■ Original article

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Epileptic Disorders

"Generalized-to-focal" epilepsy: stereotactic EEG and high-frequency oscillation patterns

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ABSTRACT

Objective. We aimed to clarify the pathophysiology of epilepsy involving seizures with apparently generalized onset, progressing to focal ictal rhythm through stereotactic EEG (SEEG) implantation, recording, stimulation and high-frequency oscillation (HFO) analysis.

Methods. We identified two patients with seizures with bilateral electrographic onset evolving to focal ictal rhythm, who underwent SEEG implantation. Patients had pre-surgical epilepsy work-up, including prolonged video scalp EEG, brain MRI, PET, ictal/interictal SPECT, MEG, and EEG-fMRI prior to SEEG implantation.

Results. Both patients had childhood-onset seizures involving behavioural arrest and left versive head and eye deviation, evolving to bilateral tonic-clonic convulsions. Seizures were electrographically preceded by diffuse, bilateral 3-Hz activity resembling absence seizures. Both had suspected focal lesions based on neuroimaging, including 3T MRI and voxel-based post-processing in one patient. Electrode stimulation did not elicit any habitual electroclinical seizures. HFO analysis showed bilateral focal regions with high fast-ripple rates.

Significance. "Generalized-to-focal" seizures may occur due to a diffuse, bilateral epileptic network, however, both patients showed ictal evolution from a generalized pattern to a single dominant focus which may explain why the focal aspect of their seizures had a consistent clinical semiology. Patients such as these may have a unique form of generalized epilepsy, but focal/multifocal cerebral abnormalities are also a possibility.

Key words: high-frequency oscillations, focal epilepsy, stereotactic EEG

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The phenomenon of seizures with bilateral symmetrical electrographic onset evolving to focal electroclinical semiology has been recognized for years. However, the underlying mechanisms of this rare epilepsy type remain poorly understood. We aimed to clarify the pathophysiology through stereotactic EEG (SEEG) implantation, recording, stimulation, and high-frequency oscillation (HFO) analysis.

Methods

We identified two patients with seizures with bilateral electrographic onset evolving to a focal ictal rhythm, who had undergone SEEG implantation.

Patients had pre-surgical epilepsy work-up, including positron emission tomography (PET), ictal/interictal single photon emission computed tomography (SPECT), magnetoencephalography (MEG), EEG-functional MRI (EEG-fMRI), and prolonged video scalp EEG prior to SEEG implantation. One patient also had 3T MRI and voxel-based post-processing. During SEEG recording, both patients had at least one overnight recording at 2000-Hz sampling rate on which HFO analysis was performed. The fast-ripple rate (250-500-Hz oscillations) was computed in a 10-minute segment during non-rapid eye movement (NREM) sleep, as well as for the full overnight recording [1].

