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Intraoperative hippocampal electrocorticography frequently captures electrographic seizures and correlates with hippocampal pathology

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HIGHLIGHTS

- Intraoperative hippocampal electrocorticography frequently captures spontaneous seizures.
- Electrographic seizures are more likely in patients without disruption of hippocampal architecture.
- Intraoperative hippocampal seizures may result from deafferentation from the temporal neocortex.

ABSTRACT

Objective: Relationship between electrographic seizures on hippocampal electrocorticography (IH-ECoG) and presence/type of hippocampal pathology remains unclear.
Methods: IH-ECoG was recorded for 10–20 min from the ventricular surface of the hippocampus following removal of the temporal neocortex in 40 consecutive patients. Correlation between intraoperative hippocampal seizures and preoperative MRI, hippocampal histopathology, and EEG from invasive monitoring was determined.
Results: IH-ECoG captured electrographic seizures in 15/40 patients (in 8/23 with abnormal hippocampal signal on MRI and 7/17 patients without MRI abnormality). Hippocampal neuronal loss was observed in 22/40 (Group 1), while 18/40 had no significant neuronal loss (Group 2). In Group 1, 4/22 had seizures on IH-ECoG, while 11/18 had electrographic seizures in Group 2. In 24/40 patients who underwent prolonged extraoperative intracranial EEG (IC-EEG) recording, hippocampal seizures were captured in 14. Of these, 7 also had seizures during IH-ECoG. In 10/24 IC-EEG patients without seizures, 3 had seizures on IH-ECoG.
Conclusions: IH-ECoG frequently captures spontaneous electrographic seizures. These are more likely to occur in patients with pathologic processes that do not disrupt/infiltrate hippocampus compared to patients with intractable epilepsy associated with disrupted hippocampal architecture.
Significance: Intraoperative hippocampal seizures may result from deafferentation from the temporal neocortex and disinhibition of the perforant pathway.

1. Introduction

In patients with pharmacoresistant temporal lobe epilepsy (TLE), the epileptogenic zone commonly involves the medial temporal lobe structures including the hippocampus. Removal of the hippocampus by resecting the medial temporal lobe either selectively or along with the temporal neocortex provides lasting seizure freedom (Datta et al., 2009; Kumar et al., 2013; Mittal et al., 2005; Olivier, 2000; Tanriverdi et al., 2008; Wiebe et al., 2001; Wieser et al., 2003; Wieser and Yasargil, 1982; Yasargil et al., 2010). Usefulness of electrocorticography (ECoG) as a tool during epilepsy surgery remains controversial (Chen et al., 2006; Mittal et al., 2016; San-juan et al., 2011; Schwartz et al., 1997; Stefan et al., 1991). Most investigators have directed their efforts at

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recording ECoG from the lateral and mediobasal temporal lobe surface during temporal lobe surgery (Fiol et al., 1991; Uda et al., 2015). There is very limited information in the literature describing intraoperative recording directly from the hippocampus prior to its removal. Interictal hippocampal spiking has been observed intraoperatively using either strip electrodes over the ventricular surface (McKhann et al., 2000; Oliveira et al., 2006; Polkey et al., 1989; Sugano et al., 2007; Tanaka et al., 1996) or using depth electrodes targeting the hippocampus (Kanazawa et al., 1996). Intraoperative ECoG recorded over the ventricular surface of the hippocampus has been used to guide the extent of hippocampal resection in patients with both lesional and non-lesional TLE (McKhann et al., 2000; Sugano et al., 2007).

Rarely, spontaneous electrographic seizures have been captured by intraoperative hippocampal ECoG (Tanaka et al., 1996). In addition, spontaneous electrical activity resembling seizures have been demonstrated by several groups *in vitro* in hippocampal slice recordings (Borck and Jefferys, 1999; Karnup and Stelzer, 2001; Swartzwelder et al., 1988). The significance of electrographic seizures captured from the hippocampus remains unclear.

We report our experience with systematic ECoG recording from the ventricular surface of the hippocampus during temporal lobe epilepsy surgery and discuss possible pathophysiological mechanisms underlying these spontaneous electrographic events.

