High-frequency oscillations in awake patients undergoing brain tumor-related epilepsy surgery

Anteneh M. Feyissa, MD, MSc, Gregory A. Worrell, MD, PhD, William O. Tatum, DO, Deependra Mahato, DO, Benjamin H. Brinkmann, PhD, Steven S. Rosenfeld, MD, Karim ReFaey, MD, Perry S. Bechtle, DO, and Alfredo Quinones-Hinojosa, MD

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Abstract

Objective
To examine the relationship between high-frequency oscillations (HFOs) and the presence of preoperative seizures, World Health Organization tumor grade, and isocitrate dehydrogenase 1 (IDH1) mutational status in gliomas.

Methods
We retrospectively studied intraoperative electrocorticography recorded in 16 patients with brain tumor (12 presenting with seizures) who underwent awake craniotomy and surgical resection between September 2016 and June 2017. The number and distribution of HFOs were determined and quantified visually and with an automated HFO detector.

Results
Five patients had low-grade (1 with grade I and 4 with grade II) and 11 had high-grade (6 with grade III and 5 with grade IV) brain tumors. An IDH1 mutation was found in 6 patients. Patients with a history of preoperative seizures were more likely to have HFOs than those without preoperative seizures (9 of 12 vs 0 of 4, \(p = 0.02\)). The rate of HFOs was higher in patients with IDH1 mutant (mean 7.2 per minute) than IDH wild-type (mean 2.3 per minute) genotype (\(p = 0.03\)).

Conclusions
HFOs are common in brain tumor-related epilepsy, and HFO rate may be a useful measure of epileptogenicity in gliomas. Our findings further support the notion that IDH1 mutant genotype is more epileptogenic than IDH1 wild-type genotype gliomas.
Brain tumor-related epilepsy (BTRE) is characterized by symptomatic, drug-resistant seizures. Approximately 40% to 70% of patients with glioma develop BTRE, with a preponderance of these with low-grade tumors. The recent identification of tumor markers associated with increased risk of seizures has improved our understanding of BTRE pathophysiology. For example, the Krebs cycle enzyme isocitrate dehydrogenase 1 (IDH1) has been shown to have a mechanistic link to BTRE. Wild type IDH1 catalyzes the conversion of isocitrate to α-ketoglutarate, while mutant IDH1 (IDH1mut) reduces α-ketoglutarate to D-2-hydroxyglutarate, which may have a seizure-inducing effect.

High-frequency oscillations (HFOs) are composed of focal bursts of electrophysiologic potentials between 30 and 600 Hz that can be detected during intraoperative electrocorticography (ECoG). HFOs have been identified as potential electrophysiologic biomarkers of pathologic, seizure-generating tissue in the brain and have been observed between seizures, at seizure onset, and during seizures. In addition, removal of brain tissue with HFOs has been shown to predict better outcome after epilepsy surgeries. Along the same lines, studies suggest that resection of areas with presurgical high HFO rates is associated with a better postsurgical seizure outcome than resection of areas with presurgical low HFO rates. An ongoing randomized controlled trial designed to investigate the feasibility and safety of using HFOs during intraoperative tailoring of nontumoral epilepsy surgery is currently underway.

HFOs have been reported in nontumoral epilepsies, but little is known about the clinical utility of HFOs, including the feasibility and safety of using them during intraoperative tailoring in patients with BTRE. This study examines the relationship between HFOs and the presence of preoperative seizures, World Health Organization (WHO) tumor grade, and IDH1 mutant status in patients with glioma.

Methods

Patients
We retrospectively reviewed the ECoG data of 16 consecutive patients with a brain tumor who underwent an awake craniotomy during intraoperative neuromonitoring—assisted surgical resection of their lesion between September 2016 and June 2017. All but 2 cases were performed by the senior surgeon (A.Q.-H.). Clinical data, including demographics, presence of preoperative seizures, tumor location, WHO tumor grade, and various genetic tumor markers such as 1p/19q codeletion, p53 overexpression, and IDH1 mutation status, were assessed.