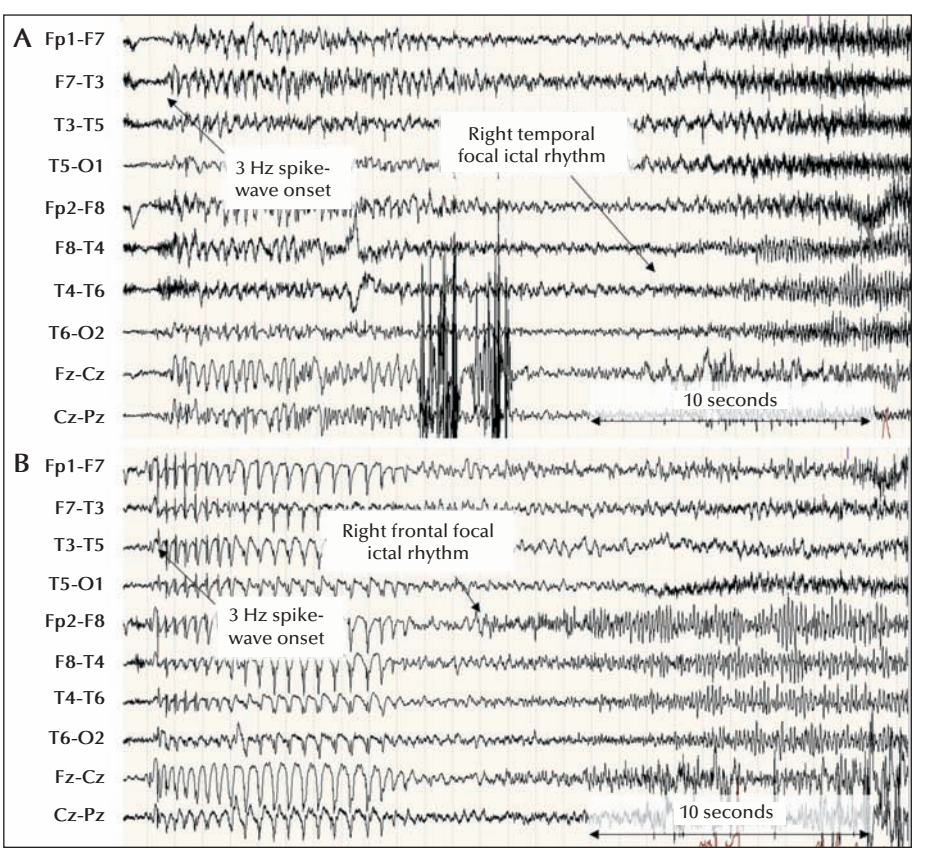
Results

Patient 1

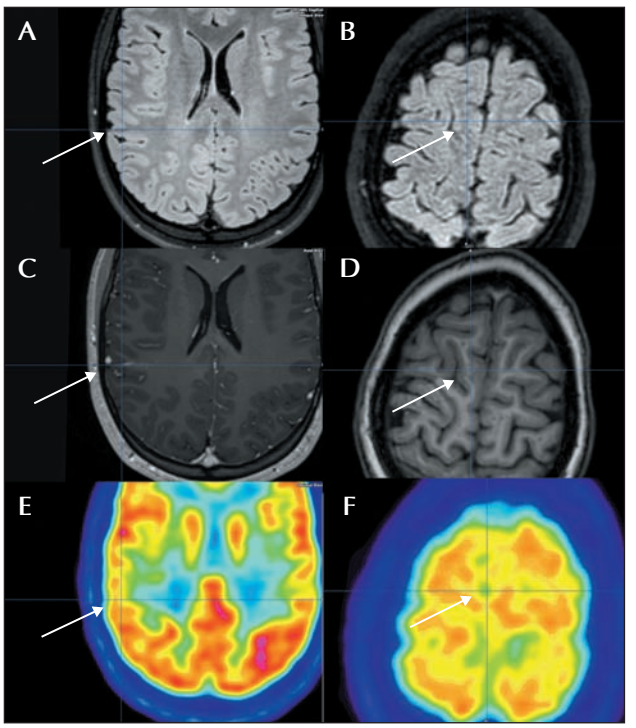
An 18-year-old woman had seizures from age 12 years, involving behavioural arrest, then left versive head and eye deviation, evolving to bilateral tonic-clonic convulsions. These clinical seizures occurred only 2-3 times per year, but she and her parents were very concerned about medication side effects. She had trials of clobazam, lamotrigine, lacosamide, topiramate, levetiracetam, and carbamazepine. There had never been concerns for absence seizures or myoclonic jerks. There was no known family history of epilepsy.

Initial scalp EEG at age 12 years showed focal sharp slow-wave discharges over the right frontal region, however, two EEG studies performed three months later showed bilateral spike-wave fragments, albeit sometimes appearing to have lead-in from the right frontal region. When admitted for prolonged video-EEG monitoring at age 15 years, abundant bursts of 3-5-Hz bilateral spike-wave and polyspike-wave discharges, lasting 4-20 seconds, were seen; at times, she had increased blinking during the episodes but there was no definite loss of awareness. She had one habitual seizure with focal-to-bilateral tonic-clonic semiology, which was preceded by the bilateral spike-wave burst (*figure 1A*).

Brain MRI showed slight hippocampal asymmetry, less on the left than the right, and developmental venous anomaly (DVA) in the area of the right post-central gyrus and supramarginal gyrus (*figure 2A, C*). Brain PET



■ **Figure 1.** Scalp EEG recordings of convulsive seizures for Patient 1 (A) and Patient 2 (B).



■ **Figure 2.** Imaging studies. For Patient 1, 3T brain MRI shows a developmental venous anomaly in the right parietal region on axial T1 with contrast (B), and suspected cortical blurring in the same area on FLAIR (A) (arrows). Brain PET shows hypometabolism in the same region (C) (arrow). For Patient 2, axial 3T FLAIR and T1 (B and D) shows a suspected focal cortical dysplasia in the right frontal region, and PET shows focal hypometabolism in the same area (F).

showed subtle hypometabolism in the DVA region (*figure 2E*). Interictal SPECT was normal and attempts at ictal SPECT were unsuccessful. MEG suggested a right frontal localization (*figure 3*), and EEG fMRI revealed two right frontal zones of significant responses.

