

Epileptogenic zone localization using intraoperative gamma oscillation regularity analysis in epilepsy surgery for cavernomas: patient series

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BACKGROUND In epilepsy surgery for cavernoma with intractable focal epilepsy, removal of the cavernoma with its surrounding hemosiderin deposition and other extended epileptogenic zone has been shown to improve postsurgical seizures. However, there has been no significant association between such an epileptogenic zone and intraoperative electrocorticography (ECoG) findings. The authors recently demonstrated that high regular gamma oscillation (30–70 Hz) regularity (GOR) significantly correlates with epileptogenicity.

OBSERVATIONS The authors evaluated the utility of intraoperative GOR analysis in epilepsy surgery for cavernomas. The authors also analyzed intraoperative ECoG data from 6 patients with cavernomas. The GOR was calculated using a sample entropy algorithm. In 4 patients, the GOR was significantly high in the area with the pathological hemosiderin deposition. In 2 patients with temporal cavernoma, the GOR was significantly high in both the hippocampus and the area with the pathological hemosiderin deposition. ECoG showed no obvious epileptic waveforms in 3 patients, whereas extensive spikes were observed in 3 patients. All patients underwent cavernoma removal plus resection of the area with significantly high GOR. The 2 patients with temporal cavernomas underwent additional hippocampal transection. All patients were seizure free after surgery.

LESSONS The high GOR may be a novel intraoperative marker of the epileptogenic zone in epilepsy surgery for cavernomas.

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KEYWORDS cavernoma; epilepsy surgery; epileptogenic zone; gamma oscillation regularity; sample entropy

Cavernomas are benign vascular malformations consisting of fragile and sinusoidal multivascular channels with no intervening brain tissue.¹ In supratentorial cavernomas, epileptic seizures occur in 40%–70% of cases, with 40% of cases presenting with drug-resistant epilepsy^{2,3} and indicated for epilepsy surgery. For better seizure control, lesionectomy plus resection of the typically surrounding hemosiderin deposits is recommended.^{4–6} However, the epileptogenic zone may be enlarged, or, especially in the temporal cavernomas, the hippocampus may have acquired secondary epileptogenicity at a distance from cavernoma lesions.⁷ Intraoperative electrocorticography (ECoG) has been reported to be useful for finding the epileptogenic region, but it remains controversial due to the uncertainty in microscopic confirmation of hemosiderin deposits.^{8–10}

In cavernoma, Ferrier et al. suggested that the amount of hemosiderin deposits does not correlate with epileptic discharge patterns in the intraoperative ECoG and that a continuous spiking pattern may reflect secondary epileptogenicity.¹¹ They also indicated an association

between the absence of a discharge pattern and a high microglial density with protective effects against epilepsy. Although the pathological mechanisms of epileptogenesis differ from disease to disease, there are indeed many similarities in the epileptic discharge patterns emanating from epileptogenic brain lesions such as glioneuronal tumor and cortical dysplasia.^{12–14} We recently showed that high gamma oscillation (30–70 Hz) regularity (GOR) calculated with interictal ECoG data analysis could sensitively detect the epileptogenic zone in focal cortical dysplasia.^{15,16} We hypothesized and tested whether this method could also be applied to epileptogenic zone localization in epilepsy surgery for cavernomas.

Study Description

Patients

We analyzed intraoperative ECoG data from 6 patients with medically refractory focal seizures secondary to cavernomas who underwent epilepsy surgery between April 2019 and March 2020 in the

ABBREVIATIONS ECoG = electrocorticography; EEG = electroencephalographic; GOR = gamma oscillation (30–70 Hz) regularity; SD = standard deviation.

