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Case Report

Relationship between high-frequency oscillations and spikes in a case of temporal lobe epilepsy

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ABSTRACT

Objective: The aim of this case report was to study the relationship between high-frequency oscillations (HFOs), spikes, and seizures in a patient with temporal lobe epilepsy.
Introduction: During intracranial electroencephalography (EEG), HFOs are thought to be a marker for the seizure onset zone (SOZ). High-frequency oscillations are classified into ripples with frequencies of 70–200 Hz and fast ripples with frequencies of 200–500 Hz. Although HFOs are thought to be a marker for the SOZ, their relationship to spikes has not been studied in detail, especially within the SOZ.
Methods: We studied the time course of ripples and spikes in a patient undergoing intracranial EEG. Medications were discontinued on day one. She suffered three seizures on day three. Her SOZ was in the left hippocampus, which displayed abundant ripples and spikes. Ripples, spikes with simultaneous ripples, and spikes without ripples were counted for this study.
Results: We found that ripples and spikes in the SOZ had a marked diurnal variation. Ripples, spikes with ripples, and spikes without ripples increased and decreased in concert until just before seizure onset, when ripples and spikes with ripples increased markedly. Spikes without ripples did not increase.
Conclusions: These results support ripples as a marker for SOZ and show that they co-occur with spikes. Seizure onset was heralded by an increase in ripples and spikes with ripples, without an increase in spikes without ripples. We hypothesize that spikes associated with ripples may have a somewhat different pathophysiological mechanism than spikes not associated with ripples, differences that may be relevant for the timing of seizure onset.

1. Clinical vignette

A 17-year-old right-handed woman underwent intracranial EEG prior to epilepsy surgery. Epilepsy began at age 12. Seizures were a single type of highly stereotyped episode in which she stared, shook both hands and arms briefly, then returned to normal after brief postictal disorientation. Seizure frequency was 5–6 per month, and her longest seizure-free interval was two weeks. Seizures were refractory to combined levetiracetam and lacosamide and to previous oxcarbazepine monotherapy.

Magnetic resonance imaging revealed a left inferior temporal meningocele. Interictal positron emission tomography showed hypometabolism in the entire left temporal lobe. Scalp video-EEG documented only one seizure and suggested left temporal onset. To define the SOZ, she underwent intracranial EEG which documented three complex partial seizures typical for the patient. All seizures started in the most medial left hippocampal depth electrode (denoted LH1), with electrographic seizure onset simultaneous with the first seizure symptom. Electrode LH1 showed frequent ripples and interictal epileptiform discharges without spread to adjacent electrodes. She underwent left anterior temporal lobectomy for medically intractable left temporal lobe epilepsy. She has had no seizures in 20 months since surgery, remaining on treatment with lacosamide and levetiracetam.

2. Introduction

The standard scalp EEG examines frequencies up to 70 Hz, but with intracranial recording, higher frequencies can be studied. Brief high-frequency discharges lasting milliseconds have been observed and classified as ripples (80–250 Hz) and fast ripples (250–600 Hz), with some recent evidence of very high-frequency bands (600–1000 Hz) [1]. Ripples and fast ripples have been found in rodent hippocampus and entorhinal cortex and are thought to be involved in normal memory consolidation [2]. Studies on rodent epilepsy models indicate that fast ripples may be associated with epileptogenesis [3]. High-frequency oscillations have been identified in mesial temporal structures of humans with epilepsy [4]. High-frequency oscillations increase before seizure onset. Therefore, ripples are thought to be a good marker for the SOZ, and resection of areas displaying ripples during intracranial recording

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is associated with better outcome [5]. Three different patterns of HFO occurrence have been described with microelectrode studies: HFOs that occur independent of spikes, HFOs that occur together with spikes visible using standard EEG filters, and HFOs occurring with spikes but not visible with standard EEG settings [6].

It is unclear whether spikes and HFOs have different pathophysiological mechanisms [7]. Prior work by Jacobs et al. suggested that spikes can be grouped into spikes with and without HFOs, and spikes with HFOs were more frequent in the epileptogenic area [8]. However, the differences between spikes with and without HFOs within the SOZ have not been investigated. Our patient had prominent ripples in the SOZ that gave us an opportunity to study various characteristics including diurnal pattern, effect of medication withdrawal, and relation to spikes. In addition, we analyzed differences between spikes with co-occurring ripples and spikes without ripples in the SOZ.