With a primary of hypothesis of a right frontal epileptic focus, the patient was admitted for SEEG implantation at age 17 years, with 11 depth electrodes in her right frontal, parietal, and temporal regions, and three in the left frontal region (*supplementary figure 1*). She was recorded for 47 days because she had not had any habitual convulsive seizures, even with rapid anti-seizure medication weaning. She had many events per day with bilateral spike-wave activity (*figure 4*). Photic stimulation at 10 Hz elicited a photoparoxysmal response with eye closure (*figure 5*). When she finally had a habitual convulsive seizure, this exhibited, similar to scalp EEG, a diffuse to focal evolution on SEEG (*figure 6*).

Electrode stimulation at high (50 Hz) and low (1 Hz) frequencies did not provoke any habitual seizures, but stimulation of the frontal regions triggered the bilateral spike-wave bursts. Interestingly, photic stimulation also provoked the bilateral spike-wave activity. HFO analysis revealed the fast-ripple rate to be highest in the right parietal lobe near the DVA (12/minute during NREM sleep, 11/minute over the whole night) in one of the EEG/fMRI sources (right middle frontal gyrus; 7/minute for NREM, 5/minute for the whole night), but also in the left supplementary motor area (7/minute for NREM, 4/minute for the whole night).

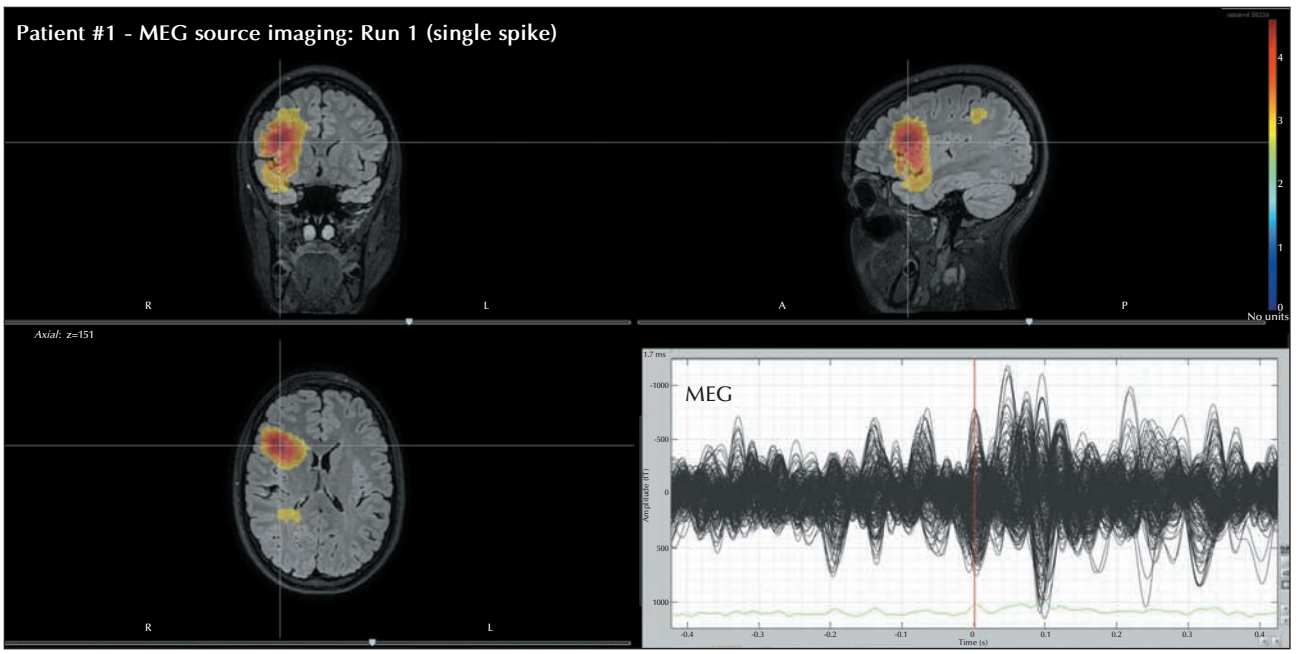
Although a focal driver was suspected, consensus could not be reached on whether to attempt a small resection of the suspected lesion, so no further surgical intervention was undertaken. Valproic acid was added to lacosamide, and she has thus far been free of convulsive seizures for 24 months.

