Epilepsia Open® The Open Access Journal of the International League Against Epilepsy

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SHORT RESEARCH ARTICLE

High-frequency oscillations detected in ECoG recordings correlate with cavernous malformation and seizure-free outcome in a child with focal epilepsy: A case report

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Epilepsia Open, 2(2):267–272, 2017
doi: 10.1002/epi4.12056

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Summary

Epilepsy associated with cavernous malformation (CM) often requires surgical resection of seizure focus to achieve seizure-free outcome. High-frequency oscillations (HFOs) in intracranial electroencephalogram (EEG) are reported as potential biomarkers of epileptogenic regions, but to our knowledge there are no data on the existence of HFOs in CM-caused epilepsy. Here we report our experience of the identification of the seizure focus in a 3-year-old pediatric patient with intractable epilepsy associated with CM. The electrocorticographic recordings were obtained from a 64-contact grid over 2 days in the epilepsy monitoring unit (EMU). The spatial distribution of HFOs and epileptic spikes were estimated from recording segments right after the electrode placement, during sleep and awake states separately. The HFO distribution showed consistency with the perilesional region; the location of spikes varied over days and did not correlate with the lesion. The HFO spatial distribution was more compact in sleep state and pinpointed the contacts sitting on the CM border. Following the resection of the CM and the hemosiderin ring, the patient became seizure-free. This is the first report describing HFOs in a pediatric patient with intractable epilepsy associated with CM and shows their potential in identifying the seizure focus.

KEY WORDS: HFO, Pediatric epilepsy, Cavernous malformation, Automatic detection, Seizure onset zone.

Cavernous malformations (CM) are dynamic vascular lesions in the central nervous system.[1] When cortical tissues are involved, CMs pose a significant risk for the development of medically refractory epilepsy that requires surgical treatment.[2,3] Invasive electrocorticography (ECoG) monitoring has been used as the gold standard for the localization of seizure onset zone (SOZ)[4] and has frequently been applied during the presurgical evaluation in patients with epilepsy associated with CM. By investigating the intracranial electroencephalogram (EEG) recordings, neurologists try to define the accurate location of seizure onset in relation to the CM, determine pathways of seizure propagation, and perform intraoperative mapping of cortical function before the excision, especially in pediatric cases.[5,6] Studies have shown that lesionectomy plus ECoG yields better seizure control outcomes; one cohort demonstrated a significant advantage with lesionectomy assisted by intracranial ECoG delineation of the SOZ.[7,8]

Recently, high-frequency oscillations (HFOs) are introduced as promising biomarkers for epileptogenesis in both lesional and nonlesional epilepsy.[9] HFOs are frequently categorized based on their spectral content into ripple and fast ripple (FR) groups, which lie in 80–250 Hz and 250–500 Hz bands respectively. To this point, HFOs have not been described in pediatric patients with CM-caused epilepsy. Here, by applying a previously published automatic

Accepted March 23, 2017.

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HFO detection algorithm, we report our experience of characterizing HFOs in ECoG and its correlation with the lesion, SOZ, and seizure freedom in a pediatric patient with intractable epilepsy associated with CM.

Methods

Data acquisition and clinical EEG monitoring

A 3-year-old boy was referred to Texas Children's Hospital with focal epilepsy due to cavernous malformation. Continuous ECoG data were acquired from an 8 × 8 grid with 2.4-kHz sampling frequency using g.HIamp (g.tec Medical Engineering, Australia) for HFO analysis. Data collection and scientific workup were approved by the Baylor College of Medicine Institutional Review Board.

The ECoG was recorded for 62 h and 39 min simultaneously with video monitoring throughout the period. ECoG data were visually inspected for characterization of the background activity, abnormal focal and generalized features, as well as interictal and ictal epileptiform activity. Electrical seizure activity was correlated with the clinical events of the patient recorded on video.

HFO analysis

A total of 150 min of ECoG data were extracted for HFO analysis (30 min immediately at the beginning of monitoring in the epilepsy monitoring unit (EMU), and then separately for 30 min during slow-wave sleep and awake states in each day over 2 days which were at least 4 h away from seizure activity). A previously validated HFO detector was used to analyze the multichannel ECoG data.[10] Briefly, raw data first went through band-pass filtering within the 80- to 500-Hz range and a series of HFO-sieving criteria. Next, we performed the short-time Fourier transform (STFT) and executed a denoising step on the time-frequency maps to eliminate background activity with small amplitude. Finally, we explored the entire ECoG bandwidth of surviving candidates to extract the three features: high-band to low-band power ratio, entropy, and frequency corresponding to maximum peak to notch ratio. These features were used for Gaussian mixture model (GMM) clustering to map candidate events into different categories.

