High-frequency oscillations in idiopathic partial epilepsy of childhood
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SUMMARY
Purpose: We explored high-frequency oscillations (HFOs) in scalp sleep electroencephalography (EEG) studies of patients with idiopathic partial epilepsy (IPE) of childhood in order to obtain a better understanding of the pathologic mechanisms underlying IPE.

Methods: The subjects were 45 patients, including 32 with benign childhood epilepsy with centrotemporal spikes (BCECTS) and 13 with Panayiotopoulos syndrome (PS). A total of 136 EEG records were investigated through temporal expansion and filtering of traces and time-frequency spectral analysis.

Key Findings: HFOs with frequency of 93.8–152.3 Hz (mean 126.2 ± 13.6 Hz) in the band of ripples were detected in association with spikes in 97 records (71.3%). Time from last seizure to the EEG recording was significantly shorter in those with spike-related HFOs than in the EEG recordings with spikes without HFOs (p = 0.006). Although time from last seizure reflects age, age at the time of recording was not significantly different between EEG studies with and without HFOs. Peak-power values of the high-frequency spots in time-frequency spectra were significantly negatively correlated with time from last seizure ($R^2 = 0.122$, $p < 0.001$) but not with age at the time of recording. Peak frequencies of the high-frequency spectral spots were not significantly correlated with age at the time of recording or with time from last seizure.

Significance: The close relationship between the generation of spike-related HFOs and the period of active seizure occurrence indicated that HFOs may tell us more about epileptogenicity in IPE than the spikes themselves. Because there is a spectrum of pediatric epileptic disorders extending from the benign end of BCECTS to the encephalopathic end of epilepsy with continuous spike-waves during slow-wave sleep (CSWS), and HFOs that have already been detected in association with CSWS were more prominent than HFOs in IPE, intense spike-related HFOs may indicate poor prognosis.

KEY WORDS: Benign childhood epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, Rolandic spike, Scalp electroencephalogram, Time-frequency analysis.

Idiopathic partial epilepsy (IPE) of childhood, particularly benign childhood epilepsy with centrotemporal spikes (BCECTS) and Panayiotopoulos syndrome (PS), is characterized by the age-dependent appearance of unique types of seizures that remit spontaneously with no neurologic sequel. The high incidence of IPE, however, marks its clinical importance (Covanis et al., 2005; Dalla Bernardina et al., 2005). The association of cognitive and/or behavioral problems with IPE has been reported (Croona et al., 1999; Deonna et al., 2000). In addition, there is a spectrum of pediatric disorders extending from BCECTS to atypical benign partial epilepsy (ABPE) (Aicardi & Chevrie, 1982) and even to epileptic encephalopathies, including epilepsy with continuous spike-waves during slow-wave sleep (CSWS) and Landau-Kleffner syndrome (LKS) (Dalla Bernardina et al., 2005; Rudolf et al., 2009). Aggravation of PS has also been reported (Kikumoto et al., 2006). The clinical variability of IPE necessitates the development of novel prognostic markers. We previously reported the detection of high-frequency oscillations (HFOs) in association with scalp-recorded spikes in epilepsy with CSWS and related disorders; this study included a patient who had epilepsy evolving from BCECTS to ABPE with CSWS (Kobayashi et al., 2010).

HFOs in electroencephalography (EEG) studies are believed to be related to epileptogenesis (Le Van Quyen et al., 2006; Ochi et al., 2007; Jacobs et al., 2009). HFOs ranging from 80–250 Hz (ripples) have been recorded from the hippocampus and entorhinal cortex of normal rodents.
(Buzsáki et al., 1992; Chrobak & Buzsáki, 1996) and also from the human hippocampus (Bragin et al., 1999a). Oscillations with even higher frequencies of 250–500 Hz (fast ripples) have been demonstrated to be closely related to epileptogenesis (Bragin et al., 1999a,b; Staba et al., 2002; Jirsch et al., 2006; Rampp & Stefan, 2006; Jacobs et al., 2008, 2009).

We aimed to examine HFOs occurring in association with scalp EEG spikes in BCECTS and PS in order to gain a better understanding of the pathologic mechanisms underlying idiopathic childhood epilepsies.

