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Resection of ictal high frequency oscillations is associated with favorable surgical outcome in pediatric drug resistant epilepsy secondary to tuberous sclerosis complex

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ABSTRACT

Resective epilepsy surgery can improve seizures when the epileptogenic zone (EZ) is limited to a well-defined region. High frequency oscillations (HFO) have been recognized as having a high association with the seizure onset zone. Therefore, we retrospectively identified ictal HFOs and determined their relationship to specific intracranial features of cortical tubers in children with TSC who underwent resective surgery. We identified 14 patients with drug resistant epilepsy secondary to TSC who underwent subdural grid and strip implantation for presurgical evaluation and subsequent resection with adequate post-surgical follow-up. We aimed to determine the relationship between ictal HFOs, post-resection outcome and neuroimaging features in this population.

The largest tuber was identified in all 14 patients (100%). Four patients (29%) had unusual tubers. HFOs were observed at ictal onset in all 14 patients. Seven of 10 patients with complete resection of HFOs were seizure free. The better seizure outcome (ILAE = 1–3) was achieved with complete HFO resection regardless of the unique TSC structural features (p = 0.0140).

Our study demonstrates the presence of ripple and fast ripple range HFOs at ictal onset in children with TSC. Our study showed that complete HFO resection led to the better surgical outcome, independent of MR imaging findings.

1. Introduction

Tuberous sclerosis complex (TSC) is a congenital syndrome characterized by the widespread development of benign tumors in multiple organs (Pan et al., 2004). Epilepsy is observed in 60–96% of individuals with TSC; 70% of children who develop epilepsy present with seizures in the first year of life (Cross, 2005). In addition, 50–80% of children with TSC and epilepsy may be drug resistant (Jansen et al., 2006). Epilepsy surgery, especially resective surgery, has been shown to decrease frequency or stop seizures in a subset of drug resistant epilepsy patients with TSC (Koh et al., 2000; Weiner et al., 2006).

Previous work has shown that a single largest cortical tuber with discrete, well-defined margins that greatly exceeds the dimensions of other tubers or a single calcified tuber are often well-correlated to the SOZ (seizure onset zone) (Koh et al., 2000). However, a significant proportion of patients with TSC have multiple tubers throughout the cerebrum, with no dominant tuber on MRI, a nonlocalizing semiology and multifocal/nonlocalizing findings on EEG. This group requires extensive evaluation prior to resection, which may include multiple stage intracranial EEG (ICEEG) (Bauman et al., 2005; Carlson et al., 2011; Weiner et al., 2006). Better methods for determining the SOZ are needed.

Recently, high frequency oscillations (HFOs) (>80 Hz) have been found to have a close relationship with the SOZ in children with

Abbreviations: EZ, epileptogenic zone; FR, fast ripple; HFOs, high frequency oscillations; ICEEG, intracranial electroencephalography; SOZ, seizure onset zone; TFA, Time-Frequency Analysis; TSC, Tuberous Sclerosis Complex.

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epilepsy (Akiyama et al., 2011; Bragin et al., 1999; Fujiwara et al., 2012; Jacobs et al., 2010). There is currently a literature gap on the prevalence and frequency of HFOs seen in TSC, and their relationship to tubers. We evaluated HFOs at ictal onset during ICEEG monitoring, and compared to specific MRI findings, including presence of the largest tuber, tubers with unusual appearance on MRI, and clinical semiology in children with TSC. We aimed to determine the relationship between ictal HFOs, post-resection outcome and neuroimaging features in this population.

2. Materials and methods

2.1. Patient population

Children with drug resistant epilepsy and TSC who were selected as surgical candidates and underwent ICEEG before resective surgery performed between January 2008 and April 2012 were retrospectively investigated. The placement of intracranial electrodes was guided by standard presurgical evaluation, including video – scalp EEG monitoring and multimodality brain imaging studies as described previously (Seo et al., 2011). This study was approved by the Cincinnati Children's Hospital Medical Center Institutional Review Board.

2.2. Intracranial EEG (ICEEG) video monitoring data acquisition and data analysis

All patients underwent surgery for the placement of intracranial grids and/or strips electrodes. The ICEEGs were recorded with a sampling rate of 2000 Hz per channel (Stellate, Natus Medical Incorporated, San Carlos, CA). All seizures included in the study were identified as the patients' habitual clinical seizures. The ictal onsets were defined by initial visual inspection and had to be clearly distinguishable from the ongoing background rhythms as well as not explained by artifact or physiological state changes using regular bandwidth filtering with high pass filter of 1 Hz and low pass filter of 100 Hz. Time-frequency analysis (TFA) for the identification of HFOs was started five minutes prior to the visualized ictal onset. TFA was performed in one second time windows over the course of the five minutes prior to the visualized ictal onset.