Operative technique
Patients had monitored anesthesia care technique used for sedation as described previously. Briefly, 2 cases were performed with general anesthesia and sleep-awake-sleep technique with remifentanil and propofol infusions as the primary anesthetic. The remainder (14 cases) were performed awake with cranial regional anesthesia with very light propofol and/or dexmedetomidine intravenous sedation only during noncritical portions such as placement of arterial line and pinning of the pinion system. Intravenous 25 to 50 μg fentanyl in divided doses and 1 g acetaminophen were used for breakthrough discomfort and pain as needed. A scalp block was performed bilaterally with 0.5% ropivacaine. Intravenous lines, an arterial line, and a Foley catheter were then inserted. The patients were placed supine with a skull clamp (Mayfield, Integra LifeSciences, Plainsboro, NJ) and positioned optimally for surgery. Patients were given dexamethasone 10 mg IV once, mannitol 0.25 g/kg, levetiracetam 1,000 mg, and vancomycin 1,000 mg. Neuronavigation (VectorVision, Brainlab, Munich, Germany) was used to plan a scalp incision. The craniotomy exposed the lesion in addition to 2- to 3-cm cortical margins around it for mapping of nearby cortex. Once the bone flap was removed, local anesthetic (0.1% lidocaine with 1:1,000 epinephrine) was administered between the dural leaflets on each side of nerves within the dura. The dura was opened to expose the lesion and was tacked up by 4.0 Nurolons.

Intraoperative recording
We use ECoG-assisted surgical resection routinely in patients with brain tumor in eloquent areas during awake tumor resections. During the procedure, the patients are typically awake and being readied for cortical stimulation for mapping. This technique is used mainly for functional cortical mapping and intraoperative monitoring to identify seizures and afterdischarges during intraoperative electrocortical stimulation. An 8 × 8 high-density grid and depth electrodes or a combination of strips and depth electrodes (Ad-Tech, Racine, WI) is placed around the tumor to be resected (figure 1). Some patients (n = 5) were monitored with only strips and depth electrodes. The high-density grid is composed of a 3-mm diameter with 5-mm center-to-center spacing. Strips are composed of 4.0-mm-diameter platinum/iridium disks (2.3 mm exposed) with 10 mm center-to-center distance. Registration was done during several minutes, at least until the ECoG, displayed with 70-Hz low-pass filter at 10 seconds per page. The ECoG was recorded with a 128-channel EEG system (Xltek, Natus Inc, Pleasanton, CA) with a 500-Hz sampling rate. Only the preresection and prestimulation recordings were analyzed.

Glossary

AED = antiepileptic drug; BTRE = brain tumor-related epilepsy; ECoG = electrocorticography; GBM = glioblastoma multiforme; HFO = high-frequency oscillation; IDH1 = isocitrate dehydrogenase 1; WHO = World Health Organization.
HFO analysis
Channels with excess line noise (60 Hz) or artifacts or containing no visible EEG signal were discarded before analysis. All artifact-free epochs recorded were reviewed, regardless of their durations. If electrode channels showed artifacts, they were omitted from analyses. Visual detection and quantification of HFOs and spikes were performed by 2 investigators (A.M.F. and B.H.B.). HFOs were defined as discrete oscillations observed in the raw, unfiltered recording lasting <400 milliseconds and a dominant oscillation frequency >30 Hz.9,11 A MATLAB-based (MathWorks, Natick, MA) program was used for an automated detection.12 The algorithm uses a cascade of adaptive frequency-dependent amplitude thresholds that are based on metric normalization. Artifacts are excluded on the basis of the frequency content dominance. Algorithm parameters were tuned with HFOs visually identified by reviewers. We did not evaluate the completeness of resection of HFO-generating tissue because most of these cases did not have a postresection ECoG. The HFOs were detected and quantified during a retrospective review of ECoG data; therefore, the presence of HFOs did not influence surgical plan.