**Methods and Subjects**

**Subjects**

The subjects of the present study were a total of 45 patients (22 boys, 23 girls) with IPE who exhibited typical focal spikes in digitally recorded sleep EEGs between November 2003 and June 2010 (32 patients with BCECTS and 13 patients with PS). Analysis was performed on digital interictal EEG data recorded for subjects <19 years of age. The diagnostic criteria of BCECTS included mostly nocturnal focal motor and/or generalized seizures with onset ranging from 3–13 years of age and centrotemporal spikes with activation during sleep in EEG (Commission, 1989). The diagnostic criteria of PS included seizures with predominantly autonomic, particularly emetic, symptoms that were often prolonged, prone to occur during sleep, and started at 1–14 years of age, and EEG spikes with variable or multiple foci, often with occipital predominance (Ferrie et al., 2006). Regarding children with PS, the current study included only patients who had predominant occipital spikes with or without concomitant rolandic or frontopolar spikes (Ohtsu et al., 2003) and who were confirmed to have a benign outcome with seizure suppression for at least 1 year, because cases of potentially nonidiopathic epilepsy were excluded. Patients who had intellectual deficit (IQ <70), neurologic deficit, and/or any lesions in the brain parenchyma in neuroimaging were excluded from the study. For the purpose of the spectral analysis of EEG data mentioned below, there must be at least 10 clear spikes at the same focus in each EEG record. The current study was therefore limited to patients with at least one sleep EEG record with 10 or more artifact-free focal spikes. All patients were treated with antiepileptic medication.

This study was approved by the Okayama University Ethics Committee.

**Methods**

EEG was recorded with a sampling frequency of 500 Hz using a Nihon-Kohden (Tokyo, Japan) Neurofax system, which used a low-cut filter at 0.016 Hz before digital sampling. The international 10–20 electrode system was used, and the analysis was performed in a referential montage, using the average EEG of the earlobes (A1 and A2) as a reference. HFOs occurring in scalp EEG spikes during sleep were investigated through 10-fold temporal expansion of the EEG traces with a low-cut frequency filter (bidirectional Butterworth, $-6 \text{ dB}$) at 70 Hz (see Fig. 1 for an example).

HFOs were examined through time-frequency power spectral analysis using the Gabor transform, which is the Fourier transform with a sliding Gaussian window of 50-ms full-width half maximum (FWHM) (Kobayashi, 2011).
et al., 2004, 2009) (see Fig. 2 for an example). Spectral analysis was performed in each of the following channels: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, and Pz, with reference to the average of A1 and A2. For each channel, we averaged 30 nonoverlapping EEG spectra at most, each spectrum being built from a data segment including an unambiguous consecutive spike at the same focus. In a patient with two or more spike foci, the focus with the most frequent spikes was selected for the analysis. EEG data with <10 spikes were not analyzed. High-frequency peaks were identified as clearly visible spectral spots with frequencies above 80 Hz. The width of each spectral segment was 300 ms, and the frequency range was 20–200 Hz. The Fourier transform was performed on 128 data points (256 ms; frequency resolution 3.9 Hz) at each time step; the step was 2 ms. Computation was performed using a program written in house for MATLAB (version 6.5.1; MathWorks Inc., Natick, MA, U.S.A.), in conformity to our previous study on CSWS (Kobayashi et al., 2010).

In the temporally expanded and high-pass–filtered EEG data, the rate of ripple occurrence per spike was also morphologically examined in the channel of greatest high-frequency power in the corresponding spectra (in patients with no high-frequency peaks in the spectra, the rate of ripple occurrence was examined in the channel in which ripples, if present, were detected). A ripple was defined as an event of at least four consecutive oscillations with a frequency of 80–250 Hz (Jacobs et al., 2008).

In the EEG data with detectable spike-associated HFOs, the electrode with the greatest high-frequency peak-power value was compared to the electrode of visually identified focus with the largest negative spike peak.

**Statistical analysis**

For each of the EEG data with a sufficient number of spikes for the analysis, time from the last seizure to the recording (a positive value in the case of time lapsed after the last seizure and a negative value in the case of time preceding the last seizure) was compared using an unpaired t-test between EEGs with and without HFOs. Because longer periods of time from the last seizure to the recording are associated with older ages at the recording, age at the time of recording itself was similarly compared between EEGs with and without spike-related HFOs. The relation between the presence of spectrally detected HFOs and the presence of visually identified HFOs associated with at least one spike was investigated by Fisher’s exact test.

In patients who exhibited HFOs in association with focal spikes, the relation was analyzed between the peak frequency of the high-frequency spectral spot and the recording age by calculation of the correlation coefficient. The relation was also investigated between the peak frequency and the time from last seizure. Similarly, the relation of the peak-power value of the high-frequency spectral spot was investigated with age at the time of recording as well as time from last seizure.