Patient 2

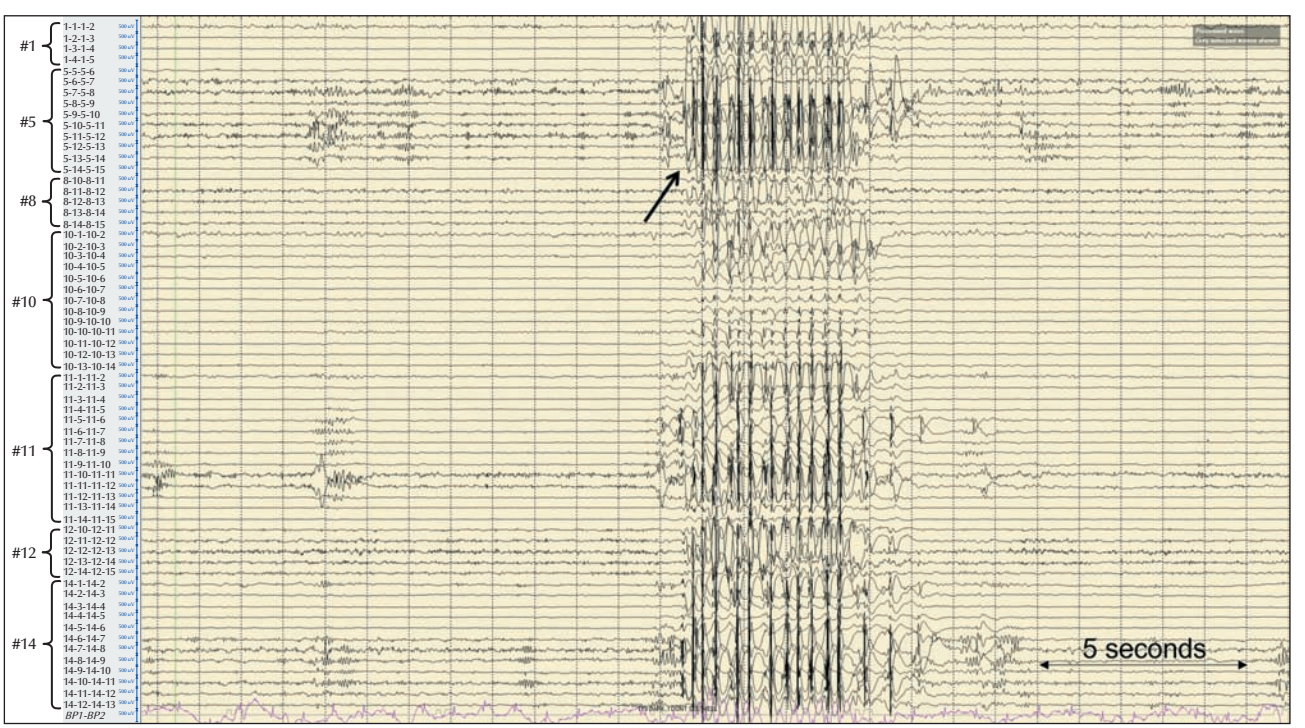
An 11-year-old girl had seizures from age nine years. Her events involved behavioural arrest with right hand automatisms and up-and-down head/eye bobbing, sometimes progressing to left head and eye deviation and subsequent bilateral tonic-clonic convulsions. She often had left post-ictal hemiparesis following the convulsive events. Seizures occurred 5-10 times per day despite trials of lacosamide, perampanel, valproic acid, clobazam, levetiracetam, ethosuximide, and lamotrigine. She developed a rash with carbamazepine, so this was stopped before receiving a therapeutic trial. There had never been concerns for absence seizures or myoclonic jerks. There was no known family history of epilepsy.

Prolonged scalp video-EEG recording identified 3-Hz bilateral spike-wave bursts, lasting 5-10 seconds, also provoked by hyperventilation and photic stimulation. During these events, she sometimes had increased blinking and behavioural arrest, but often no clear clinical change. With habitual seizures with focal-to-bilateral tonic-clonic semiology, a bilateral burst of epileptiform activity was seen initially, evolving into a right frontal focal ictal rhythm, which then spread bilaterally (*figure 1B*).