Statistical analysis
Data were expressed as mean, range, and SD for continuous variables and as counts (percentages) for categorical variables. The occurrence and rate of HFOs in each recording were compared to the presence or absence of preoperative seizures, WHO tumor grade, tumor location, and IDH1 mutant status with the Fisher exact test. All statistical tests were 2 sided, and values of \( p < 0.05 \) were considered statistically significant.

Standard protocol approvals, registrations, and patient consents
This study was approved by the Mayo Clinic Institutional Review Board. Informed consent was obtained for all study participants.

Results

Patients
In total, 16 patients who underwent awake craniotomy-assisted tumor resection with ECoG were included in the study. Demographic and clinical characteristics of the cohort are shown in table 1. The mean age of the patients was 47.4 years (range 18–68 years). Twelve of the 16 patients presented with seizures. The prevalence of preoperative seizures did not differ between high-grade (grade III and IV) (8 of 11) and low-grade (grade I and II) (4 of 5) tumors or IDH1mut (5 of 6) and IDH1 wild-type (IDH1wt) (6 of 9) genotypes. In addition, preoperative seizure frequency did not differ by IDH1 mutation status. Brain MRI showed tumor location in the frontal, temporal, and parietal lobe in 6, 5, and 5 patients, respectively. The majority of the tumors were located in the left hemisphere (n = 10). Three patients were not receiving any preoperative antiepileptic drugs (AEDs). About half (5 of 12) of those presenting with seizures underwent tumor resection within a month of seizure onset. We have provided details of seizure history, including type and onset, as well as preoperative EEG findings of the cohort in table e-1 (links.lww.com/WNL/A297). All patients received perioperative
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<th>Frequency bands, Hz</th>
<th>Contactswith HFOs, n</th>
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<th>Histopathology (grade)</th>
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Abbreviations: ATRX = α-thalassemia/mental retardation syndrome X-linked; ECoG = electrocorticography; GFAP = glial fibrillary acidic protein; HFOs = high-frequency oscillations; IDH1mut = mutated isocitrate dehydrogenase 1 genotype; IDH1wt = isocitrate dehydrogenase 1 wild-type genotype; MGMT = methylguanine-DNA methyltransferase; NA = not applicable; TERT = telomerase reverse transcriptase; WHO = World Health Organization; * = present/retained.

* Spikes and sharp waves seen but without accompanying HFOs.
** IDH1 mutation status not available.
AEDs (4 never experienced seizures). The most commonly prescribed AEDs were levetiracetam (9 of 12) and lacosamide (4 of 12).

**ECoG analysis and HFOs**
A summary of the ECoG findings of the cohort is provided in table 1. The mean duration of recording was 9.75 minutes. HFOs with spikes were observed in 9 patients (figure 1), and 1 patient had periodic sharp waves without HFOs (patient 1). In the remainder of patients, the recording did not show spikes, sharp waves, or HFOs. In the 9 patients with HFOs, the mean rate was 5.5 per minute and involved up to 9 contacts (table 1 and figure 2). Patients with preoperative seizures were more likely to have HFOs than those without preoperative seizures (9 of 12 vs 0 of 4, p = 0.02). The occurrence of HFOs, however, did not differ between high-grade (5 of 11) and low-grade (4 of 5) tumors. In addition, the occurrence of HFOs did not differ by IDH mutation status. However, in patients with HFOs, the rate of HFOs was higher in those with IDH1mut (mean 7.2 per minute) than IDH1wt (mean 2.33 per minute, p = 0.03) (figure 3). Multivariate analysis showed that the difference in the rate HFOs between the 2 groups was independent of duration of ECoG recording, tumor location, and other tumor genetic markers, including p53 overexpression and 1p/19q codeletion. Moreover, anesthesia used during the awake craniotomy had no impact on the occurrence of HFO because the majority of patients received cranial regional anesthesia with very light propofol and/or dexmedetomidine, except 2 cases who received remifentanil to supplement propofol (1 of the 2 had HFOs). Of note, given the lack of IDH1 mutation status in papillary glioneuronal tumors,20 1 case (patient 6) was excluded from the analysis of HFO rate by IDH1 mutation status.

