



Can EEG Abnormalities be a Biomarker of Epileptogenesis?

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Commentary on Scalp Ripples Can Predict Development of Epilepsy After First Unprovoked Seizure in Childhood

Klotz, Sag Y, Schönberger J, Jacobs J. *Ann Neurol.* 2021;89(1):134-142. doi:10.1002/ana.25939

Objective: Identification of children at risk of developing epilepsy after a first unprovoked seizure can be challenging. Interictal epileptiform discharges are associated with higher risk but have limited sensitivity and specificity. High-frequency oscillations (HFOs) are newer biomarkers for epileptogenesis. We prospectively evaluated the predictive value of HFOs for developing epilepsy in scalp electroencephalogram (EEG) of children after a first unprovoked seizure. **Methods:** After their first seizure, 56 children were followed prospectively over 12 months and then grouped in “epilepsy” or “no epilepsy.” Initial EEGs were visually analyzed for spikes, spike ripples, and ripples. Intergroup comparisons of spike-rates and HFO-rates were done by Mann-Whitney *U* test. Predictive values and optimal thresholds were calculated by receiver operating characteristic curves. **Results:** In the epilepsy group ($n = 26, 46\%$), mean rates of ripples (0.3 vs 0.09/minute, $P < .0001$) and spike ripples (0.6 vs 0.06/minute, $P < .05$) were significantly higher, with no difference in spike rates (1.7 vs 3.0/minute, $P = .38$). Of those 3 markers, ripples showed the best predictive value (area under the curve ripples = 0.88). The optimal threshold for ripples was calculated to be ≥ 0.125 /minute with a sensitivity of 87% and specificity of 85%. Ripple rates were negatively correlated with days passing before epilepsy diagnosis ($R = -0.59, P < .0001$) and time to a second seizure ($R = -0.64, 95\% \text{ CI} = -0.77 \text{ to } 0.43, P < .0001$). **Interpretation:** We could show that in a cohort of children with a first unprovoked seizure, ripples predict the development of epilepsy better than spikes or spike ripples and might be useful biomarkers in the estimation of prognosis and question of treatment.

Commentary

There are many studies of intracranially recorded electroencephalogram (EEG) high-frequency oscillations (HFOs): most aim at the localization of the epileptogenic zone and appear very promising for this purpose. Intracranial HFOs are usually divided into ripples (80-250 Hz) and fast ripples (250-500 Hz). When it was discovered that, despite their small amplitude and the small volume of their generator as seen in intracerebral EEG, ripples could be recorded in scalp EEG,¹ hope was expressed that this could become an easily available noninvasive new biomarker of epilepsy. Some early studies of scalp HFOs nevertheless concentrated on focus localization² but Kobayashi et al³ demonstrated that there was a relationship between scalp EEG ripple rate and treatment effectiveness in children with West syndrome. Van Klink et al⁴ published an exciting study linking the presence of ripples in Rolandic epilepsy with the likelihood of seizures occurring. The study we discuss here indicates that scalp ripples also appear to have a powerful potential for predicting the appearance and the evolution of epilepsy. The study by Klotz et al⁵ demonstrates that the presence of ripples in the scalp EEG of children with a first

unprovoked seizure is a powerful predictor of an eventual diagnosis of epilepsy and of seizure recurrence. The study is prospective and includes a relatively large number of children, making it convincing. It makes it clear that a criterion of simple presence or absence of ripples is insufficient and defines objectively a rate threshold beyond which a prediction can be made. The value of this threshold, however, will not be easy for others to use, as discussed below.

For a biomarker of epileptogenesis to be optimally useful, it should appear before epilepsy is first diagnosed. The patients studied here all had one unprovoked seizure when they were evaluated but most were not diagnosed with epilepsy at the time of the study and one can therefore argue that the study presents evidence for a biomarker of epileptogenesis. Even for the children for whom a diagnosis had been made, it is early in the development of their epilepsy and we know that epileptogenesis continues after the first appearance of epilepsy. The study of Rolandic epilepsy mentioned above as well as the study of Bernardo et al⁶ in children with the Tuberous Sclerosis Complex, in whom fast Ripples were only found in those with epilepsy, indicate the interesting potential of scalp HFOs in



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children as an important biomarker of epilepsy and of epileptogenesis.

One can consider the following as an interesting paradox. The definition of epilepsy by the International League against Epilepsy states that one unprovoked seizure and a 60% probability of seizure recurrence allow making the diagnosis of epilepsy. In this context, the study of Klotz et al can be said to predict the occurrence of epilepsy since HFOs are often found before diagnosis. If, however, it becomes solidly established in the future that HFOs are a strong predictor of seizure recurrence, then they could be used to establish this 60% probability. If they are thus incorporated in the diagnosis process, then they would lose their ability to be a biomarker of epileptogenesis but become only a biomarker of epilepsy, as they would allow an earlier diagnosis.

The relatively high rate of ripples was surprising, even in the absence of spikes. An early study in adults with medically refractory epilepsy had indicated that scalp ripples were absent if spikes were absent.⁷ The results from Klotz et al may indicate that ripples are more common in children and not as linked to spikes as they are in adults. The high rate may also be related to the ability of experienced authors to identify scalp ripples. If this is indeed a factor, it would have been useful for the authors of this study and for future authors to make available, as part of their papers or otherwise, a large number of examples of what they marked as scalp ripples, as well as what they considered marking but rejected. A consensus on what are scalp ripples is particularly important because the authors propose a specific threshold, in terms of ripple rate, to make a prediction. This threshold applies for their markings but can only be useful to others if others mark events in the same way, with exactly the same selectivity. Similar markings would be more likely with the availability of a large set of samples, but the ideal way of solving this problem is with automatic detection, so that everybody can use the same detector. A few detectors of scalp HFOs have been published but it would be important to obtain a consensus on a detector and its settings. Even if editing of automatic detections is necessary to reject events that are obviously false, this is more likely to lead to similar markings than if everyone uses their own visual or automatic approach.

In the study of Klotz et al, it could have been interesting to record in which brain region the marked ripples took place and see how this relates to the future development of the patients' epilepsy, be it generalized or focal, and if focal, in a region related to the localization of the scalp ripples.


Early in the study of HFOs, Bragin and his collaborators demonstrated the ability of HFOs to act as a biomarker of epileptogenicity in experimental models of epilepsy.⁸ They found that the presence and rates of HFOs were related to whether and how early after an initial insult spontaneous seizures would develop. Further studies confirmed that HFOs were markers of the likelihood of seizure occurrence⁹ and the pattern of epilepsy development.¹⁰

In conclusion, it appears that scalp-recorded HFOs, even though they are not frequent and not a prominent EEG pattern,

may be an important biomarker or epileptogenesis and of epilepsy. Most studies have been performed in children, but it is not clear why the situation would be different in adults. Maybe it is time to start looking!

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