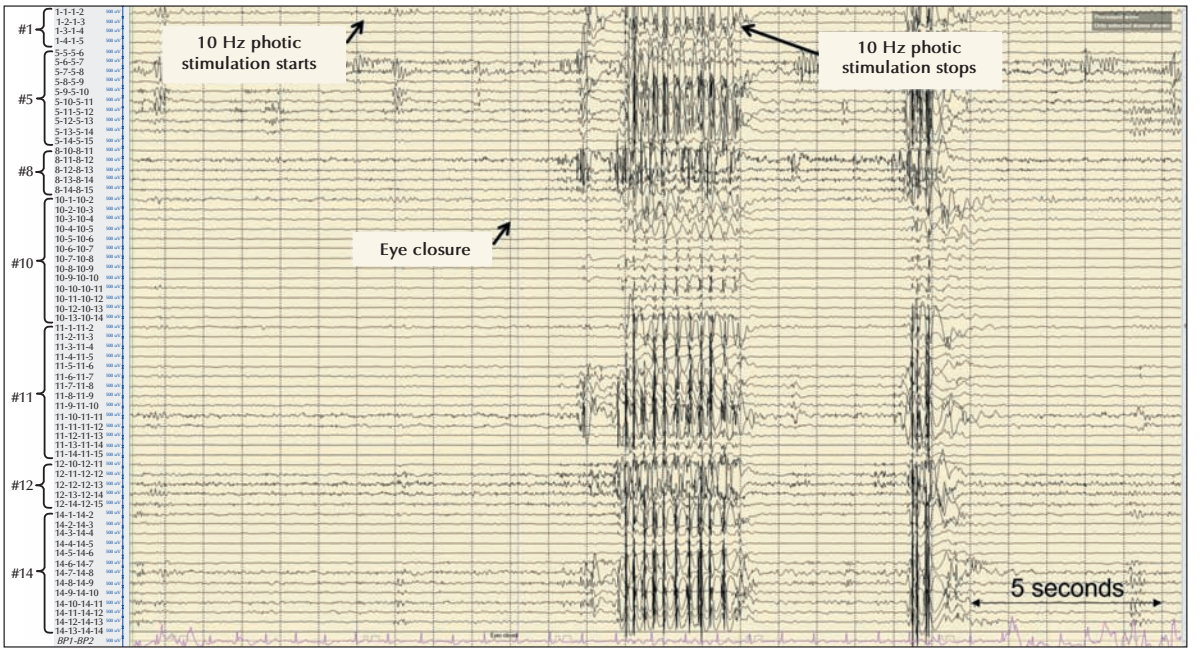
Brain MRI showed non-specific T2 hyperintensity in the frontal white matter. Voxel-based texture analysis identified an area of increased cortical thickness and blurring in the right frontal region compatible with focal cortical dysplasia, associated with enlarged perivascular spaces (*figure 2B, D, supplementary figure 2*). Brain PET showed extensive hypometabolism in the right frontal region (*figure 2F,*



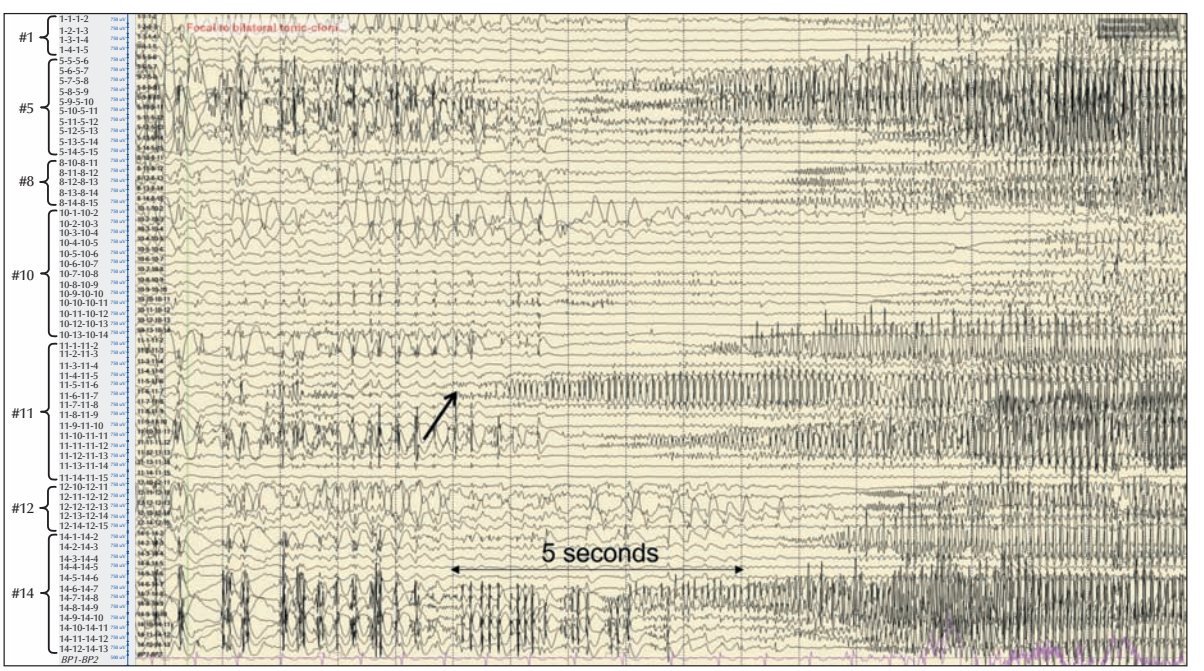
■ **Figure 3.** Magnetoencephalography study for Patient 1. Magnetoencephalography analysis from one spike suggested a right frontal localization, as shown.