3. Methods

Our patient underwent intracranial video-EEG for 71 h. The electrodes were three bilateral temporal epicortical electrodes, six left

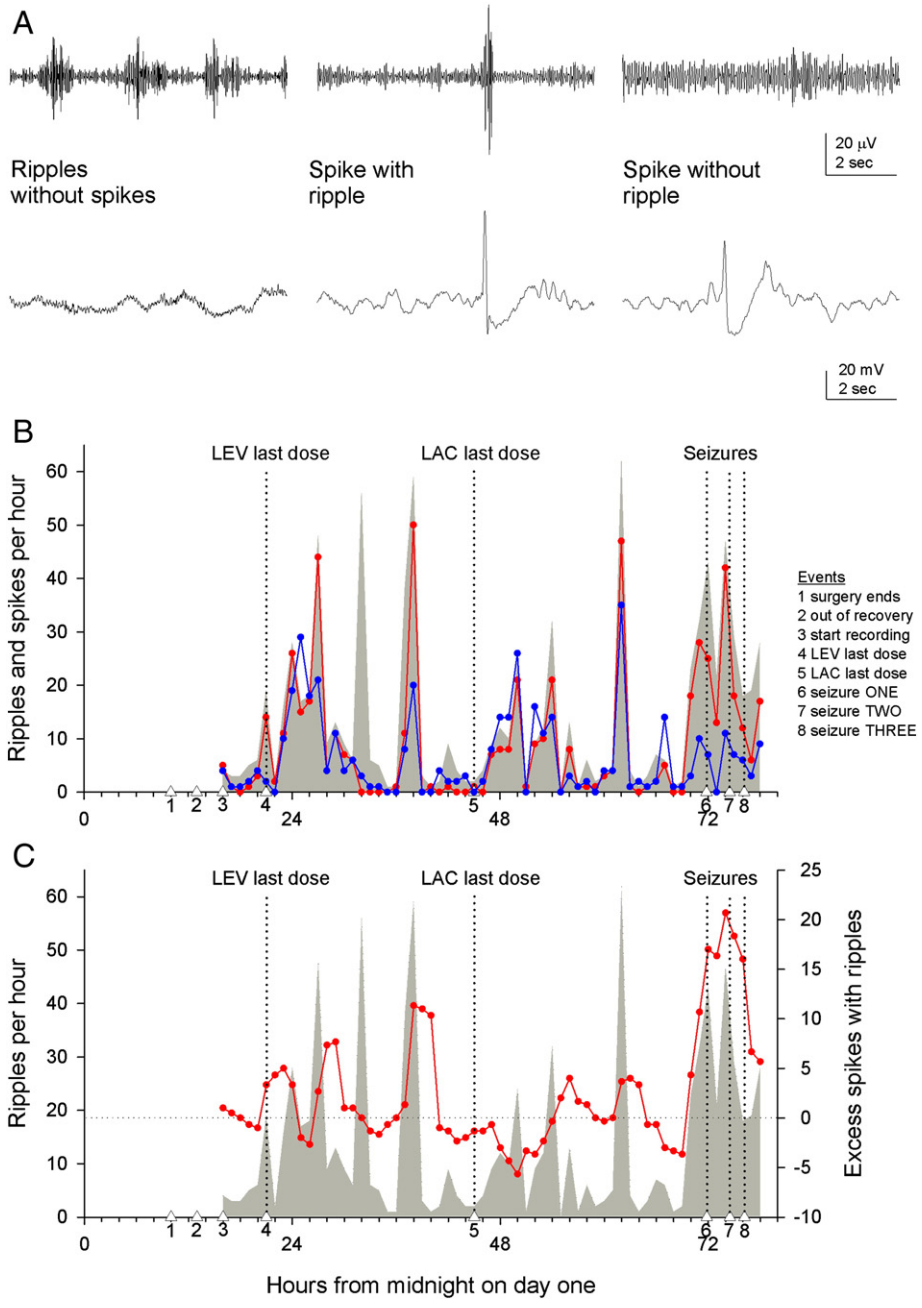

Fig. 1. Time course of ripples, spikes with ripples, and spikes without ripples. A) These are examples of a ripple without a simultaneous spike (left), spike with a ripple (center), and spike without a ripple (right). B) This is the time course of ripples (gray area), spikes with ripples (red), and spikes without ripples (blue). Note that ripples and spikes of both types increased markedly during late evening and early morning hours when the patient slept. Note that prior to and during seizures on night three (with the first seizure at about hour 72), ripples and spike with ripples increased without a corresponding increase in spikes without ripples. Increases in ripple frequency are accompanied by a corresponding increase in spikes with ripples, except at hour 28, when there is a marked increase in ripples without spikes. Times are given on the horizontal axis and are measured from the midnight before surgery. Relevant times are indicated by numerals and explained in the inset (LEV, levetiracetam; LAC, lacosamide). Five minutes of EEG were examined hourly, with the times indicated by the circles. Straight lines merely connect the actual measurements, and no data were analyzed except during the 5-minute sections. C) This shows the frequency of ripples (left axis, gray area) and excess of spikes with ripples over spikes without ripples (right axis, red line and circles). Note the marked preponderance of spikes with ripples beginning at hour 70, 2 h before her first seizure and continuing through seizures two and three. Electroencephalography was discontinued after hour 78.