**Tumor molecular markers**
IDH1mut expression was identified in 6 patients (5 presented with seizures), a-thalassemia/mental retardation syndrome X-linked gene retention in 7 (2 presented with seizures), p53 overexpression in >50% of tumor cells in 5 (2 presented with seizures), and 1p/19q codeletion in 3 (2 presented with seizures). All cases with glioblastoma (2 presented with seizures) were IDH1wt, but in 2 cases, methylguanine-DNA methyltransferase promoter methylation was present (both presented with seizures) (table 1).

**Surgery**
All patients except 3 had gross-total resection of the tumor, of whom 1 had seizure recurrence (patient 10). Subtotal resection was performed in 3 patients because of tumor overlying eloquent cortex, and seizures recurred in 2 (patients 5 and 8). Retrospective review of MRIs along with intraoperative photos showing grid or strip placement suggests that in all patients except 1 (patient 8) preresection HFO-generating tissues appear to be completely resected with postoperative seizure recurrence. The extent of resection as previously reported31 for the 9 cases, along with the localization of HFOs approximated with preoperative, intraoperative, and postoperative MRI as well as MRI volumetric analysis, is provided in figure 2. Seizure freedom outcome of the cohort is provided in table e-1 (links.lww.com/WNL/A297). All of the patients with BTRE remained on AEDs at the most recent follow-up (mean 8 months).

**Discussion**
This study examined the intraoperative ECoG in 16 patients with brain tumor who underwent awake craniotomy and surgical resection. This study demonstrated that HFOs can be safely and reliably recorded with high-density grid, strips, or depth electrodes during awake craniotomy in patients with BTRE. We also found that HFOs are prevalent in BTRE and that the rate of HFOs was higher in patients with IDH1mut than in those with IDH1wt.

In this cohort, 12 of 16 (75%) patients presented with seizures as an initial manifestation of brain tumor. Five of 6 patients with the IDH1mut genotype presented with seizures as an initial manifestation. This finding is similar to the recent observation that patients whose tumors expressed IDH1mut were more likely to have experienced seizures at diagnosis than patients with IDH1wt.5,6 The overproduction of D-2-hydroxyglutarate with its structural similarity to glutamate may play a role in the mechanism of neuronal excitation leading to seizures.7,8 In our cohort, the rate of preoperative seizures did not differ by IDH1 mutation status. This finding is not surprising because there is a possibility that other tumor markers, including p53 overexpression, may have played a role in generating seizures in addition to the activation of glutamate receptors in patients with IDH1wt.3 The latter could suggest that tumor-specific pathophysiologic mechanisms might be involved in the generation of seizure.
In brain slice preparations harvested from patients with low-grade glioma, HFOs have been shown to be generated in the peritumoral neocortical regions that are infiltrated by glioma cells. HFOs were found in the majority of our patients with BTRE, and none were detected in those without preoperative seizures. Our finding is not unexpected because accumulating data suggest that HFOs are biomarkers for the epileptogenic zone in nontumoral epilepsies. The occurrence of HFOs did not differ by IDH mutation status; however, the rate of HFOs was higher in patients with IDH1 mutant than IDH1 wild-type genotype. Previously, HFO rates were shown to be higher in patients with focal cortical dysplasia type II lesions compared to those with type I lesions; type II lesions usually are more epileptogenic with an earlier onset of seizures and a higher seizure frequency. Our observation is congruent with recent reports that IDH1 mutant gliomas are more epileptogenic than those expressing IDH1 wild-type. The increased rate of HFOs in the mutant IDH1 glioma seen in our series could also reflect the possibility that these tumors have been around longer, allowing a longer period of time for the surrounding brain to develop a glial reaction with seizures as a consequence. Indeed, IDH1 mutation in glioblastoma multiforme (GBM) is felt to be equivalent to secondary GBM, i.e., GBM arising from a preexisting low-grade glioma. However, it is worth noting that not all HFOs are pathologic. Physiologic ripples occur in different brain regions and have been related to cognitive functions. Given the coexistence of HFOs and that spikes on ECoG occurred in all patients, we believe that the HFOs seen in this series are likely epileptogenic. Moreover, HFOs were prevalent in those with a history of preoperative seizures and were absent in those without preoperative seizures. Nevertheless, further studies are recommended to further examine the role of HFOs in BTRE to provide a bridge from transitional research observations to therapeutics such as tailoring glioma resections according to nongenotype biomarkers.