■ **Figure 4.** Interictal SEEG for Patient 1. Occasional bursts of bilateral spike-wave activity are seen (arrow).



■ **Figure 5.** Photoparoxysmal response during SEEG recording for Patient 1. With voluntary eye closure during photic stimulation at 10 Hz, diffuse bilateral spike-wave and polyspike-wave discharges are seen. Only selected electrode contacts are shown. The implantation map is presented in *supplementary figure 2*.



■ **Figure 6.** Focal-to-bilateral tonic-clonic seizure during SEEG recording for Patient 1. Focal ictal rhythm is first seen at the mid-contacts of Depth 11 (right frontal; arrow), spreading in a sequential manner to other contacts on Depth 11, as well as adjacent depth electrodes. As usual, the focal seizure is preceded by a burst of diffuse, bilateral spike-wave discharges. Only selected electrode contacts are shown. The implantation map is presented in *supplementary figure 2*.

supplementary figure 2). An interictal SPECT scan was obtained, but injection was made 20 minutes after one of the "absence" events – this study showed a region of hyperperfusion in the right dorsolateral frontal region involving the supplementary motor area, with corresponding hyperperfusion in the left cerebellum suggesting a crossed diaschisis.

At age 10 years, she had SEEG implantation with coverage of the suspected MRI lesion, with 11 electrodes in the right frontal lobe and five in the left frontal lobe (*supplementary figure 1*). Interictal recording showed at least three independent foci of epileptiform discharges (spike-wave and/or paroxysmal fast activity) in the right frontal lobe, one of which involved the perilesional electrodes, and an additional focus in the left frontal region. She had up to several per hour bilateral spike-wave events, though awareness usually appeared at least partially preserved (*figure 7*). With photic stimulation at 14 and 16 Hz, she had photoparoxysmal response with eye closure. With low-frequency stimulation (1-Hz) of selected electrodes, no seizures, after-discharges, or physiological clinical responses were seen. High-frequency (50-Hz) stimulation produced after-discharges from all electrodes stimulated, and in some cases, 3-Hz bilateral spike-wave bursts were seen, though these did not result from stimulation from a particular cerebral region.

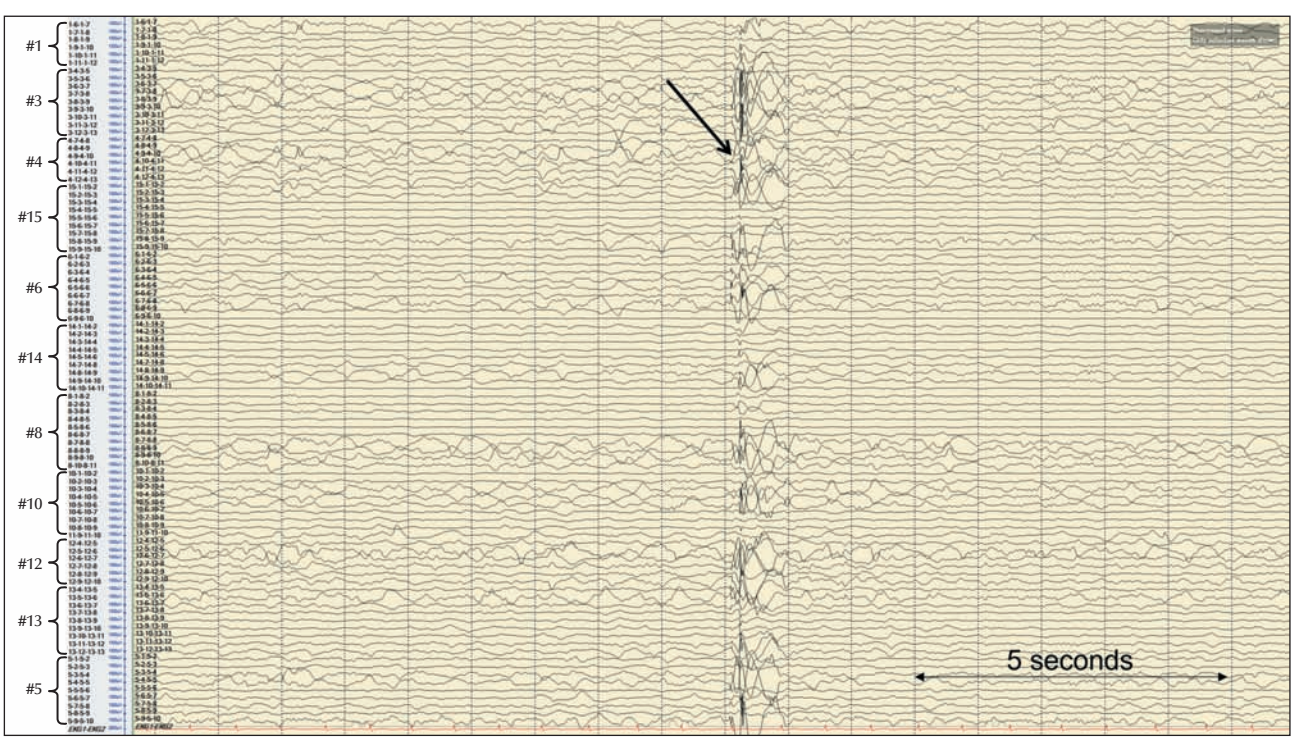
During the 16-day recording, she had one bilateral tonic-clonic seizure. The seizure clinically began with staring, intermittent eye blinking, and was time-locked to an initial diffuse/bilaterally synchronous burst of 3-Hz spike-wave, lasting seven seconds. This was immediately followed by evolving low-voltage rhythmic fast activity that appeared simultaneously over both frontal regions, with rapid spread more broadly, at which time she developed bilateral tonic stiffening and clonic jerking (*figure 8*). No clear or sustained head or eye deviation (or other focality) was observed.