Results

Case presentation

The 3-year-old left-handed male patient was referred to Texas Children's Hospital with focal epilepsy initially presenting as recurrent spells of loss of awareness starting at 2.5 years of age. The seizures were stereotyped and clinically consisted of eyes slowly closing and the patient swaying back and forth in association with unresponsiveness lasting 2–6 s. The seizures occurred in clusters of 20–30 events, with the clusters occurring up to 3–4 times per day. The patient was given trials of levetiracetam, oxcarbazepine, zonisamide, and clobazam without resolution of seizures. Seizure medications have not been adjusted up to this point.

Initial scalp EEGs showed spikes that were maximal in the left frontal region (F3). They were often seen focally restricted to this region but other times were seen quickly propagating to the left mid-to-posterior temporal region (T7/P7). Brain MRI revealed a 1.7 cm × 1.5 cm × 1.5 cm lesion in the left frontal operculum (Fig. 1B). The lesion had a heterogeneous "popcorn" appearance on T2-weighted images, with a rim of hypointensity and mild surrounding edema, consistent with a CM. Positron emission tomography (PET) CT showed a corresponding focal area of hypometabolism, suggestive of a seizure focus (Fig. 1D). Magnetic source imaging showed frequent spikes localizing to the left frontal cavernoma and posterior perisylvian region (Fig. 1E). Upon presenting the patient's case to the epilepsy surgery conference, the consensus was to implant intracranial EEG to define surgical resection borders.

An 8 × 8 subdural ECoG grid electrode was placed over the left frontal lobe. Contacts were labeled 1 to 64, with contact 1 representing the most anterior-inferior aspect. Contacts 20–21 and 28–29 were approximately overlying the left frontal CM. A sketch of the grid and the 3D reconstruction of MRI and CT images are provided in Fig. 1F,G. The CM area was segmented using the MRI data and represented in white.

ECoG findings

Frequent epileptiform discharges were seen over much of the subdural grids. As it is shown in Fig. 1F, the most frequent spike population was seen at contacts 37-45-53, propagating inferiorly and anteriorly to contacts 28-36-44, 19-27-35, 2-10-18, and 1-9. The second-most frequent spike population was seen at contacts 14-16, 23, 24, 32, 40, covering the posterior/inferior part of the grid. Visual identification of the ictal onset zone suggested the anterior/superior perilesional cortex with some more distant sites being involved in seizure initialization. More than 70 of the habitual seizures were captured, with >90% of the seizures appearing to arise from contacts 27, 34-36, and 42. When seen, the ictal pattern consisted of a dramatic buildup of spikes at the onset of the clinical seizures. The remainder of the clinical seizures had indeterminate EEG onset. A 20-second segment of raw ECoG data in bipolar montage showing the ictal onset is given in Fig. 1A.

HFO findings

Using 150 min of ECoG data, a total of 23,810 HFO events and 12,365 spikes were detected by the algorithm. For each segment, the detected events were identified as three subgroups, as shown in Fig. 2A. In general, one cluster (C_H) was a mixture of ripple and FR, one cluster (C_S) was composed of spikes, the rest (C_I) was a group of