Statistical analysis was performed using SPSS (Japanese ver. 17; SPSS, Tokyo, Japan). Relationships were considered statistically significant if p < 0.05. In this comparison, the signal power was converted to a logarithmic scale to obtain a more Gaussian distribution (Gasser et al., 1982).
RESULTS

There were a total of 200 EEG records; 136 had a sufficient number of spikes for the analysis, with the number of analyzed spikes in each record ranging from 22–30 (mean 29.9 ± 0.7). HFOs were detected in association with spikes in 97 records (71.3% of analyzed records) in time-frequency spectra (representative EEG of BCECTS depicted in Fig. 1 and the corresponding spectrum in Fig. 2; representative EEG of PS depicted in Fig. 3 and the corresponding spectrum in Fig. 4). It is of note that HFOs were also observed in time-frequency spectra built from bipolar data excluding the possibility of high-frequency noise contamination from the reference (representative bipolar spectrum of BCECTS depicted in Fig. S1 corresponding to the monopolar spectrum in Fig. 2; representative bipolar spectrum of PS depicted in Fig. S2 corresponding to the monopolar spectrum in Fig. 4).

In 64 of 97 EEG records with spectrally detected HFOs, the spike count with visually identified ripples ranged from 1–24 (mean 5.6) among 30 spikes at most; the spike count was zero in the remaining EEG studies with spectrally detected HFOs and in all EEG studies with no spectrally detected HFOs. The nonzero spike count was significantly related with the presence of spectrally detected HFOs (p < 0.001). Ripples could be observed only in filtered EEGs.

Age at first seizure, at last seizure, and at the time of EEG recording for each patient is indicated in Fig. 5 (BCECTS in Fig. 5 top and PS in Fig. 5 bottom; individual row indicating each patient with EEGs arranged according to recording age, first seizure as red cross, and last seizure as blue cross). It is illustrated that EEG recordings tended to have HFOs at young age and to lose HFOs with development out of the period of seizures. Time from last seizure to EEG recording was significantly shorter in the EEGs with HFOs than those without (mean 0.4 ± 2.1 years vs. 1.6 ± 2.3 years; p = 0.006). Age at the time of EEG recording, however, was not significantly different between EEGs with and without HFOs (mean 8.5 ± 2.3 years vs. 9.5 ± 3.2 years; p = 0.110). In terms of each epileptic syndrome, patients with BCECTS had a total of 125 EEG records, 88 of which had a sufficient number of spikes, and 65 of which exhibited HFOs. Patients with PS had a total of 75 records, 48 of which had a sufficient number of spikes, and 32 of which exhibited HFOs.

The peak frequencies of the high-frequency spectral spots in time-frequency spectra ranged from 93.8 to 152.3 Hz (mean 126.2 ± 13.6 Hz) in all records with HFOs. Therefore, the spike-associated HFOs were in the frequency band of ripples. The peak frequency was not significantly correlated with age at the time of recording (R² = 0.000, p = 0.858) (Fig. 6A) or with time from last seizure (R² = 0.002, p = 0.631) (Fig. 6B). The peak-power values of the high-frequency spectral spots ranged from −21.5 to −2.0 dB (mean −12.1 ± 3.8 dB) in all records with HFOs. The peak-power value was not significantly correlated with age at the time of recording (R² = 0.029, p = 0.098) (Fig. 6C), but it was significantly negatively correlated with time from last seizure (R² = 0.122, p < 0.001) (Fig. 6D).

With respect to the relation between the location of spike focus and the electrode with the greatest high-frequency power, the electrode of the spike focus was, by definition,
fully rolandic in 65 EEG records with HFOs in BCECTS: C3/C4 in 12 and T3/T4 in 53. Of 32 EEG records with HFOs in PS, the spike focus involved O1/O2 in all and concomitant focus was at C3/T3/C4/T4 or Fp1 in 7. The electrode of the greatest high-frequency peak power was identical or adjacent to that of the spike focus in all patients.

Clinical characteristics of each patient are indicated in Table S1. The duration of epilepsy was 2.0 ± 1.5 years in BCECTS and 2.7 ± 1.9 years in PS with no significant difference (p = 0.173 by t-test).

There were two patients with BCECTS and two patients with PS who were excluded from the study because of no or too few digitally recorded spikes for the analysis. The four excluded patients did not differ from the included ones in clinical aspects other than EEG spikes; three had many spikes in paper EEGs before digital EEG recording (Table S1). Visual analysis of EEGs recorded from these patients revealed no ripples.

