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Intracranial EEG analysis in tumor-related epilepsy: Evidence of distant epileptic abnormalities

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HIGHLIGHTS

- In most patients with TRE, at least part of SOSz lies distant from the tumor.
- Resection of the brain tumor plus SOSz results in excellent seizure outcome.
- On iEEG, interictal spikes are most abundant and sharpest in the peritumoral region.

ABSTRACT

Objective: In patients with tumor-related epilepsy (TRE), surgery traditionally focuses on tumor resection; but identification and removal of associated epileptogenic zone may improve seizure outcome. Here, we study spatial relationship of tumor and seizure onset and early spread zone (SOSz). We also perform quantitative analysis of interictal epileptiform activities in patients with both TRE and non-lesional epilepsy in order to better understand the electrophysiological basis of epileptogenesis.
Methods: Twenty-five patients (11 with TRE and 14 with non-lesional epilepsy) underwent staged surgery using intracranial electrodes. Tumors were outlined on MRI and images were coregistered with post-implantation CT images. For each electrode, distance to the nearest tumor margin was measured. Electrodes were categorized based on distance from tumor and involvement in seizure. Quantitative EEG analysis studying frequency, amplitude, power, duration and slope of interictal spikes was performed.
Results: At least part of the SOSz was located beyond 1.5 cm from the tumor margin in 10/11 patients. Interictally, spike frequency and power were higher in the SOSz and spikes near tumor were smaller and less sharp. Interestingly, peritumoral electrodes had the highest spike frequencies and sharpest spikes, indicating greatest degree of epileptic synchrony. A complete resection of the SOSz resulted in excellent seizure outcome.
Conclusions: Seizure onset and early spread often involves brain areas distant from the tumor.
Significance: Utilization of epilepsy surgery approach for TRE may provide better seizure outcome and study of the intracranial EEG may provide insight into pathophysiology of TRE.

1. Introduction

About 30–50% of patients with brain tumors present with seizures (van Breemen et al., 2007). In patients with intrinsic low-grade gliomas and glioneuronal tumors, the incidence is

Abbreviations: TRE, tumor-related epilepsy; SOSz, seizure onset and seizure spread zone; qEEG, quantitative electroencephalography; iEEG, intracranial EEG; MRI, magnetic resonance imaging; CT, computerized tomography.

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>90% (Kurzwelly et al., 2010). Seizures can increase morbidity in these patients and hence, there is growing interest in developing methods, which achieve optimal seizure control along with aggressive tumor removal. Complete removal of the lesion results in better seizure control compared to subtotal excision, though not everyone becomes seizure-free (Chang et al., 2008; Englot et al., 2011). In fact, in a comprehensive systematic review of the literature of seizure outcomes in 1181 patients with tumor-related epilepsy (TRE) across 41 studies, only 43% of patients were seizure-free after subtotal tumor resection whereas 79% achieved seizure freedom following gross-total lesionectomy (Englot et al., 2012). Recently, use of tailored resection with intraoperative electrocorticography to identify electrographic abnormalities around tumor margin often yielded improved seizure outcome (Mikuni et al., 2006; Seo and Hong, 2003; Sugano et al., 2007). The prevailing thought is that the immediate peritumoral area shows the most frequent epileptiform activity, possibly due to microscopic tumor infiltration (Mikuni et al., 2006; Rassi-Neto et al., 1999; Weber et al., 1993). Most studies have focused on temporal lobe lesions and electrocorticography restricted to brief intraoperative period done under anesthesia, which may itself alter epileptiform activity.

In the present study, we combined brain tumor resection with a tailored two-stage surgical approach of prolonged extraoperative intracranial EEG (iEEG) monitoring used for epilepsy surgery to investigate the spatial relationship between the tumor and the SOSz. We also performed quantitative EEG (qEEG) analysis of interictal spikes in patients with TRE and compared the spike parameters to patients without lesions.

2. Methods

2.1. Patient data and EEG recordings

A total of 25 patients with intractable epilepsy, 11 patients with a primary brain tumor (metastatic brain tumors and suspected high-grade gliomas were excluded) and 14 patients with non-lesional epilepsy undergoing epilepsy surgery during the same time period, were included in the study. All patients underwent a two-staged surgery with implantation of arrays of subdural grids and depth electrodes. Prolonged (usually 5 days) extraoperative iEEG recordings were obtained using a 128-channel Harmonie system (Stellate Inc., Montreal, Canada) and reviewed using a referential montage with frontopolar midline (FPz) scalp electrode as a reference.