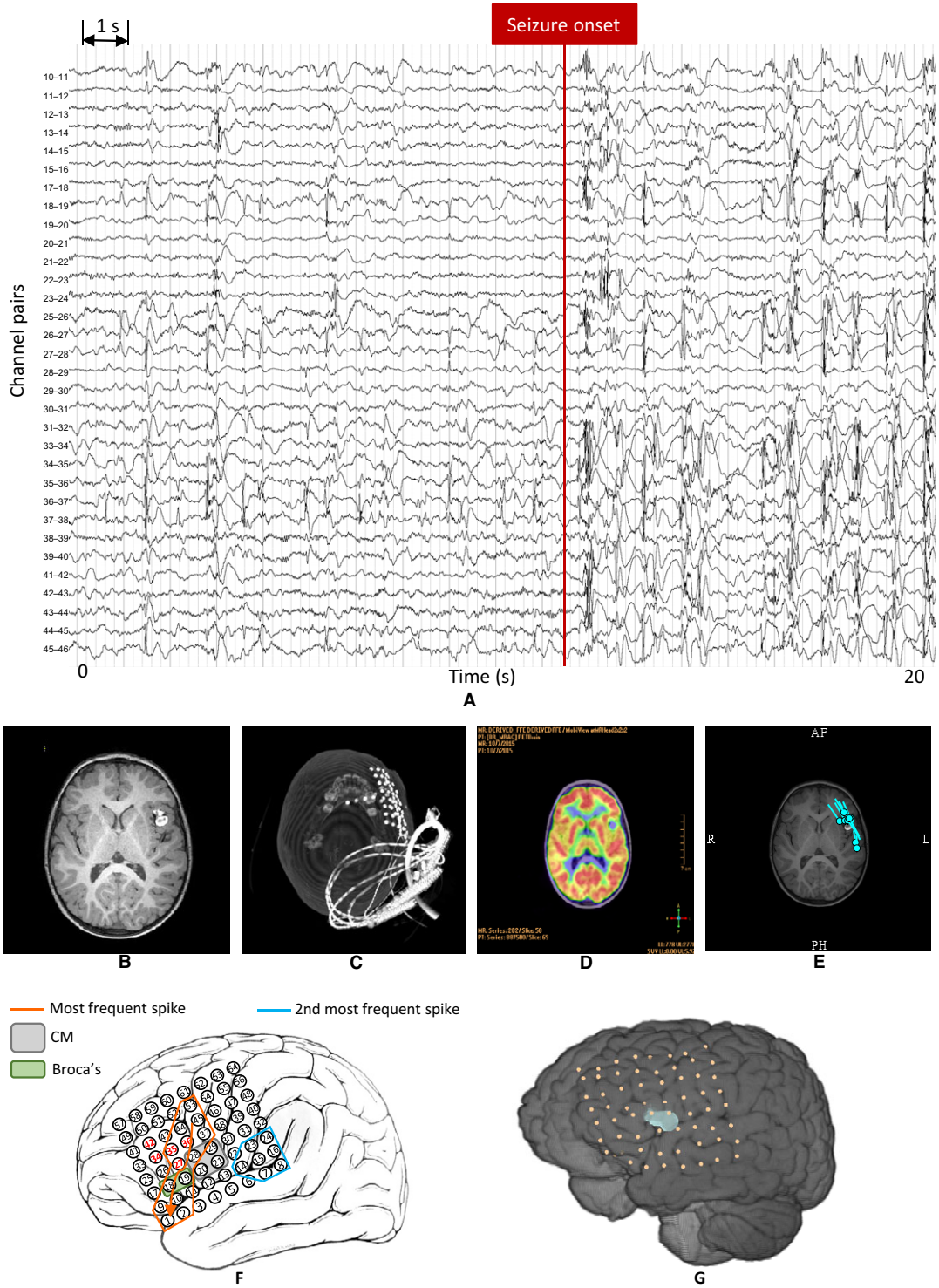

Figure 1.

(**A**) Twenty seconds of ECoG recording in bipolar montage, with seizure onset represented by the red vertical line. Thirty-two channel pairs are shown. (**B**) Structural MRI showing the CM in the left frontal operculum. (**C**) Postoperative CT image reveals the 8 × 8 grid electrode implanted over the CM and surrounding cortex. (**D**) PET image showing hypometabolism in the CM area. (**E**) Magnetic source imaging showing spike distribution. (**F**) A schematic of grid channel orders. Contacts 18-19, representing Broca's area, are marked in green; contacts 20-21 and 28-29, demonstrating the CM location, are marked in gray. Contacts with frequent spike populations were marked in colors, with the arrow representing the direction of spike propagation. Presumed SOZ contacts 27, 34-36, and 42 are marked in red. (**G**) 3-D rendering of the individual brain with electrode model obtained from MRI and CT co-registration. The white region indicates the CM, which was generated by MRI segmentation.

