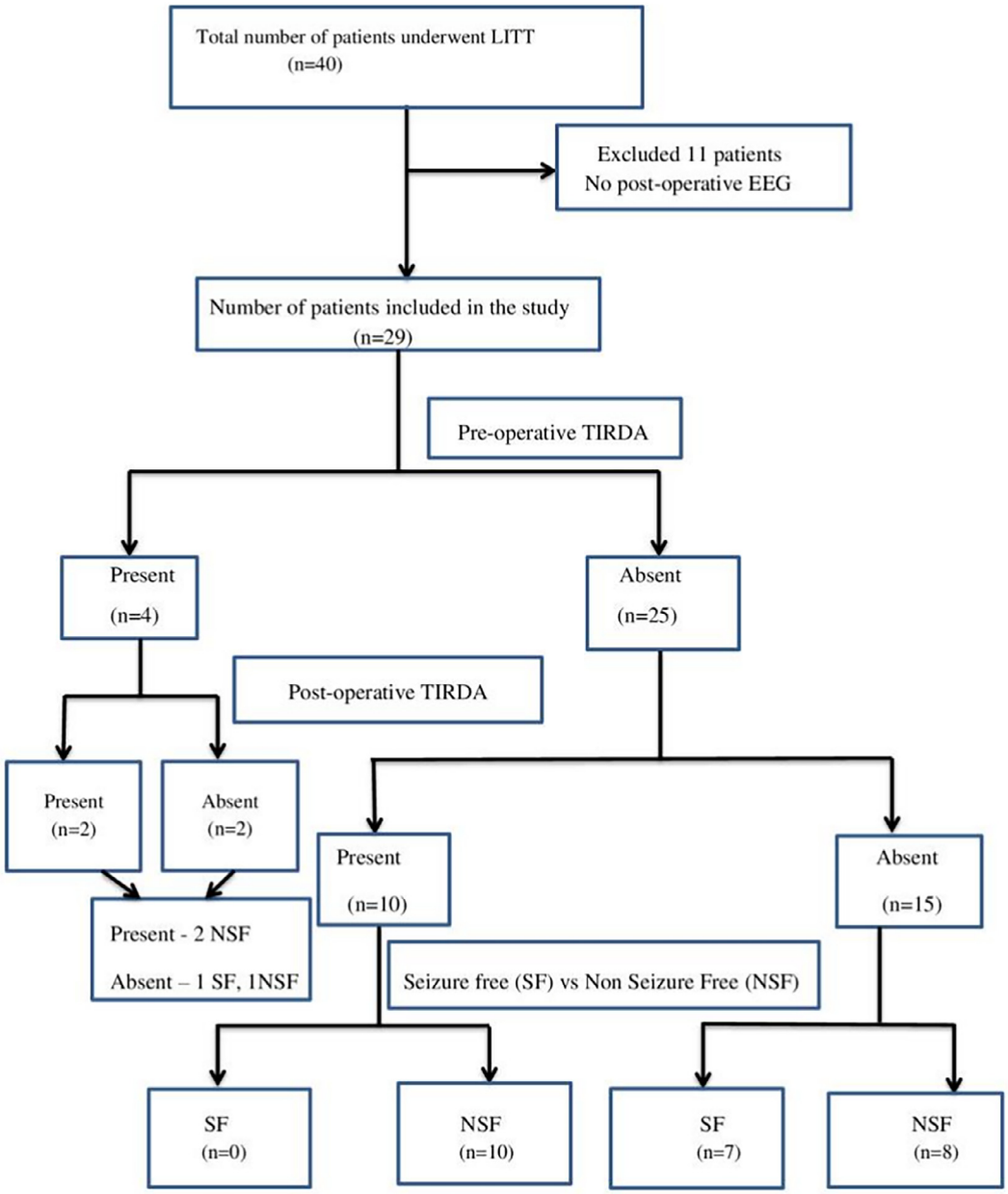

Fig. 1. Flow diagram of patients evaluated for TIRDA after LITT. SF = seizure-free, NSF = Not-seizure free.

3.4. Surgery

Twenty-nine patients underwent LITT during the study period with a mean follow-up of one year. The occipital-temporal approach to the mesial temporal anatomical structures was taken in all cases. The amygdala and hippocampus were partially ablated in every case. Seventeen patients (58.6%) underwent left temporal LITT and 12/29 (41.4%) patients had right-sided ablation. 23/29 patients (79.3%) had pre-LITT MTS which correlated with TIRDA while patients without MTS on pre-LITT MRI never develop post-LITT TIRDA ipsilateral to the side of ablation. Those evaluated for anterior temporal lobe open resection after failed LITT underwent repeat video-EEG monitoring to validate the approach to same-side surgery.