frontal epicortical electrodes, and an intracranial depth electrode with five electrical contacts in the left temporal lobe. The most medial depth electrode contact (denoted LH1) was in the anterior left hippocampus and the most lateral in the lateral temporal cortex. An epicortical reference electrode was placed near the right vertex. A Natus XLTEK system (Oakville, Ontario, Canada) was used. The A/D conversion rate was 512 Hz. For standard EEG, a low-pass filter of 70 Hz and a high-pass filter of 1 Hz was used (XLTEK filter type not specified). Examples (Fig. 1A) were converted to European Data Format, filtered (8-pole Bessel filters) using EDFbrowser (www.teuniz.net/edfbrowser/) and plotted using SigmaPlot 11 (Systat Software, Inc., San Jose, CA).

There were frequent interictal epileptiform discharges localized exclusively to LH1. Electrode LH1 also showed frequent ripples. Fast ripples were not investigated. Ripples and interictal spikes were visually counted by a single observer (VS) on a reduced data set consisting of 5 min per hour of EEG. Electrode LH1 was selected for visual analysis of both interictal spikes and ripple frequency oscillations, which were displayed in the same montage on the same screen. For ripples, the time scale was set to maximum resolution, amplification was set to 2 μV/mm, low-pass filter was set at 250 Hz, and high-pass filter was set at 70 Hz. Interictal spikes were analyzed with an amplification of 30 μV/mm, low-pass filter at 70 Hz, and high-pass filter at 1 Hz. The operational definition of "ripple" for the purpose of this analysis included any oscillation that clearly stood out of the background, with at least six phases in the oscillation and a peak-to-peak amplitude of more than 25 μV (Fig. 1A).

The patient was given 1500 mg of levetiracetam twice a day and 150 mg of lacosamide twice a day on admission. Her medications were discontinued on day one of recording. Three seizures occurred on day 3 of recording, each one with onset clearly localized to LH1. This provided an opportunity to compare the time course of ripple and spike occurrences in the SOZ.

4. Results

We analyzed the time course of ripples and spikes in our patient with respect to electrode implantation, discontinuation of medication, and occurrence of seizures. Ripples, spikes with ripples, and spikes without ripples were counted (Fig. 1A). A total of 889 ripples were observed. The rate of ripples and spikes increased gradually over time. There was a dramatic increase in ripples and spikes during sleeping hours (Fig. 1B). There was a transient rise in the frequency of ripples and spikes after the last dose of levetiracetam. A second transient rise in ripples occurred after the last dose of lacosamide. Seizure onset was preceded by a rise in the frequency of ripples and interictal spikes associated with ripples, but spikes not associated with ripples did not change significantly with seizures (Fig. 1B).

5. Discussion

This case is consistent with several previously described characteristics of HFOs. First, high-frequency oscillations may be a marker for the SOZ [7] because HFOs were abundant in the electrode where seizures originated. Second, HFOs in the SOZ co-occur with spikes [9]. Spikes in the patient's SOZ were highly stereotyped and easy to count. Spikes outside the SOZ were much more rare and variable. Third, with antiepileptic drug discontinuation, HFOs transiently go up in bursts [9]. In our patient, brief bursts of HFOs and spikes were noticed at unpredictable times during recording, the significance of which is unclear. Our patient showed a clear increase in HFOs during sleeping hours (10 PM to 8 AM). We observed that HFOs and spikes associated with HFOs increased in frequency before seizure onset and during seizures, whereas spikes not associated with HFOs did not go up significantly. This observation has not been previously reported and raises the question of whether spikes associated with HFOs and spikes without HFOs have different pathophysiological mechanisms. It is possible that the lack of spikes without HFOs increases neuronal network synchrony in such a way as to promote seizures.

Much modern EEG analysis involves sophisticated mathematical analysis with measures and methods unlike ordinary visual analysis of EEG. A single case can serve only as an 'existence proof', not as an indication of what is usual, but our observations suggest that, in the SOZ, an increase of spikes with HFOs without a corresponding increase in spikes without HFOs may precede and accompany seizures. Our case illustrates that simple visual EEG analysis may still yield unique observations potentially useful in patient care.

Author contributions

Vishwanath Sagi was involved in the study concept and design and acquisition and analysis of data. M. Steven Evans was involved in the interpretation of data and critical review of the manuscript for intellectual content.

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Author disclosures

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