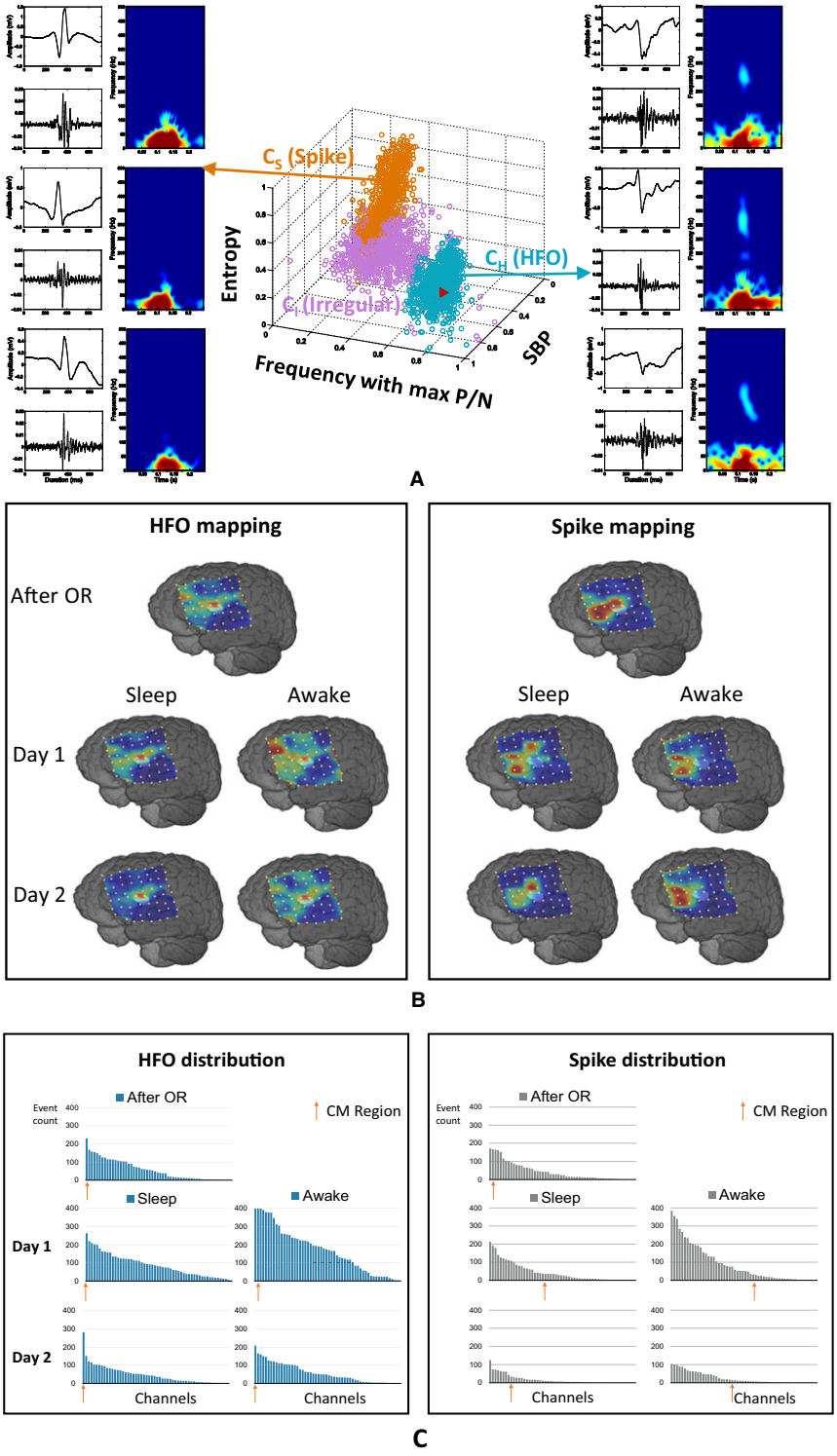

Figure 2.

(**A**) Feature distribution of the three clusters calculated from the first 10 min of recording. C_H: HFOs, C_S: spikes, C_I: irregular waveforms. For C_H and C_S, three random sample events are shown with their raw signal, band-pass-filtered signal and time-frequency maps. (**B**) 3D rendering of the individual MRI with electrode model and spatial distribution maps, with red representing the locations with most of the captured events. The spatial maps were interpolated based on cubic convolution. (**C**) Spatial distribution of HFOs and spikes in bar plot. Channels are sorted by the event number.

irregular waveforms with noisy background. C_H and C_S were hereby used for the spatial analysis.

Consistently in all segments, the spatial maps indicated that most of the HFOs were generated from channels 28-29 located above the superior border of the cavernoma. Moreover, channels 35-36 and 37-38, representing the area superior to the lesion, were also involved as HFO-generating sites but with less consistency. Some less active locations responsive to HFO generation were found in channels 31-32, 39-40, and 41-42, covering the perilesional area and the posterior and anterior/superior parts of the electrode, especially in waking states (Fig. 2B).