3.5. Outcome

Nineteen patients of 40 (47.5%) were seizure-free with a median follow-up of 15 months (minimum duration 6 months). Complications included quadrantanopsia (n = 2), post op headaches (n = 5) and memory complaints (n = 6) and mood changes (anxiety n = 2; depression, n = 3) published previously (Petito et al., 2018). None of the patients with TIRDA on their post-LITT EEG became seizure-free (Table 2). The sensitivity of post-LITT TIRDA in predicting post-ablation failure was 57.14%. However, the specificity was 100% in our cohort when TIRDA was present on the post-LITT EEG with a positive predictive value in every patient with this finding on EEG possessing a non-seizure free outcome. Negative predictive value was 47.06%. The overall probability that a patient will be correctly classified as having seizure-free or non-seizure free outcome was 68.97%.

The total ablation volume, percentage ablation of hippocampus, percentage ablation of amygdala was not found to have statistical significance with presence or absence of TIRDA post-LITT (p-values −1, 0.44, 0.7 respectively). Six patients post-LITT eventually underwent anterior temporal lobectomy (ATL) due to continued seizures. Four patients had evidence of TIRDA on the post-LITT EEG, and 4/6 (66.7%) of post-ATL patients remained seizure-free.

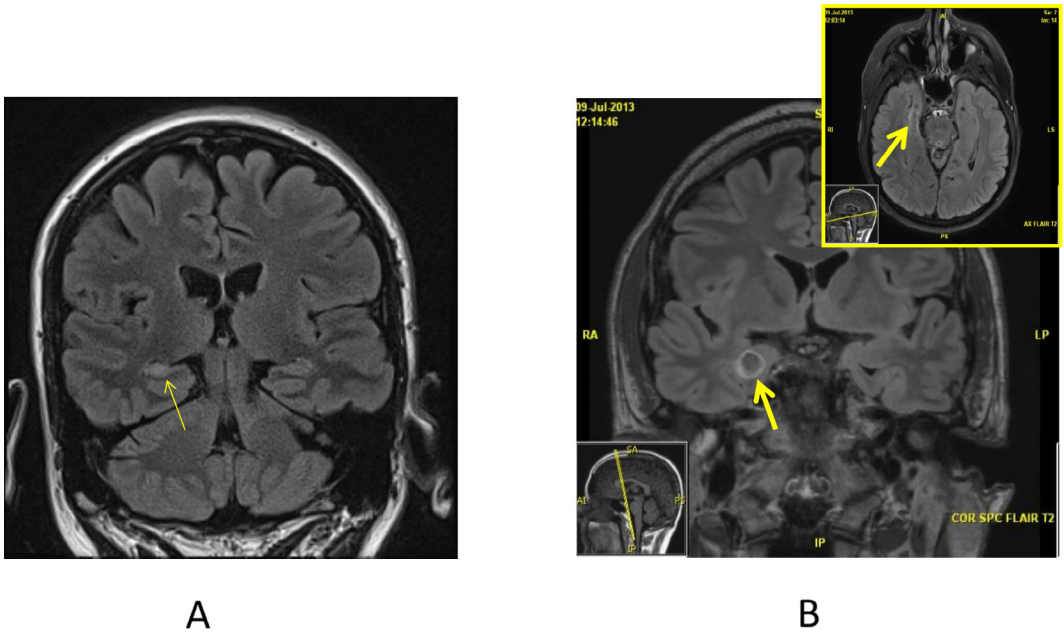

Fig. 2. (A) Pre-operative Brain MRI demonstrating right MTS (thin arrow) and (B) post-LITT in the coronal and transverse (insert) plane demonstrating ablated amygdalohippocampal complex (thick arrow). Post-operatively the patient has remained seizure-free.

Table 1
LITT and the presence of TIRDA and no TIRDA.

LITT	TIRDA	No TIRDA	Total
Pre-LITT	4	0	4
Post-LITT	10*	15	25
Total	14	15	29

For this calculation, to make both groups mutually exclusive, only 10 patients were new post-LITT TIRDA patients (2 other patients we included in the pre-LITT group. P = 0.042.