HFO analysis showed the highest fast-ripple rate in the right postcentral gyrus (22/minute for NREM, 11/minute over the whole night), the right insula (11/minute for NREM, 6/minute over the whole night), and the left posterior middle frontal gyrus (6/minute for NREM, 2/minute over the whole night).

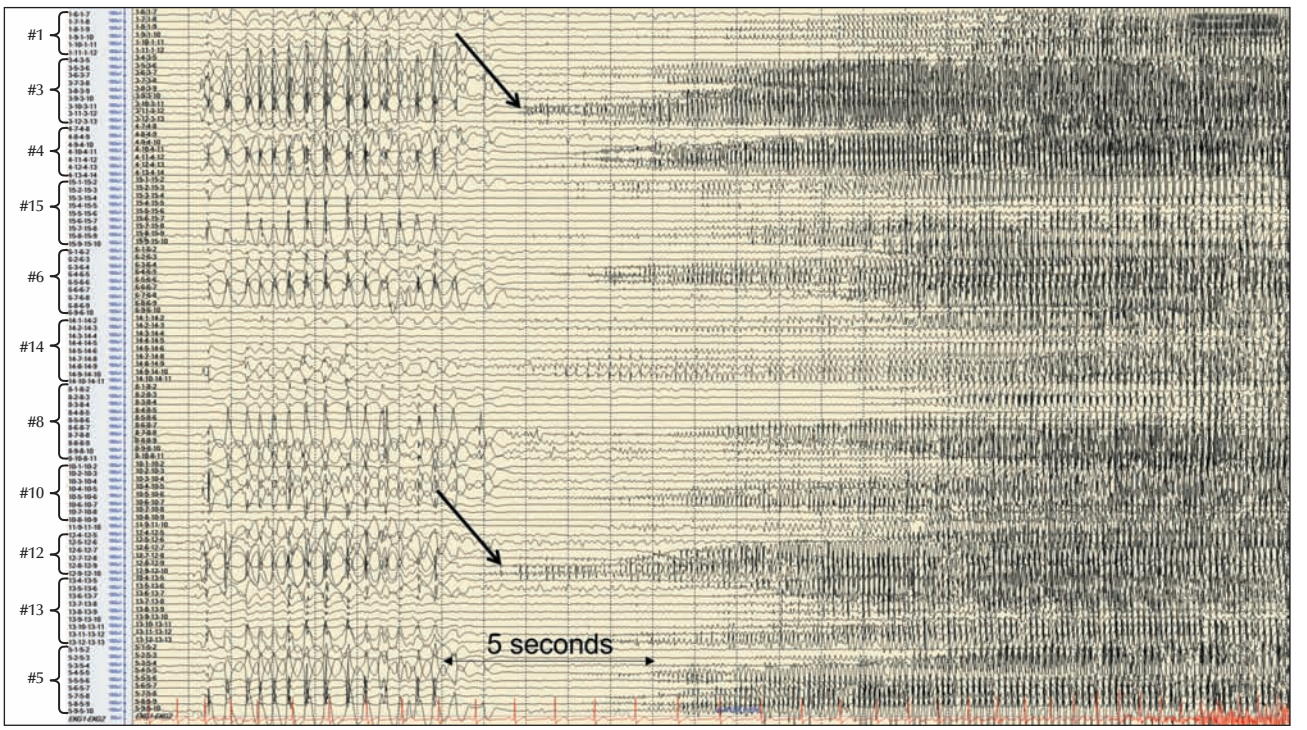
Following the SEEG implantation, the consensus was to not proceed with any surgical resection; although her clinical semiology, scalp EEG, and neuroimaging had appeared consistently lateralized, the HFO and SEEG analysis raised concerns that she might have a multifocal process. She has been seizure-free for 14 months post-SEEG implantation despite no changes in her medication, however, the potential for seizure recurrence remains.

