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Do Interictal Rates Influence Treatment Outcomes in Temporal Lobe Epilepsy?

Quantitative Electrocorticographic Biomarkers of Clinical Outcomes in Mesial Temporal Lobe Epileptic Patients Treated With the RNS System

Desai N, Tchen T, Morrell MJ. *Clinical Neurophysiology.* 2019;130:1364-1374. doi:10.1016/j.clinph.2019.05.017.

OBJECTIVES: Find interictal electrocorticographic (ECoG) biomarkers of clinical outcomes in mesiotemporal lobe (MTL) epilepsy patients. METHODS: In the NeuroPace RNS System clinical trials with 256 patients, 20 MTL patients with the most reduction in clinical seizures at year 7 compared to baseline (upper response quartile: 96.5% median change) and 20 with the least reduction in clinical seizures (lower response quartile: 17.4% median change) were evaluated. Clinical and interictal ECoG features from the 2 response quartiles were compared. RESULTS: Demographic and clinical features were similar in the upper and lower response quartiles. Interictal spike rate (ISR) was substantially lower ($P < .0001$) in the upper quartile patients, while normalized θ (4-8 Hz) and normalized γ ($>$25 Hz) were also different ($P < .05$) between the 2 response quartiles. Interictal spike rate was positively correlated ($P < .05$) with clinical seizure rates in 71% of the channels analyzed. Electrocorticographic records captured during months with no clinical seizures had the lowest ISR. CONCLUSIONS: Interictal spike rate is a strong differentiator of clinical response in MTL patients. Normalized θ and γ also differentiates clinical response. SIGNIFICANCE: In MTL patients, the ISR along with spectral power computed from chronic ambulatory baseline ECoGs may serve as biomarkers of clinical outcomes and maybe used as treatment end points.

Commentary

Temporal lobe epilepsy (TLE) is a syndrome often highly refractory to medical treatment. Some patients with a unilateral focus can be treated with resective or ablative procedures or with neuromodulation when dealing with bitemporal foci. When discussing the surgical treatment of unilateral TLE, concordance of ictal activity with neuroimaging abnormalities and cognitive dysfunction predicts a good outcome to treatment. The clinical significance of interictal epileptiform abnormalities (IEA) is not as clearly defined as other electrographic data. Yet the majority of patients with TLE show IEA on serial electroencephalogram (EEG) recordings.[1] So, can IEA serve as a biomarker or predictor of outcome in the treatment of these patients?

A review of the literature shows a paucity of studies and conflicting conclusions regarding the correlation between IEAs and surgical outcome. Some reports indicate that absolute spike frequency is predictive of postoperative seizure control. For example, Krendl et al[2] studied 55 patients with refractory TLE, all associated with unilateral hippocampal atrophy (HcA), who were treated with temporal lobectomy. An average of 10 hours of interictal EEG were obtained during the presurgical evaluation and analyzed for IED frequency and distribution. Patients were then classified as having either frequent or infrequent ($>$60 spikes vs $\leq$ 60 spikes/h), and unilateral or bilateral ($\geq$90% or $<$90% ipsilateral to the side of HcA) distribution of IEA. Absolute spike frequency, but not relative spike distribution, correlated with seizure control following a temporal resection. Similarly, in a study of patients classified as oligospikers (rare $<$1/h or absent surface IEAs) who underwent a surgical resection, Rosati et al[3] report similar postoperative outcomes when compared to patients with frequent spikes, independent of the presence of HcA.

In contrast, Ngo et al[4] report a series of 47 patients, 62% with unilateral HcA, who underwent a temporal lobectomy. Absolute spike frequency was assessed on at least 1 hour of EEG data acquired during noninvasive inpatient EEG monitoring. The authors did not find a significant difference in spike frequency between patients who achieved postoperative seizure freedom and those who did not.

For the most part, these reports relied on data obtained from short-term monitoring of surface EEG activity, which typically is limited to 1 to 2 weeks of inpatient video/EEG telemetry. Interictal epileptiform abnormalities analysis was done on a subset of data, from predetermined EEG samples, and without controlling for the presence of sleep. Divergent findings can be

explained by the inclusion of interictal EEG samples of variable length, different sample sizes, and the inclusion of subgroups of TLE patients with diverse etiologies. Because isolated hippocampal spikes cannot be detected on scalp EEG,[5] the exclusion of bitemporal ictal foci cannot be excluded. The complex temporal relationship between IEAs and clinical seizure rates may depend on the anatomical location of the ictal zones within the mesiotemporal lobe (MTL).