**DISCUSSION**

The detection of HFOs in association with scalp EEG spikes in IPE is remarkable because HFOs are found in invasively recorded EEG (Jirsch et al., 2006; Jacobs et al., 2009), and invasive recording is not feasible in IPE. Analysis of scalp EEGs has inherent difficulties, such as the differentiation of high-frequency activity from noise, and a more careful investigation of scalp EEGs than invasive records was therefore needed. Analysis was thus limited to scalp EEG data with minimum noise in this study, and only clear discrete spots in the time-frequency spectra were identified as HFOs. Although the majority of spikes were not associated with visually identified ripples even in EEGs with spectrally detected HFOs, these two types of measurements were indicated to have a statistically significant and close relation. Ripples in visual EEG and HFOs in spectra may not have the same clinical impact or neurophysiologic correlate, and visually identified ripples may represent the full-blown part of HFOs associated with spikes.

The presence of spike-related HFOs was significantly related to EEG recording with shorter latency from the last seizure. The high-frequency peak power was demonstrated to dissipate with the passage of time after the last seizure. It is of note that neither the presence of HFOs nor high-frequency peak power was statistically related to age at the time of EEG recording, although longer periods since the last seizure are associated with older ages at recording. In IPE, epileptogenicity generally decreases in adolescence, but EEG spikes tend to persist after the termination of seizures. The close relation between the generation of spike-related HFOs and the period of active seizure occurrence indicated that HFOs may tell us more about epileptogenicity in IPE than the spikes themselves. It was suggested that invasively recorded HFOs may be a better biologic marker of epileptogenic tissue than spikes (Zijlmans et al., 2009). We are aware that time from the last seizure was not an ideal parameter to represent epileptogenicity in IPE, but EEG spikes tend to persist after the termination of seizures. The close relation between the generation of spike-related HFOs and the period of active seizure occurrence indicated that HFOs may tell us more about epileptogenicity in IPE than the spikes themselves.

In the present study, the number of patients was insufficient to clarify the separate characteristics of spike-related HFOs in BCECTS and PS, although individual
age-dependent changes in HFOs appeared more diverse in PS than in BCECTS (Fig. 5). The current patients may be biased to epilepsy with more frequent seizures because 26 (57.8%) of all 45 patients had five or more seizures, in contrast to the general notion of infrequent seizures in IPE (Covanis et al., 2005; Dalla Bernardina et al., 2005). This seizure frequency and the concurrent parental anxiety that drove them to visit our hospital were the reasons for the medical treatment of these children with IPE. The effects of antiepileptic drugs on HFOs could not be investigated.

Transitory cognitive impairment (TCI) has been demonstrated to be related to rolandic spikes (Binnie & Marston, 1992), but the effect of HFOs on cognitive function, including TCI, could not be investigated in this study using previously recorded EEG data.

HFOs observed in association with spikes in IPE were much less prominent and had weaker power than HFOs in EEGs with CSWS (peak-power ranging from −7.7 to 4.7 dB) (Kobayashi et al., 2010). The clinical spectrum of pediatric epileptic disorders ranging from the benign end of BCECTS to the encephalopathic end of epilepsy with CSWS may correspond to the spectrum of HFOs with gradating intensity, although epilepsy with CSWS is often symptomatic and the difference in etiologies must influence the generation of HFOs. PS is suggested to have an etiology and pathogenesis similar to those of BCECTS (Ferrie et al., 2006). Because spikes in IPE are not always harmless (Jacobs, 2011), HFOs associated with spikes may be a predictive indicator of whether or not the given spikes are actually benign or if they have a propensity for aggravation.
In the future, a well-designed prospective study is required to clarify the clinical meaning of HFOs associated with spikes in IPE.

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**Disclosure**

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

**References**


EEG HFOs in Idiopathic Partial Epilepsy


Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Representative time-frequency power spectra of bipolar EEG data recorded from a patient with BCECTS (same EEG data as in Fig. 2).

Figure S2. Representative time-frequency power spectra of bipolar EEG data recorded from a patient with PS (same EEG data as in Fig. 4).

Figure S3. Time-frequency power spectra of all 10–20 electrodes in a patient with BCECTS (same patient as in Figs. 1 and 2).

Figure S4. Time-frequency power spectra of all 10–20 electrodes in a patient with PS (same patient as in Figs. 3 and 4).

Table S1. Patients.

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