4. Discussion

The presence of TIRDA may infrequently occur in extratemporal epilepsy but strongly suggests ipsilateral TLE (Geyer et l., 1999). In a previous study of 127 patients Reiher et al. found TIRDA in 45 (35%) patients with TLE (Reiher et al., 1989). In a more recent series DiGennaro et al found TIRDA in 52 out of the 129 patients (40.3%) patients studied with focal epilepsy (Di Gennaro et al., 2003**).** Pre-operative correlation has been made associating TIRDA and mTLE, MTS, anterior temporal interictal epileptiform discharges on inter-ictal EEG and a 5–9 Hz temporal ictal discharge during video-EEG monitoring supporting the mesial temporal lobe as a generator (Di Gennaro et al., 2003). We found that 12/29 (41.4%) of patients who underwent LITT showed development of TIRDA on their post-LITT EEG and none of them became seizure free. Furthermore, 66% of patients with post-LITT TIRDA required ATL for continued drug-resistant TLE. In this study, we found TIRDA incidence quadrupled following LITT. While the presence of TIRDA on EEG is a favorable localizing feature during the preoperative evaluation of TLE, we found post-LITT TIRDA portends an unfavorable prognosis for seizure freedom with none of the patients seizure-free when TIRDA was present on the post-LITT EEG.

The unique technique using LITT to spare the neocortex and ablate only mesial temporal structures, provides opportunity for research in functional connectivity of neural networks involved in TLE. Our findings support the amgdalohippocampal complex as one of the principal site involved in generating TIRDA as suggested by prior investigators (Geyer et al., 1999; Di Gennaro et al., 2003), but in contrast to others who have suggested TIRDA originates from lateral temporal neocortex and unrelated to mTLE (Serafini et al, 2016). We speculate that TIRDA reflects a release mechanism that is projected to overlying neocortical regions by disconnection of the hippocampus. This suggests that both mesial and lateral temporal neocortical interconnecting subcortical white matter tracks are necessary for expressing TIRDA on EEG via a mesial-lateral temporal neurophysiological neural network. From a qualitative standpoint, our patients with TIRDA on EEG several months after LITT often manifested a degree and frequency of TIRDA that was atypical. We speculate that post-LITT TIRDA is due to incomplete ablation of the neural network involved in the mesial TLE syndrome, which explains why those manifesting TIRDA on EEG were not seizure-free following LITT. Other forms of intermittent rhythmic delta activity have been identified but typically reflect extratemporal origin (Motomura et al., 2012; Brigo, 2011).

Our findings are robust. In addition to the ability of LITT to anatomically localize a mesial temporal source on a standard inter-ictal EEG, the presence of TIRDA predicted surgical failure in the majority of patients where it was encountered. In our prior report of 33 patients undergoing LITT, more than half became seizure-free following LITT and four of five failures became seizure-free after ATL (Petito et al., 2018). In this study, we found TIRDA was significantly increased over baseline in patients where LITT failed to produce post-operative seizure freedom. We did not address other biomarkers in this report (e.g., spikes, sharp waves, intermittent polymorphic delta, etc.), though our post-LITT results regarding TIRDA contrast the favorable effect observed when inter-ictal epileptiform discharges are eliminated by LITT (Luedke et al., 2016). In fact, none of the patients with de novo appearance of post-operative TIRDA became seizure-free after LITT. This suggests newly identified post-LITT TIRDA may be an early and easily obtained biomarker to indicate surgical failure. We suggest when post-LITT TIRDA is encountered, early consideration of ATL in patients with mesial TLE be given at the first indication of surgical failure. In our cohort 66.7% of patients who underwent ATL post-LITT had TIRDA on their follow up EEG and ultimately became seizure-free.