Discussion

Both patients had near-identical presentations with stereotyped convulsive seizures with consistent focal



■ **Figure 7.** Interictal SEEG for Patient 2. Occasional bursts of bilateral spike-wave activity are seen (arrow).



■ **Figure 8.** Focal-to-bilateral tonic-clonic seizure during SEEG recording for Patient 2. Focal ictal rhythm is first seen simultaneously at the superficial contacts of depths 3 (right frontal) and 12 (left frontal) (arrows), spreading more broadly in a sequential manner. As usual, the focal seizure is preceded by a burst of diffuse, bilateral spike-wave discharges. Only selected electrode contacts are shown. The implantation map is presented in supplementary *figure 2*.

semiology. In each, clinical events were electrographically preceded by diffuse, bilateral activity resembling absence seizures. Bilateral bursts also occurred independently, resembling brief absence seizures, and could be provoked by hyperventilation and photic stimulation. Our data suggest that bilateral-to-focal presentation may be due to a diffuse, bilateral network, however, a single dominant focus could explain why the focal aspect of seizures was associated with a consistent clinical semiology. In particular, Patient 2 had early EEG and advanced neuroimaging findings highly suggestive of a right frontal epileptogenic lesion. Patients with such bilateral-to-focal presentations could have an unusual form of generalized epilepsy versus focal/multifocal cerebral abnormalities recruiting a bilateral network.

There are previous reports of similar patients, many of whom are described as having genetic generalized epilepsy (GGE) phenotypes with focal features. For example, Usui *et al*. reported two patients diagnosed with juvenile myoclonic epilepsy who had seizures with "generalized" onset, with a focal ictal rhythm emerging later in the seizure; as with our patients, version direction was consistent and contralateral to the EEG ictal rhythm [2]. This group and others have considered these patients to have atypical GGE [3], however, there are many well-documented reports of focal lesions giving rise to generalized-appearing discharges and seizures, which can resolve following surgery [4-7].

Previous studies have sought to clarify the underlying pathophysiology of such "generalized to focal" epilepsy presentations. Chassagnon *et al*. performed EEG-fMRI analysis on a patient with both focal and generalized-appearing epileptiform discharges, with MRI showing a small focal cortical dysplasia in the left central sulcus [8]. Using blood oxygenation level-dependent activity analysis, they found that both the focal and generalized-appearing discharges caused perilesional activation, however, clearly distinct neuronal networks were involved in the two discharge types. Our finding of bilateral focal regions of HFO is important but does not completely resolve the issue. This finding could be interpreted as suggestive of multifocal lesions, as such high rates of fast ripples are closely associated with abnormal brain tissue [1]. However, since patients with straightforward generalized epilepsy do not undergo SEEG implantation, we cannot definitively say that this HFO pattern does not

occur in patients with classic GGEs. There is, however, evidence from scalp EEG recordings that patients with GGEs have variable amounts of HFO ripples, often lateralized [9].

In summary, our analysis showing generalized-to-focal electrical dynamics suggests that the underlying pathophysiology may involve a diffuse bilateral network. A leading hypothesis is that one or more focal lesions are responsible for recruitment of a secondary pathological network. However, we cannot rule out that some patients with generalized epilepsy have a susceptible focus from which focal seizures may be triggered by the generalized activity.

Key points

- People with "generalized-to-focal" seizures may have multifocal regions of increased high-frequency oscillation fast ripples.
- "Generalized-to-focal" epilepsy may be associated with focal cortical dysplasia identified only by voxel-based post-processing.
- Some cases of "generalized-to-focal" epilepsy may occur due to focal or multifocal brain lesions.

Supplementary material.
Supplementary data and summary slides accompanying the manuscript are available at www.epilepticdisorders.com.

Disclosures.
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TEST YOURSELF

(1) What high-frequency oscillation pattern is observed with SEEG implantation of patients with generalized-to-focal seizure patterns?

(2) In generalized-to-focal epilepsy, can patients have a stereotyped semiology for their seizures?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com.