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FULL-LENGTH ORIGINAL RESEARCH

A study on spike focus dependence of high-frequency activity in idiopathic focal epilepsy in childhood

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Summary

Objective: Spike foci in benign epilepsy with centrotemporal spikes (BECTS) are related to seizure semiologies, but this relationship is inconspicuous in Panayiotopoulos syndrome (PS). We analyzed spike-associated high-frequency activity (HFA) and its relationship to spike foci in the electroencephalograms (EEGs) of patients with BECTS and PS in order to elucidate the pathophysiology of these epileptic syndromes.

Methods: In 35 patients with BECTS and 29 with PS, focal spikes in scalp sleep EEGs were first classified by clustering according to their characteristics, including shape and distribution. For each patient, three or fewer spike clusters were investigated by time-frequency spectral analysis and single-dipole analysis using a realistic three-dimensional head model to explore the relationships between the presence or absence of spike-associated HFA and the distribution of estimated spike sources.

Results: A total of 159 spike clusters were analyzed (96 in BECTS and 63 in PS). HFA was detected in 73 spike clusters (76.0%) in BECTS and 37 (58.7%) in PS, with a significant difference in the proportion of spike clusters with HFA ($p = 0.024$ by Fisher's exact test). In BECTS, spikes had relatively uniform distributions, but the proportion of spikes with associated HFA was significantly higher in the spike group with dipoles in the perirolandic areas (42 of 49) than in that with dipoles outside of the perirolandic areas (23 of 36; $p = 0.037$). In PS, The proportion of spikes with associated HFA was significantly higher in the spike group with dipoles in the occipital lobes (20 of 26) than in that with dipoles outside of the occipital lobes (13 of 33; $p = 0.020$).

Significance: The proportion of spike-associated HFA was higher in BECTS than in PS. Particular pathophysiological meaning was indicated in spikes with dipoles in the perirolandic areas in BECTS and in spikes with dipoles in the occipital lobes in PS owing to the high proportions of spike-associated HFA in these areas.

KEY WORDS: Benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, High-frequency oscillations, Time-frequency analysis, Dipole analysis.

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There are several characteristic age-dependent epileptic syndromes in childhood. In particular, idiopathic focal epilepsies of childhood are prevalent and include Panayiotopoulos syndrome (PS) in early childhood and benign epilepsy with centrotemporal spikes (BECTS) in preschool and school-aged children. Interictal electroencephalogram (EEG) shows a characteristic spike form in the centrotemporal (rolandic) regions in BECTS and in the occipital regions in PS. However, the spike foci often move to other locations, and some patients with PS do not exhibit occipital spikes. The predisposing factors are speculated to be shared in BECTS and PS because there are cases with overlapping clinical and/or EEG features. Seizures in BECTS are mainly

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Key Points

- The proportion of spike clusters with associated HFA was higher in BECTS than in PS
- In BECTS, the dipole sources of spikes with associated HFA were located closer to the central sulci than those without associated HFA
- In PS, spikes with dipole sources located in the occipital lobes had a higher rate of associated HFA than those located outside of the occipital lobes
- Particular pathophysiological meaning was indicated in spikes with dipoles located in the perirolandic area in BECTS and spikes with dipoles in the occipital lobes in PS
- Spectrally defined HFA and visually detected HFOs did not show a consistent relationship with the number of seizures, probably because the present study involved only patients with typical BECTS or PS

a type of focal motor seizure called sylvian seizures, and the spike foci are related to the ictal semiologies. Seizures in PS, however, are mainly characterized by autonomic symptoms, including nausea and vomiting, and this relationship is inconspicuous. As such, we believe that the relationship of spikes to epileptogenicity may differ between BECTS and PS.

It has been indicated that high-frequency oscillations (HFOs) in EEG are related to epileptogenicity[1–3] and include ripples (80–200/250 Hz) and fast ripples (200/250–500 Hz). The relationship of HFOs to epileptogenicity is considered to be stronger than that of spikes to epileptogenicity. Epileptic HFOs are mainly detected from intracranial recordings, but the detection of HFOs in association with scalp-recorded spikes has been reported in epilepsy with continuous spike waves during slow-wave sleep (CSWS)[4] and adult focal epilepsies.[5]

van Klink et al. also analyzed ripples superimposed on rolandic spikes in scalp-recorded EEGs. They reported that the number of ripples had a significantly positive correlation with the number of seizures.[6] van Klink et al. studied visually detected HFOs in the ripple band. In contrast, Kobayashi et al. studied the high-frequency activity (HFA) detected using time-frequency analysis. HFA is indicated to have a weaker relationship with epileptogenicity than HFOs,[7] but it is empirically useful to use HFA to detect weak activity.