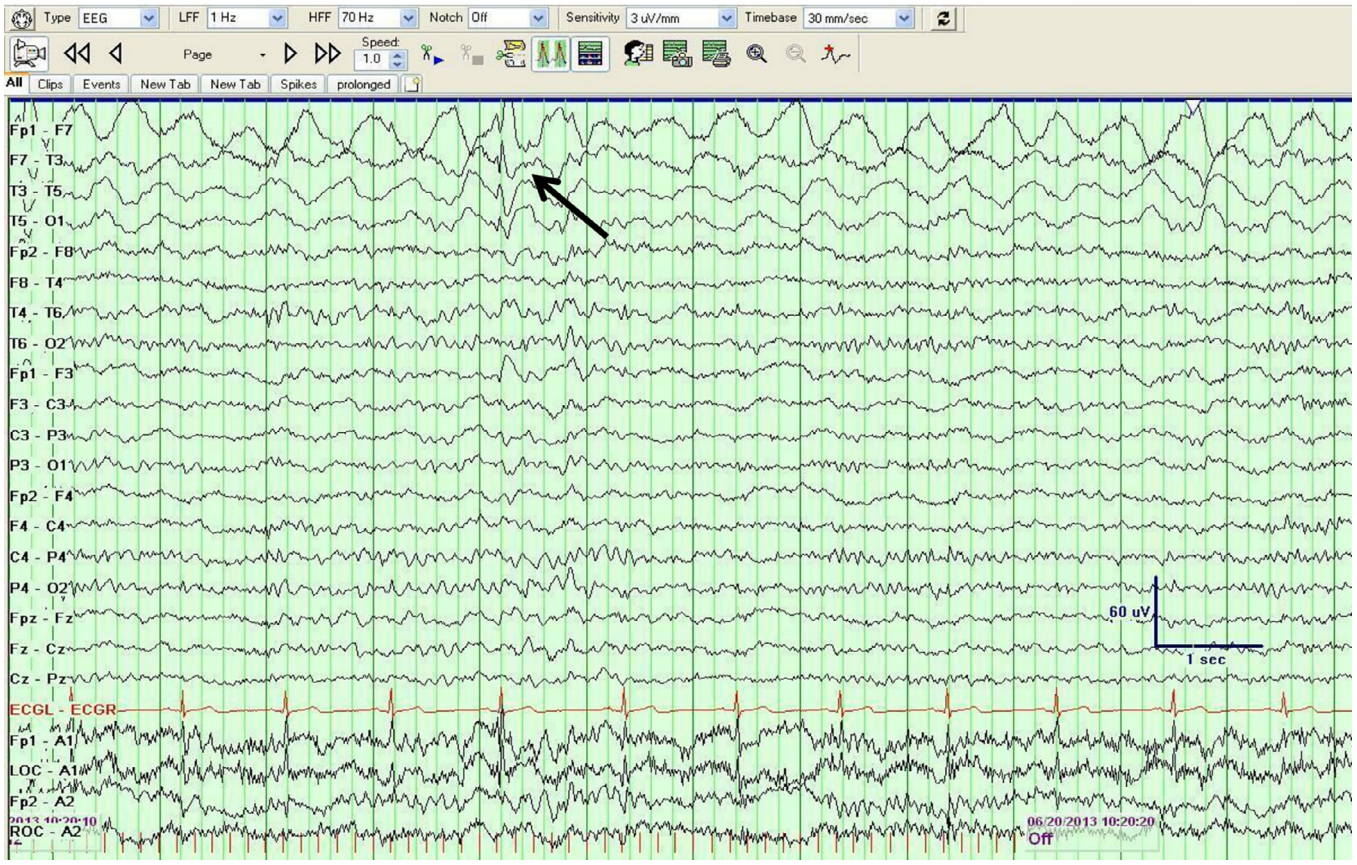

Fig. 3. Pre-operative run of left TIRDA with left regional temporal spike simultaneously supporting different generator regions.