2. Methods

2.1. Patients

The study population consisted of 40 consecutive patients with medically intractable TLE who underwent tailored temporal lobe resection including medial temporal lobe structures by a single epilepsy surgeon (SM). A subset of this study group underwent staged epilepsy surgery with long-term extraoperative video-EEG recording with intracranial electrodes (IC-EEG). All patients were treated at the Wayne State University/Detroit Medical Center Comprehensive Epilepsy Center. The clinical, electrophysiological (including long-term video-telemetry and IC-EEG), radiographic, and histopathological characteristics were prospectively collected for each patient. Relationship between electrographic seizures [recorded during intraoperative hippocampal ECoG (IH-ECoG) and/or during long-term extraoperative IC-EEG monitoring in patients undergoing staged surgery] and clinical parameters, preoperative MRI, hippocampal histology, as well as, seizure outcome was analyzed. Patients with less than one year follow-up were excluded from the seizure outcome analysis. The study was approved by the local Institutional Review Board.

2.2. Surgical technique

Patients were placed in supine position with the head turned away from the side of surgery. Most patients were under general anesthesia using a combination of midazolam, pancuronium, fentanyl, and propofol (n = 29); while propofol and remifentanil was used for patients that underwent surgery under local sedation (n = 11). Following craniotomy, patients underwent intraoperative ECoG (10–20 min) over the lateral surface of the temporal lobe to help define the posterior resection margin in cases of one-stage tailored temporal lobe resection. This was followed by *en bloc* microsurgical resection of the temporal neocortex with exposure of the ventricular surface of the hippocampus in all individuals. The hippocampus and parahippocampal gyrus along with their blood supply were preserved. After neocortical resection, patients underwent a brief (10–20 min) IH-ECoG using a 4-contact strip electrode placed along the long axis of the hippocampus (see below). Subsequently, the entire head and body of the hippocampus (3.5–4 cm) was microsurgically removed *en bloc* up to the lateral mesencephalic sulcus (along with the parahippocampal gyrus) followed by subpial removal of the amygdala. The extent of hippocampal resection was not influenced by the results of IH-ECoG. Also, post-resection IH-ECoG of the residual tail of the hippocampus was not performed. Hemostasis was obtained after removal of the mesial temporal structures followed by routine closure.

2.3. Intraoperative hippocampal ECoG

The depth of anesthesia sedation was adjusted during ECoG to obtain continuous EEG recording without suppression. Antiepileptic medication was not discontinued prior to surgery. Intraoperative ECoG was recorded over the exposed ventricular surface of the hippocampus following *en bloc* removal of the temporal lobe neocortex including the temporal pole while preserving the entorhinal cortex (Fig. 1). IH-ECoG was performed using a 4-contact subdural strip electrode with platinum contact of 0.3 cm and interelectrode distance of 1 cm (PMT Corp., Chanhassen, MN or Ad-Tech Medical Instrument Corporation, Racine, WI) with electrode #1 placed over the tail of the hippocampus and electrode #4 covering the hippocampal head. *In situ* hippocampal EEG recording was performed over 10–20 min in a digitized monopolar referential format with a reference placed over the forehead at a sampling rate of 200 or 1000 Hz (Xltek EEG system, Natus Medical Corp., San Carlos, CA). EEG data were analyzed using a low frequency filter of 1 Hz and a high frequency filter of 70 Hz using referential and bipolar montages. EEG rhythms that exhibited temporal evolution in amplitude, frequency, and/or morphology were identified as electrographic hippocampal seizures.

2.4. Statistical analysis

We assessed whether there was an association between presence of intraoperative hippocampal seizures with various clinical, radiographic, electrophysiological, and histopathological variables using chi-square analysis, one-way between groups ANOVA, and appropriate descriptive statistics using SAS 9.3 for Windows. A p value of less than 0.05 was considered significant.

3. Results

Of the 40 patients included in this study, 15 (37.5%) had EEG rhythms on IH-ECoG that exhibited temporal evolution in amplitude or frequency usually recognized as electrographic seizures (Fig. 2). Hence, we refer to these intraoperative events as spontaneous electrographic hippocampal seizures. Table 1 outlines the relevant clinical, electrophysiological, neuroimaging, and histopathologic findings.

3.1. Patient demographics

There were slightly more females than males (22 vs 18) in the study population, but this did not reach statistical significance ($\chi 2 = 0.40$, n.s.). Average age for the sample was 39 years (SD = 39.6, range = 21–67) overall, 39.3 years (SD = 9.96) for females, and 38.7 years (SD = 13.7) for males. ANOVA indicated the difference in age was not significant. The difference in mean age for subjects with or without hippocampal seizures on IH-ECoG was not significant ($F[1,38] = 0.11$, n.s.). The mean seizure duration for patients with seizures recorded on IH-ECoG was 12 years, while it was 11 years in the patients without such seizures on IH-ECoG.