Although one study analyzed the HFA associated with the rolandic spikes of BECTS and the occipital spikes of PS,[8] to the best of our knowledge, no studies have been undertaken regarding the nonoccipital spikes of PS. We hypothesized that the detection rate of spike-associated HFA may differ depending on spike foci. Therefore, in the present study, we classified spikes in scalp EEGs recorded from patients with BECTS and PS according to their foci and analyzed the relationship between spike foci and associated HFA to elucidate the pathophysiology of these syndromes.

Subjects and Methods

Subjects

The subjects of the present study were a total of 64 patients (33 boys, 31 girls) with idiopathic focal epilepsy in childhood who exhibited typical focal spikes in digitally recorded sleep scalp EEGs between January 2004 and December 2013 in Okayama University Hospital. Thirty-five patients were diagnosed with BECTS and 29 patients with PS. The diagnostic criteria of BECTS included mostly nocturnal focal motor and/or generalized seizures with onset ranging from 3 to 13 years of age and centrotemporal spikes with activation during sleep in EEG.[9] One patient who fulfilled the diagnostic criteria of BECTS but who had seizure onset at 2 years and 6 months of age was exceptionally included in the BECTS group. 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.[10] Patients who had intellectual deficit (IQ < 70), neurologic deficit, and/or any lesions in the brain parenchyma in neuroimaging were excluded from the study. Regarding the neuroimaging studies, brain magnetic resonance imaging (MRI) was performed in all patients except for 5 with BECTS, 6 with PS who were examined using computed tomography (CT), and 3 with BECTS who did not undergo neuroimaging studies: the patients with only CT or with no neuroimaging studies did not need MRI because of their typical benign clinical courses with a small number of seizures and absence of neurological abnormalities. For each patient, we selected the first clean scalp sleep EEG data for analysis that was recorded during the period of active seizure occurrence, which was assumed to not extend beyond 6 months after the occurrence of the last seizure.

This study was approved by the Okayama University Ethics Committee.

Methods

EEG was recorded with a sampling rate of 500 Hz using a Nihon-Kohden Neurofax system (Tokyo, Japan), which used a low-cut filter at 0.08 Hz before digital sampling. The international 10- to 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.

First, we detected and collected focal spikes from sleep EEGs automatically using Reveal software (Persyst Development, Prescott, AZ, U.S.A.) to avoid selection bias according to Ochi et al.[11] Reveal can discriminate spikes into several groups according to their morphology and

topography by means of clustering analysis and create a cluster tree based on a dissimilarity level. A cluster tree was created using a hierarchical clustering algorithm that calculates the similarity between pairs of spikes and then iteratively combines those that are most alike. We set the dissimilarity level at 5.0. We visually excluded any spike that was associated with artifacts or other spikes within 500 ms before or after it. In each patient, three or fewer spike clusters, with each cluster including at least 20 spikes, were investigated through a combination of the frequency and single-dipole analyses discussed below. When there were more than three spike clusters, the three with the largest spike numbers were selected. Figure S1 shows the representative data of spike clusters obtained from a patient with BECTS (the same patient as in Fig. 1).

As in our previous study, frequency analysis was performed to detect HFA related to spikes.[4,8] In the present study, HFA was defined in the time-frequency domain in