Time-Frequency Analysis (TFA) was performed using the power spectrum with short-time Fast Fourier Transform (STFT) (Prism: Spectrum and Insight II, Persyst Development Corp, Prescott, AZ, USA) as described previously (Fujiwara et al., 2012). At the time of visualized ictal onset the time windows examined were changed to each 200 msec. In addition to TFA, each of these shorter duration time window segments (200 msec) was analyzed with frequency domain analysis (FDA, [Prism: Spectrum and Insight II, Persyst Development Corp, Prescott, AZ, USA]) as described previously (Fujiwara et al., 2012).

SOZ electrodes were defined by TFA as described previously (Fujiwara et al., 2012). SOZ inclusion criteria were: 1) presence of a group of $\leq$5 electrodes showing significant spectral power shift in the measured bands (ripple: 80–250 Hz and fast ripple [FR]: 250–500 Hz separately) and 2) onset of ictal HFOs prior to clinical seizure. Electrodes with early HFO spread were included up to the point of diffuse spread, defined as EZ (epileptogenic zone).

2.3. MRI findings

MR imaging was performed using a standardized protocol optimized for tuberous sclerosis patients at our institution. All available CT imaging was also reviewed. MR imaging included volumetric 1 mm isotropic FSPGR T1-weighted images before and after gadolinium administration as well as axial FSE T2 and T2 FLAIR sequences (4–5 mm slice thickness at 4–6.5 mm intervals). Imaging studies were assessed by a neuroradiologist (ABR certified with added qualification in neuroradiology) with 15 years of experience in epilepsy imaging (JLL). Location and size of cortical tubers (expanded gyrus with abnormal cortical and subcortical signal) were classified as 1) the largest tuber: the largest area of cortical and subcortical signal associated with a tuber without consideration of other factors, 2) most unusual/atypical tuber: tuber with most prominent localized features (cortical thickening, T2 hypointensity, calcification, or cystic change).

2.4. Classification of surgical outcome

Surgical outcome was measured using the ILAE classification (Wieser et al., 2001). The clinical outcome at the most recent postsurgical follow-up clinic visit was used. Categorical variables were compared using two-tailed Fisher exact test. For statistical analysis, outcome was dichotomized to favorable seizure outcome (ILAE = 1–3) versus poor outcome (ILAE = 4–6).

3. Results

3.1. Patient characteristics

Fourteen patients (range of age at the surgery: 2–16 years, median age: 3.9 years, male: female = 7:7) met inclusion criteria (Table 1). Age at seizure onset was less than 14 months in all cases. At the time of presurgical evaluation, eight (57%) had partial seizures as clinical semiology and six (43%) had epileptic spasms. Six of 14 had infantile spasms as the initial seizure type (43%).

3.2. Surgical sites, type and outcome

Overall surgical outcomes were assessed following ILAE classification: class 1 = eight patients, class 2 = one patient, class 3 = one patient, class 4 = two patients and class 5 = two patients (Table 2).

Seven of 14 patients (50%) underwent resective surgery within a single lobe (Table 1). The largest tuber/most unusual tuber location and surgical location were concordant in 5 of these 7 patients who received resective surgery in a single lobe. For these 5 patients, the surgical outcome was seizure free (ILAE 1) in 3 patients and two were poor outcome (ILAE 5). For two patients, the largest/most unusual tuber and surgical location were discordant, and outcomes were seizure free for one; the other was ILAE 3.

The other seven (50%) underwent multilobar lobectomy and/or corticectomy. The largest tuber and surgical locations were concordant in 5 patients with good surgical outcome (4 = ILAE 1 and 1 = ILAE 2). For two patients of 7 who had poor surgical outcome (ILAE 4), one had the most unusual tuber concordant with surgical location but the largest tuber was in left frontal lobe and was not resected (#14). For the other patient (#12) with poor outcome, neither the largest or most unusual tuber location was discordant with the surgical locations.

3.3. Relationship between HFO in SOZ and the largest/unusual tuber, completeness of HFO resection and outcome

Complete HFO resection was observed in 10 patients: 9/10 had good outcome (Table 1). Only one of four patients who had incomplete HFO resection had a good outcome. There is a statistically significant association between complete resection and favorable seizure outcome (ILAE1-3) ($p = 0.0410$). However, there was no statistical significant difference between complete HFO resection and seizure freedom (ILAE1) ($p = 0.2448$). There was no significant association between complete resection of the largest tuber or the most unusual tuber and outcome.