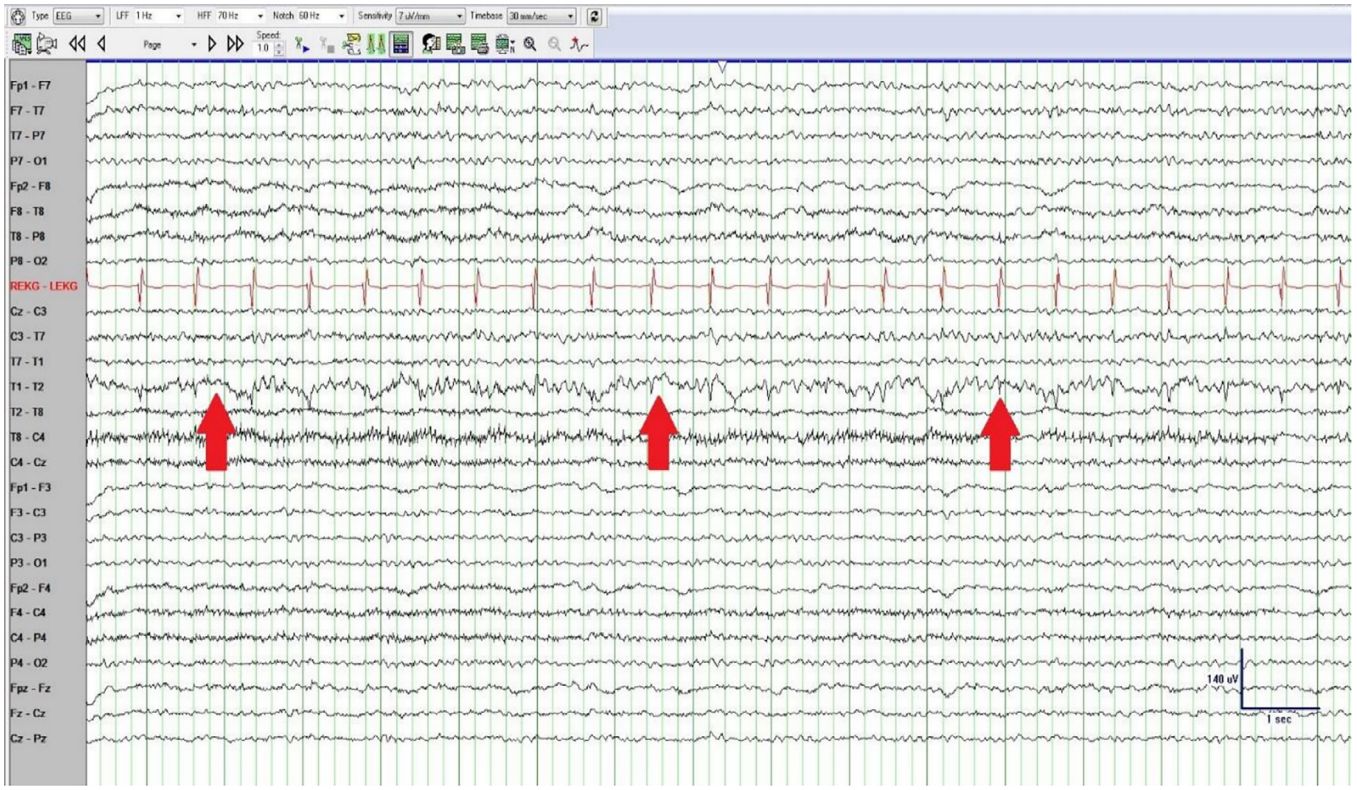

Fig. 4. Post-operative EEG demonstrating slow (1–1.5 Hz) right TIRDA following LITT in a patient with right MTS and concordant pre-surgical evaluation. Post-operatively the patient had persistent seizures (Engel Class III).

Table 2
Post-LITT TIRDA and seizure-free compared with non-seizure free outcome.

Post-LITT TIRDA	Seizure free	Not seizure free	Total
TIRDA present	0	12	12
TIRDA absent	8	9	17
Total	8	21	29

P = 0.0089.

Our study has the usual limitations of a retrospective study introducing bias in patient selection. Nonetheless the cohort selected was fairly homogeneous with MTS as the principal etiology and included all patients undergoing LITT at our center. Additionally, the pre and post-LITT assessment used the patient as a "control". Another potential limitation was the inherent sampling bias that limited the ability to compare the true prevalence of ipsilateral and contralateral TIRDA to that identifiable using standard EEG. In addition, some variability was inherent relative to timing of the post-LITT EEG and stages of sleep recorded to draw further detailed comparison between TIRDA before and after surgery. While the relationship of TIRDA to the amygdalohippocampal complex appears reproducible, we were unable to verify that the presence of pre-LITT TIRDA was specific only for this region as opposed to other locations abutting the temporal lobe (e.g., insula, subcortical nodular heterotopias, neocortical location, etc.). The number of patients in our study is relatively small, however it is comparable to other series (Waseem et al., 2015; Ellis et al., 2016; Wicks et al., 2016; Kang et al., 2016; Jermakowicz et al., 2017) reporting outcome in patients after LITT. Still, the relationship of the post-operative TIRDA to surgical failures is compelling and suggests our finding should be validated in larger studies involving additional centers.

5. Conclusion

We observed an increase in de novo TIRDA on post-operative EEG in our patients undergoing LITT for mTLE. TIRDA may be an EEG biomarker that predicts a poor prognostic outcome for seizure freedom following LITT. This in turn be used to help counsel patients and may prompt early consideration of re-operation in the form of repeat LITT or ATL. With the increasing role of minimally invasive surgery in the management of patients with epilepsy, more staged operations and the number of procedures is anticipated to increase.

Funding

None.

Conflict of interest

None of the authors have potential conflicts of interest to be disclosed.

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