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Prospective and "live" fast ripple detection and localization in the operating room: Impact on epilepsy surgery outcomes in children

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ABSTRACT

Objective: Fast ripples (FR, 250–500 Hz) are proposed biomarkers of the epileptogenic zone on the basis of several retrospective reports linking postoperative seizure freedom to their complete resection. There are no clinical trials or prospective reports validating the use of FR as characterized by electrocorticography (ECoG), to guide the scope of epilepsy surgery, and to inform prognosis thereafter. We set out to prospectively evaluate the utility of FR resection to predict postoperative epilepsy outcomes, and examine the feasibility of "live" intraoperative FR ascertainment.
Methods: FR were prospectively reviewed in 30 consecutive pediatric cases including 11 reviewed "live" during surgery. Intraoperative ECoG studies were recorded at 2000 Hz sampling rate, interpreted conventionally to guide surgical resection, and visually inspected for FR. Seizure outcome was tallied for all 30 children.
Results: Median age at surgery was 9.1 years (interquartile range [IQR] 4.7–13.2), median ECoG duration was 10.5 min (IQR 8.0–13.2), and median postoperative follow-up was 58.4 months (IQR 25.7–79.0). FR were identified in 24 of 30 ECoG studies. The incomplete resection of FR was strongly linked to postoperative seizures (hazard ratio 11.6, $p = 0.005$). "Live" ECoG review in the operating room to ascertain FR proved feasible and did not differ from conventional FR ascertainment.
Significance:: In a prospective fashion, including "live" review, FR were detected in 80% of pediatric ECoG studies, and incomplete resection of FR cortex predicted postoperative seizures. These findings extend the notion that interictal FR are surrogate markers of the epileptogenic zone, and that their intraoperative localization could be used to inform prognosis and guide surgical resections in children.

1. Introduction

Interictal fast ripples (FR; 250–500 Hz) are high frequency oscillations, initially noted in animal models (Bragin et al., 1999b) and subsequently in human epilepsy (Bragin et al., 1999a,b), and constitute a potential biomarker of the epileptogenic zone. Retrospective studies (Akiyama et al., 2011; Jacobs et al., 2010; Okanishi et al., 2014; van Klink et al., 2014; van't Klooster et al., 2015; Wu et al., 2010), including one from this group utilizing intraoperative electrocorticography (ECoG) (Wu et al., 2010), have linked complete surgical resection of FR-containing cortex to seizure freedom, and incomplete FR resection to continued postoperative seizures. However, no prospective study has validated this association nor established the feasibility of "live" FR assessment during surgery.

The principal goals of this study were to extend our previously reported findings from a retrospective series to a prospective cohort, and to specifically determine whether postoperative seizure freedom is predicted by the complete resection of interictal FR-containing neocortex. Our secondary aim was to explore the feasibility of "live" intraoperative FR ascertainment.

2. Material and methods

2.1. Standard protocol approvals, registrations, and patient consents

The institutional review board at the University of California Los Angeles (UCLA) approved the use of human subjects and waived the need for written informed consent, as all testing was deemed

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clinically relevant for patient care. This study is not a clinical trial, and it is not registered in any public registry.

2.2. Study population

Children with medically refractory epilepsy who underwent epilepsy surgery for resection with the Pediatric Epilepsy Program at UCLA were consecutively recruited between October 2008 and August 2009, immediately following the enrollment of the last patient from our retrospective series (Wu et al., 2010). Refractory epilepsy was defined as monthly or greater seizure frequency, and failure of a minimum of three appropriately selected antiepileptic drugs (AEDs) (Kwan et al., 2010).

2.3. Patient evaluation

Our procedures for identifying appropriate surgical candidates have been described previously (Wu et al., 2010). Briefly, all children with medically refractory epilepsy referred during the study period underwent a standardized presurgical evaluation, which consisted of inpatient video-EEG monitoring, high resolution (1.5 T) brain magnetic resonance imaging (MRI), and ^{18}fluoro-deoxyglucose positron emission tomography (FDG-PET). Clinical characteristics abstracted from the medical record included sex, age of onset of epilepsy, age at surgery, duration of epilepsy (time between epilepsy onset and surgery), history of infantile spasms (including whether spasms were ongoing at the time of surgery), and the number of AEDs at surgery. FR data were unknown prior to surgery, and the surgical team was blinded to the presence and localization of FR at the time of surgery. The margins and extent of resections were determined according to our standard protocols, which have been described elsewhere (Wu et al., 2010). Postsurgical follow-up occurred at six months and at least annually thereafter.