On the basis of previously published work, each electrode was labeled by an experienced electroencephalographer (AKS) in one of three categories: (i) seizure onset (earliest sustained EEG changes distinct from background rhythms associated with the patient's habitual seizures); (ii) early seizure spread (ictal EEG pattern propagation recorded consistently within 10 s of electrographic seizure onset); or (iii) non-epileptogenic zone (non-EZ, electrodes not included in seizure onset or early spread category) (Asano et al., 2003; Spencer et al., 1992). The electrodes identified as seizure onset or seizure spread were, together, labeled as SOSz. If there were variations in electrode involvements between different seizures, electrodes from all habitual seizures involved in seizure onset or first 10 s of spread were included as SOSz electrodes.

Ten-minute iEEG segments were selected by the same encephalographer from periods of quiet wakefulness at least six hours after a clinical seizure. These samples were then processed with our validated interictal spike detection algorithm (see below) (Barkmeier et al., 2012b). All surgical procedures were performed by the same epilepsy/brain tumor neurosurgeon (SM). The patients with TRE were divided into two groups based on histopathology (infiltrating versus non-infiltrating tumors). Seizure and tumor outcome data were collected at one and two years following surgery. Informed consent was obtained from all subjects for protection of patient information and tissue collections and approved by the Wayne State University Human Investigation Committee.

2.2. qEEG analysis of ictal and interictal EEG

A validated spike detection algorithm was used initially to mark the interictal spikes of each 10-min iEEG sample (Barkmeier et al., 2012b). Obvious artifacts were removed from the data by manually reviewing marked spikes. Custom MATLAB scripts (MathWorks Inc., Natick, MA) were then used for extraction of data related to each interictal spike. The average frequency of spikes was calculated for each electrode. Each spike was further analyzed by dividing it into two half-waves with midpoint being the peak (Fig. 1A). To calculate the amplitude, duration, and slope of each half-wave, 80 ms of data were searched on either side of the peak to find the lowest value in that range designated as the spike's trough. Distance to the peak value was used to calculate duration while the difference in voltage was used to calculate amplitude. Values preceding trough to peak were defined as 'amp1' and 'dur1' while values from peak to succeeding trough were defined as 'amp2' and 'dur2'. Slope was calculated as amplitude/duration for each half-wave.

2.3. Three-dimensional reconstructions and tumor segmentation

To investigate the spatial relationship between the tumor and electrographic activity, we generated 3D reconstructions of each patient's brain, including segmentation of the tumor and overlay of the intracranial electrodes. To achieve this, we utilized Visual C++ and OpenGL to implement an image analysis and visualization software system consisting of the following modules: (i) co-registration of multimodality image volumes (Hu and Hua, 2009; Muzik et al., 2007; Zou et al., 2007); (ii) partial differential equation-based deformable model for 3D-structure segmentation (Hua and Qin, 2004); (iii) subdural grid mapping and rendering; and (iv) surface mapping and composited visualization (Hua et al., 2008; Zou et al., 2009). Cortical surfaces were generated from preoperative volumetric T1-weighted MR images using the automated cortical surface reconstruction software (BrainSuite09, http://neuroimage.usc.edu/neuro/BrainSuite) (Shattuck and Leahy, 2002). Post-implantation skull X-rays and/or CT scans were co-registered with the pre-implantation MRI to localize precisely the intracranial electrodes on the patient's 3D-brain reconstruction. In all cases, accuracy of electrode localization was manually confirmed by matching gyral patterns between intraoperative photographs and 3D-reconstructions. Using these images, color-coded heat maps were generated on the cortical surface with a green-to-red color scale corresponding to various electrical parameters of interictal spikes including spike frequency, amplitude, duration, and slope. In addition, each electrode was identified based on its seizure category as either SOSz (seizure onset and early seizure spread) or non-EZ.

2.3.1. Measurement of distance between tumor margin and electrodes

To compute the distance between the electrodes and the tumor border, tumor margins were manually outlined on preoperative FLAIR images. The marked points in each slice were connected with Bspline-based interpolation to form a closed contour defining the tumor border within the MRI slice. After all slices were marked, the contours were combined to generate a 3D-mask defining the tumor. The final tumor surface was reconstructed using the Marching Cubes algorithm, which was saved in the original MRI coordinate space (Lorensen and Cline, 1987).

To calculate distance, the location of each electrode was identified on the 3D-brain surface. Our algorithm then determined the