Our retrospective single-center design has inherent limitations. The small sample size limits definitive conclusions to be drawn regarding the association between HFOs and seizures in BTRE. In our cohort, HFOs were not detected independently of spikes or sharp waves, although in 1 patient we saw periodic sharp wave discharges without accompanying HFOs. This raises the question of whether HFO analysis adds any degree of sensitivity over standard “Berger band” analysis of ECoG in this population. Our observation should, however, be interpreted cautiously, particularly given the low sampling rate, which might have resulted in higher-frequency HFOs (fast ripples) being missed. Oscillations in the gamma frequency range, as seen in the majority of our cohort, have been implicated in generating ictal-like discharges in an in vitro model of epilepsy. Moreover, locally generated gamma oscillations preceding interictal discharges have been found to occur more frequently in the seizure-onset zone in nontumoral epilepsies. Conversely, some studies suggest that fast ripples are more reliable biomarkers for the epileptogenic zone than slower-frequency oscillations. Although the distinction between the type of HFO and epileptogenicity is not absolute, it is of interest to determine whether these observations endure in BTRE. Although we observed that in our cohort HFO-generating tissue was completely resected (on the basis of postoperative MRI findings along with intraoperative photos of grid and/or strip placement), we did not examine the completeness of resection of HFO-generating tissue because of the lack of postresection ECoG in the majority. However, the favorable seizure freedom outcome of the cohort (9 of 12 become seizure free), albeit with a short follow-up period, could reflect the extent of surgery, with a majority (9 of 12) undergoing gross-total resection. Indeed, peritumoral tissue could be associated with subtle pathologies such as mild forms of cortical dysplasia that could be highly epileptogenic and may result in seizure recurrence if left unrected.

Future prospective studies assessing the completeness of resection of HFO-generating tissue vis-à-vis seizure freedom outcome in BTRE are needed. Given the short-term postoperative follow-up, the seizure freedom outcome of our cohort should be interpreted cautiously. Taken together, given that HFOs were seen only in those presenting with seizures, the lack of surgical tailoring using HFOs as a surrogate, and the noncontrolled surgical outcome data, our observation should be interpreted cautiously. Prospective studies addressing these issues are needed to reproduce our findings and to further highlight the clinical utility of HFOs in BTRE.

HFOs are prevalent in patients with BTRE and served as a useful surrogate of epileptogenicity in our patients with brain
tumor. Our results support greater epileptogenicity with an IDH1 mutant genotype compared to IDH1 wild-type genotype gliomas. Larger prospective studies to establish the clinical utility of HFOs in BTRE are needed to identify new biomarkers to assist genotype-specific therapy in this patient population.

Authors contributions
Study concept and design: Drs. Feyissa, Worrell, and Quinones-Hinojosa. Acquisition of data: all authors. Drafting of the manuscript: Dr. Feyissa. Analysis and interpretation of data: Drs. Feyissa, Mahato, Brinkmann, and ReFaey. Manuscript editing for appropriate grammar and syntax: Drs. Worrell, Tatum, Rosenfeld, and Quinones-Hinojosa. Critical revision of the manuscript for important intellectual content: Drs. Feyissa, Worrell, Tatum, Rosenfeld, and Quinones-Hinojosa. Study supervision: Drs. Worrell, Rosenfeld, and Quinones-Hinojosa.

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Disclosure
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