2.4. Surgical procedures and ECoG recording

Our intraoperative procedures, including anesthetic considerations (Constant et al., 2005), have been described previously (Wu et al., 2010). Similar to our retrospective series, all ECoG studies utilized macroelectrodes (AdTech, Racine, WI), 2000 Hz sampling rate with an anti-aliasing 500 Hz high-frequency filter and no low-frequency filter, on the Harmonie long-term monitoring system (Alpine Biomed; Montreal, Canada).

Importantly, the final area of resection was determined solely by combining video-EEG, neuroimaging, and ECoG data. FR location was not considered in surgical planning, as the ultimate determination of the location and spatial extent of the resection was made before FR review, either prospectively or "live" (see below). To minimize ECoG sampling bias, at least one non-contiguous "control" region not suspected to be epileptogenic from presurgical testing was recorded. At least two lobes were sampled for each ECoG, with the exception of several cases such as completion of a hemispherectomy in which no reasonable control region was accessible. Extraoperative intracranial recording was not conducted for any patients in this cohort.

The scope of ECoG sampling was expected to vary among patients on a clinical basis. In general, clinicians sought to interrogate cortex within the boundaries and at the margins of each planned resection, as well as cortex with a "control" region thought to be well outside of the epileptogenic zone. This strategy was limited in some cases based on physical accessibility (i.e. small craniotomy) or abundant scarring or absent cortex based on prior injury. ECoG sampling was limited to a single hemisphere in all cases.

All prospective FR ascertainment took place within one week of surgery, and often within 24 h, outside of the operating room. A subset of these intraoperative ECoG studies were also assessed for FR "live", immediately after the end of recording, while still in the operating room and before resection began. After the "live read" phase, the usual prospective review, similar to all other prospective reviews described above, was performed to re-review these ECoGs. This was intended to establish the reproducibility with which FR are identified and localized, with both the time-limited "live read" in the operating room and the unhurried prospective read outside the operating room.

Whether the surgical resection included all, some, or none of the FR events was tallied. In addition, we determined whether FR were located inside or outside the MRI lesion, the FDG-PET hypometabolic region, or both. As in our prior publication (Wu et al., 2010) and as advocated by v'ant Klooster and colleages (van't Klooster et al., 2015) for statistical considerations, we have focused on the presence or absence of FR rather than normalized or adjusted event rates which take into consideration the total number of channels in which any particular ECoG marker is observed.

2.5. FR identification

Methods of FR review and identification were previously published (Wu et al., 2010). Briefly, for both the prospective review and the "live" review, each ECoG was reviewed twice, such that the blinded reviewer had no knowledge of the type and location of resection, the type and location of neuroimaging finding, and the location of "control" region not suspected to be epileptogenic. The entire ECoG sample was first reviewed with a referential montage (reference electrode on the contralateral frontal scalp), with a high-pass 250 Hz filter and a low-pass 500 Hz filter, at a maximally allowed time scale of 338 mm/sec, to visually identify and mark candidate FR events. This minimized the potential bias of selecting FR events on the basis of coincident epileptiform discharges. The entire record was reviewed a second time with a vertically-split screen, with the above settings on the right screen, and no filters and standard time scale of 30 mm/s on the left screen to distinguish FR from artifacts. High-frequency oscillations were required to contain at least four consecutive peaks clearly visible above the background signal to be considered FR (Bagshaw et al., 2009).

2.6. Statistical methods

Continuous summary data were presented as median and interquartile range based on non-parametric distributions where appropriate. Comparisons of proportions and medians were accomplished using the Fisher exact test (FE) and Wilcoxon rank-sum test (WRS), respectively. Survival analyses were conducted using Cox proportional hazards regression. Survival functions were constructed using the Kaplan-Meier procedure. Comparisons with $p < 0.05$ were considered statistically significant. STATA software (version 11, College Station, Texas, USA) was used for all calculations.

3. Results

3.1. Cohort characteristics

This prospective cohort included 30 children (15 females) with intractable epilepsy. Median age at surgery was 9.1 years (IQR 4.6–13.3), median age of seizure onset was 8.0 months (2.0 months–5.5 years), and median duration of epilepsy was 4.0 years (1.6–8.0). The median number of AEDs at the time of surgery was