The advent of chronically implanted devices that have the ability to monitor EEG data for extended periods has provided new insights into the relationship between IEA and seizures. For example, using an implantable seizure advisory system which sampled 16 channels of intracranial EEG between 4 months and 2 years, Karoly et al[6] reported data from 15 patients, including 4 with bitemporal lobe epilepsy. Subjects with high rates of seizure activity did not necessarily demonstrate the highest rates of interictal spiking, and spike rate showed greater variance than mean across all subjects. The authors suggested that spikes may be useful biomarkers of cortical excitability.

In a recent study, Desai et al[7] analyzed potential electrographic biomarkers of seizure frequency. Long-term data were collected from 78 patients with MTL epilepsy who were treated and monitored with the NeuroPace device (Mountain View, CA). The device is a cranially implanted stimulator that is connected to up to 2 cortical strip or depth leads, each containing 4 electrode contacts, that continuously monitors EEG activity. The device is programed to capture short recordings of predefined electrographic biomarkers that comprise up to 5 minutes of EEG data per 24 hour. Stored data can then be retrieved by the patient allowing for more data to be captured and stored. Scheduled electrocorticographic (ECoG) records serve as the patient's interictal baseline.

Quarterly clinical responses were calculated as change in patient-reported clinical seizure counts. Electrographic features were compared between the upper and lower clinical response quartile groups, defined as having a median change in the rate of clinical seizures of—96.5% with respect to baseline versus a—17.4% change, at 7 year of follow-up. Median values for interictal spike rate, total spectral power, and spectral band power were computed for each ECoG channel at every year since implant.

Interictal spike rate was lower in the good responders compared to poor responders. These differences were apparent at year 3 of follow-up and this coincided with the most robust clinical response. Importantly, clinical or demographic features such as etiology, number of seizure foci, or duration of epilepsy were not significantly different. Interictal epileptiform abnormalities were superior to spectral power in differentiating between good and poor responders. The authors suggest that IEAs may be used as a biomarker to measure clinical response to a therapeutic intervention.

Desai et al[7] focused on identifying electrographic features that differentiate good and poor responders, irrespective of the reason for the change in clinical seizure rates. Despite this limitation, the results strongly suggest that IEAs are positively correlated with clinical seizures in MTL epilepsy. A way to establish a *causal* relationship between IEDs and seizure rates would require continuous ECoG record storage, while controlling for variables that affect the clinical response, such as changes in anticonvulsant treatment or changes in lifestyle. Additionally, future studies need to include patients with diverse etiologies and epilepsy syndromes. If replicated, these results suggest that interventions aimed at suppressing IEA can improve the clinical response to neuromodulation and/or other therapeutic interventions.

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References

1. Ajmone-Marsan C, Zivin LS. Factors related to the occurrence of typical, paroxysmal abnormalities in the EEG records of epileptic patients. *Epilepsia*. 1970;11(2):361-381.
2. Krendl R, Lurger S, Baumgartner C. Absolute spike frequency predicts surgical outcome in TLE with unilateral hippocampal atrophy. *Neurology*. 2008;71(5):413-418.
3. Rosati A, Aghakhani Y, Bernasconi A, et al. Intractable temporal lobe epilepsy with rare spikes is less severe than with frequent spikes. *Neurology*. 2003;60(8):1290-1295.
4. Ngo L, Sperling MR, Skidmore C, Mintzer S, Nei M. Absolute spike frequency as a predictor of surgical outcome in temporal lobe epilepsy. *Seizure*. 2017;47:83-86.
5. Marks DA, Katz A, Booke J, Spencer DD, Spencer SS. Comparison and correlation of surface and sphenoidal electrodes with simultaneous intracranial recording: an interictal study. *Electroencephalogr Clin Neurophysiol*. 1992;82(1):23-29.
6. Karoly PJ, Freestone D, Boston D, et al. Interictal spikes and epileptic seizures: their relationship and underlying rhythmicity. *Brain*. 2016;139(pt 4):1066-1078.
7. Desai N, Tchen T, Morrell MJ. Quantitative electrocorticographic biomarkers of clinical outcomes in mesial temporal lobe epileptic patients treated with the RNS system. *Clin Neurophysiol*. 2019; 130(8):1364-1374.