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Department of Neurosurgery at Showa University School of Medicine. All patients met the following criteria: 1) the capture of habitual seizures with preoperative long-term video electroencephalographic (EEG) monitoring, 2) the presence of hemosiderin around the cavernoma confirmed by T2-weighted star magnetic resonance imaging, 3) the detection of the estimated epileptic focus by using interictal ¹²³I-iomazenil single-photon emission computed tomography, and 4) the postsurgical histopathological diagnosis of cavernoma. The postsurgical seizure outcome was evaluated according to the International League Against Epilepsy classification system.¹⁷ The resected tissues were evaluated by board-certified pathologists. This study was approved by the research ethics board at the Showa University School of Medicine. All procedures were performed according to the latest version of the Declaration of Helsinki. All patients gave informed consent.

Intraoperative ECoG Data Recordings

The grid electrodes (Unique Medical Co., Ltd.) were placed so that the cavernoma lesion was well covered, and they were also placed on the surface of the hippocampus in the cases with mesial temporal lobe epilepsy. The ECoG data were acquired using a Nihon Kohden Neurofax EEG system and a bandpass filter from 0.16 to 300 Hz with a sampling rate of 1 kHz. A 60-Hz notch filter was applied to all channels, and sensitivity was between 30 and 100 μ V/mm according to the amplitudes of the background activities and epileptic discharges. The recordings were performed referentially with the reference electrode placed in the forehead or in an inactive area that never registered epileptic discharge. ECoG was also performed after resection. We randomly selected a 20-second epoch for GOR analysis for each patient. All selected epochs were inspected to ensure that they were not contaminated with artifacts.

GOR Analysis

The detailed algorithm for GOR analysis using the sample entropy method is described in our previous study.¹⁵ The ECoG data were

downsampled to 200 Hz, where the timescale factor $\tau = 3$ to 7 corresponded to the gamma frequency (28.6–66.7 Hz). We defined the GOR as the average score with $\tau = 3$ to 7. We calculated the GOR for 20-second epochs without any significant artifacts. Then we calculated the mean and standard deviation (SD) of the measured GOR within a given patient. Z values were calculated using the following equation: $Z = (\text{individual GOR} - \text{mean GOR}) / (\text{SD of GOR})$.

Calculations were performed for each electrode of each patient. Z values less than -2 were defined as significant according to our previous report.¹⁶ Lower Z values represent higher GOR. To visually assess the GOR, we created the color-coded GOR (opposite values of Z values) superimposed onto the electrodes of the subdural grid. These procedures were performed using a custom program developed in cooperation with EFken Inc.

Results

The results for each patient are summarized in Table 1 and Fig. 1. In 4 patients (cases 2, 3, 4, and 5), the GOR was significantly high in the area with the pathological hemosiderin deposition. In 2 patients (cases 1 and 6) with temporal cavernomas, the GOR was significantly high both in the hippocampus and in the area with the pathological hemosiderin deposition. Intraoperative ECoG showed no obvious epileptic waveforms in 3 patients (cases 3, 4, and 5) and extensive spikes in 3 patients, including microscopic normal areas around the lesions (cases 1, 2, and 6). In 2 patients with temporal cavernomas (cases 1 and 6), the spikes were also found in the ECoG on the surface of the hippocampus. All patients underwent cavernoma removal plus resection of the area with significantly high GOR, and hippocampal transection was added in 2 patients with temporal cavernomas (cases 1 and 6). The ECoG findings showed significant normalization, and the GOR showed decreased levels, in each patient after resection. Pathological hemosiderin deposition was observed in the resected regions with significantly high GOR in all 6 patients. All patients were seizure free at the follow-up after surgery.