The HFO mapping results estimated from 30-min ECoG segments consistently highlighted the perilesional region, regardless of the day of recording. In particular, the HFO distribution was more compact and robust over days in sleep state, concentrating on channels 28-29 sitting immediately above the border of the CM. Remarkably, the HFO spatial map obtained from ECoG data of a short period recorded right after the electrode placement had also correlated with the CM and perilesional location. On the contrary, spikes were initially found in channels 17-18-19, covering Broca's area, along with channels 28-29 and 34-37, representing the CM and its anterior/superior region. During the monitoring period, spike channels shifted anteriorly and inferiorly surrounding the CM. The distribution also changed through the sleep-wake cycle, as shown in Fig. 2B,C.

Surgical resection and outcome

Cavernous malformation does not contain neural parenchyma, thus the perilesional cortex, not the lesion itself, is always implicated in ictogenesis. The preictal spiking patterns of ECoG data indicated a perilesional cortex anterior and superior to the CM as the SOZ. Taking into account the proximity of the nearly eloquent language regions, the neurologists decided to perform a cautious and conservative resection of the CM and adjacent hemosiderin-affected cortex only with plans to reevaluate for further resection if the seizures remained unaffected.

Considering the associated risk, postsection intraoperative ECoG was not performed in this patient. As of today, the patient remains seizure free with follow-up of 1 year.

Discussion

In this report, we investigated the spatial characteristics of HFOs and interictal spikes in a pediatric patient with CM-caused epilepsy. The clinical EEG evaluation results indicated a dramatic buildup of preictal spikes across channels 27-28, 35-36, and 42 located anterior/superior to the CM. The interictal epileptiform discharges extended far beyond the limits of the lesional area and furthermore extended to the majority of the grid. Interestingly, most of the HFOs were localized at channels 28-29 consistently over all awake and sleep states as well as in a brief 30-min recording right after the electrode implantation. We noted that both HFOs and spiking activity patterns at the seizure onset pointed to the superior/anterior perilesional cortex. However, compared to the ictal data, HFOs were more localized to the perilesional area superior to the CM. Based on the clinical evaluation, a conservative excision was limited to the resection of the CM and hemosiderin ring only, which correlated well with the HFO distribution and provided seizure freedom to the patient.

Epileptic seizures are the most frequent symptom in patients with CM. During the presurgical evaluation, neurologists need to accurately define the resection territories in order to abolish the seizures. However, the precise identification of the seizure focus and resection border is cumbersome, because the epileptogenic zone is complex in most cases and could involve not only the perilesional region but also brain sites that are geographically distant from the lesion and functionally independent. Studies show that only 75% of patients with CM-caused epilepsy who undergo lesionectomy solely achieve postoperative seizure freedom because of the presence of independent epileptogenic regions, insufficient estimation of the planned resection area, or postoperative scar formation.[11,12] To identify the epileptogenic areas more accurately, prolonged invasive monitoring is often required to guide a tailored resection for optimal seizure control.[13] Despite the potential benefits, the expense and risk of adverse events during intracranial monitoring have been documented, and the associated complications are significantly more common in pediatric patients.[14] There is an urgent demand for the investigation of reliable neurobiomarkers, which may potentially shorten the undefined monitoring period and assist presurgical planning.

HFOs have proven to be excellent indicators of SOZ.[15] Their spatial distribution tends to be more specifically restricted to the SOZ compared to spikes and independent of the type and extension of the lesion, presenting as a sign of intrinsic epileptogenic activity rather than lesion pathology.[9] In this study, by analyzing an extended length (150 min) of multichannel ECoG recording with an automated detector that explores the time-frequency content of the data, the HFOs and spikes were identified and grouped by unsupervised approach. The HFO clustering results clearly pointed to the actual perilesion location consistently in all analyzed data segments. The brain sites with most of the HFOs were stably limited to contacts 28-29, which were located immediately above the superior edge of the CM, and further linked to seizure-free outcome. We also observed that the HFO spatial distribution was more compact in sleep compared to in the waking state. Compared to the HFO maps, the spatial distribution of spikes was not robust because it varied over days as well as during the sleep-wake cycle.

This is the first report describing HFOs in a pediatric patient with CM-caused epilepsy and shows their potential in identifying the seizure focus in an accurate and efficient manner. The result suggested that the epileptic perilesional

structure could be identified from the HFO spatial distribution estimated from 30-min ECoG data recorded immediately after the electrode placement. This observation needs to be investigated in studies with larger numbers of patients to explore whether the HFOs can be used as an early predictor of resection zone.

Disclosure

None of the authors has any conflicts of interests to declare. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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