TABLE 1. Patient characteristics

Case No.	Sex	Age (yrs)	Cavernoma Location	Seizure Type	Epilepsy Surgery Plus Cavernoma Removal	No. of Electrodes w/ Significantly High GOR	ECoG Findings	Pathological Hemosiderin Deposition	Postsurgical Seizure Outcome
1	F	31	Lt temporal lobe	Focal impaired awareness seizure	Focal resection & hippocampal transection	2 on temporal lobe, 1 on hippocampus	Extensive spikes	+	Class I
2	F	45	Rt parietal lobe	Focal sensory seizure	Focal resection	1	Extensive spikes	+	Class I
3	M	42	Lt frontal lobe	Focal to bilat tonic-clonic seizure	Focal resection	1	None	+	Class I
4	F	47	Lt occipitoparietal lobe	Visual hallucination	Focal resection	1	None	+	Class I
5	M	24	Lt frontal lobe	Aphasic seizure	Focal resection	2	None	+	Class I
6	M	56	Rt temporal lobe	Focal impaired awareness seizure	Focal resection & hippocampal transection	3 on temporal lobe, 2 on hippocampus	Extensive spikes	+	Class I

+ = present.

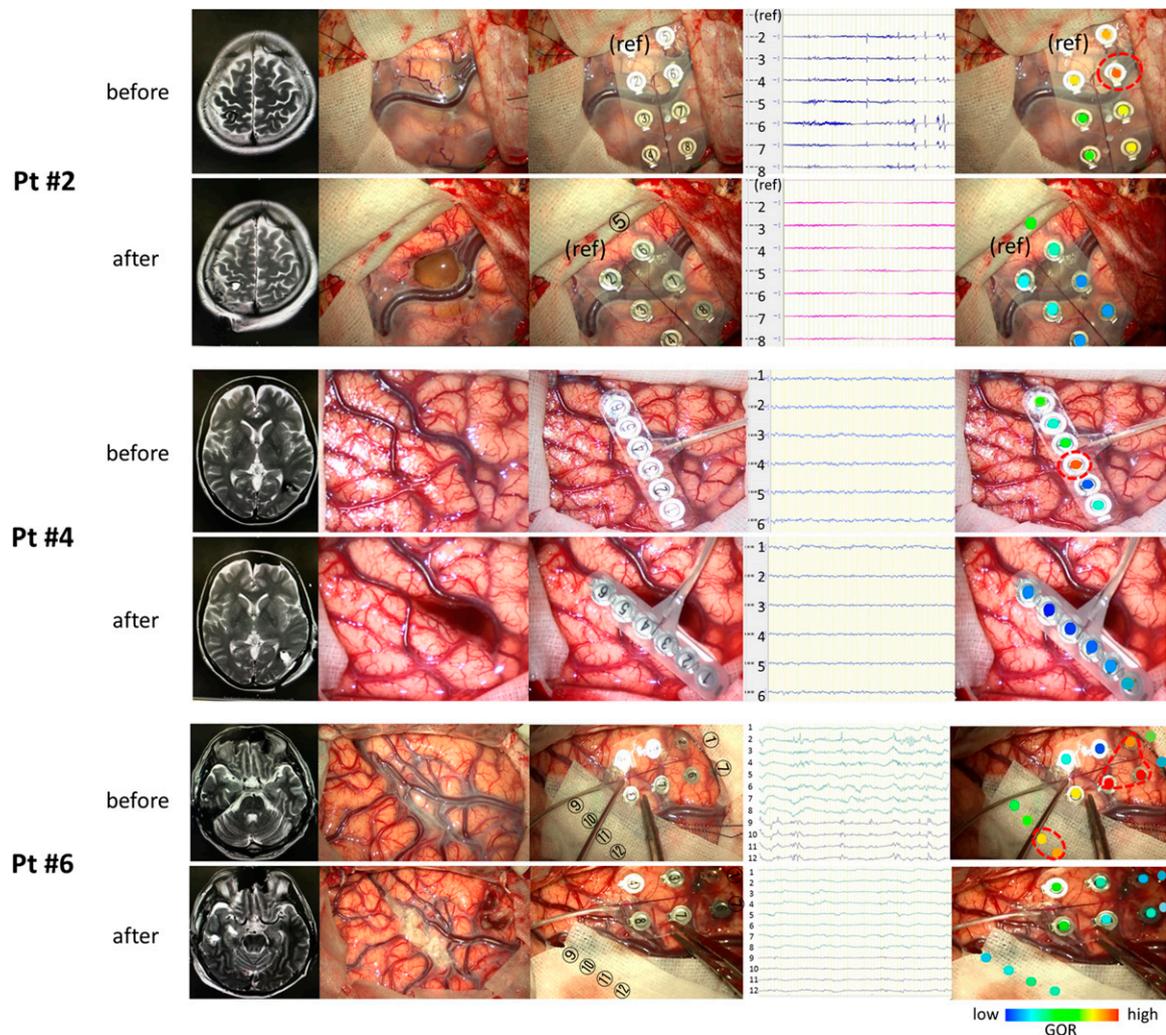


FIG. 1. Results of 3 representative patients (cases 2, 4, and 6). For each patient, the columns (from left to right) show T2-weighted magnetic resonance imaging studies, intraoperative photographs of the brain surface, grid electrodes, ECoG findings, and color-coded GOR maps before (upper row) and after (lower row) resection. The red dotted circles in the GOR maps show the area with significantly high GOR, where the focal resection or hippocampal resection was performed. Pt = patient; ref = referential electrode.

Discussion

Observations

We believe that the significantly high GOR regions may be the epileptogenic zone in patients with cavernomas who have intractable focal epilepsy because (1) the good postsurgical seizure outcome was achieved in our 6 patients after removal of those high GOR locations and (2) the pathological hemosiderin deposition was observed in those regions that are normally difficult to identify microscopically.

It has been demonstrated that complete resection of the hemosiderin deposits around cavernomas correlates with better postsurgical seizure outcomes.^{4-6,8} Although careful intraoperative visualization of hemosiderin deposits is needed for epilepsy surgery, there is often no visible hemosiderin deposition on the brain surface (which was the case in all patients in this study). Furthermore, it has been reported that there is no association between Fe³⁺ staining and intraoperative ECoG discharge patterns,¹¹ and intraoperative ECoG assessment is not significantly reflected in postsurgical seizure outcomes for patients with cavernomas.⁹ Indeed, intraoperative ECoG findings before resection

did not show any significant epileptic discharges or extensive spikes in 3 of our patients, making it difficult to localize the epileptogenic area from these findings. Instead, limited resection of the areas with significantly high GOR resulted in ECoG normalization and an overall GOR decrease after resection in our 6 patients, which indicates that our GOR method could be more accurate than conventional ECoG assessment.

In temporal cavernoma cases, previous studies have measured only conventional intraoperative ECoG epileptic discharges in temporal lobes. Although gross-total resection or aggressive resection has improved postsurgical seizure outcomes, it has also increased the risk of complications.^{7,10,18} In our 2 patients with temporal cavernoma, ECoG before resection showed an extensive spiking pattern on the surface of the temporal lobe, including the cavernoma lesion, as well as on the hippocampal surface, whereas significantly high GOR areas were very localized. Interestingly, limited resection of areas with significantly high GOR improved ECoG dramatically not only in the areas around the lesions but also in the hippocampus, resulting in an

overall decrease of GOR in both brain regions. This may also suggest that the measurement of high GOR can help surgeons to perform minimally invasive resection of epileptogenic regions in cavernoma surgery.

Although the number of cases is small and our findings require further validation, we hope that our method will be widely used as a robust, minimally invasive, and safe intraoperative epileptogenic zone localization in epilepsy surgery for cavernomas.

Lessons

The high GOR may be a novel intraoperative marker of the epileptogenic zone in epilepsy surgery for cavernomas that does not yield significant findings on ECoG and in which no hemosiderin deposits are visible on the brain surface.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Sato, Mizutani. Acquisition of data: all authors. Analysis and interpretation of data: Sato, Tsuji. Drafting the article: Sato, Tsuji. Critically revising the article: Sato, Tsuji. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Sato. Statistical analysis: Sato. Administrative/technical/material support: Sato, Sugiyama, Mizutani. Study supervision: Sato, Mizutani.

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