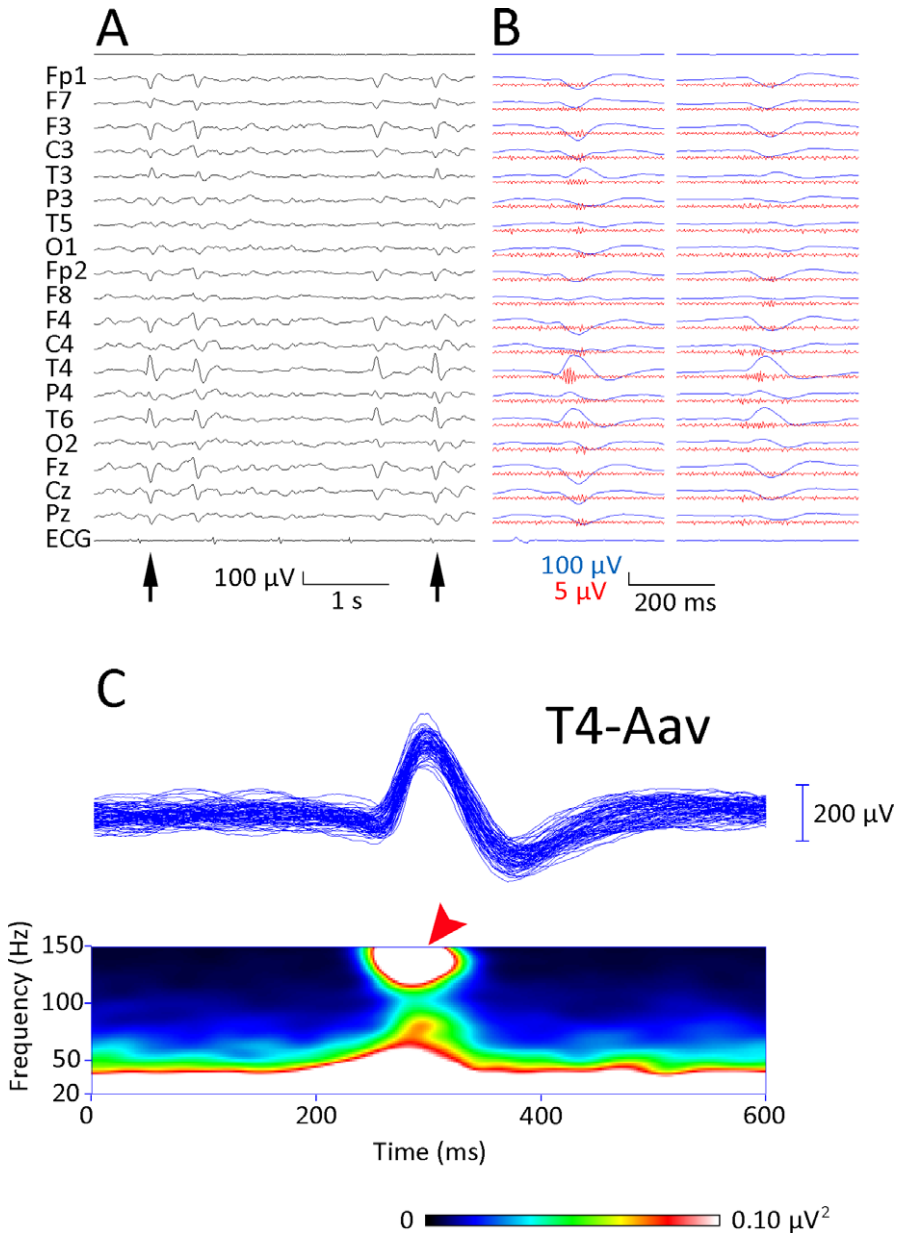

Figure 1.

Representative EEG data recorded from a patient with benign epilepsy with centrotemporal spikes (BECTS). (**A**) A raw EEG trace exhibiting right rolandic spikes. (**B**) Temporally expanded and overlaid EEG traces of representative spikes in (A) (arrows) with two low-cut filters (0.5 Hz in blue and 70 Hz in red) showing ripples in temporal association with the ascending slope of the rolandic spikes. A referential montage is used, employing the average of A1 and A2 (Aav) as a reference. (**C**) The time-frequency spectrum of T4 exhibits a spectral blob with a peak frequency of 136.7 Hz (arrowhead) in temporal association with the spikes in the overlaid EEG traces.

conformity to our previous studies: HFA was 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 at half maximum (FWHM).[12,13] 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 built EEG spectral data from individual data segments and then averaged all spectral data in each channel in each spike cluster. The width of each spectral segment was 600 ms, and the frequency range was 20–150 Hz. The Fourier transform was performed on 256 data points (512 ms; frequency resolution 1.95 Hz) at each time step; the step was 2 ms. High-frequency peaks were identified as clearly visible spectral blobs with frequencies above 80 Hz and peak power of at least 0.01 μV^2. Each of Figs. 1 and S2 shows representative data recorded from patients with BECTS and PS, respectively. In the EEG data with detectable spike-associated HFA, 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.

For comparison, EEG data with spikes were investigated through fivefold temporal expansion of the EEG traces with a low-cut frequency filter (bidirectional Butterworth, −6 dB) at 70 Hz. In the temporally expanded and high-pass-filtered EEG data, the rate of ripple occurrence per spike was also morphologically examined and compared to the spectrally identified HFA. A ripple was defined as an event of at least four consecutive oscillations with a frequency of above 80 Hz.[14]

In dipole analysis, we averaged all spikes in each spike cluster and used a single moving dipole inverse-solution algorithm with a realistic three-dimensional (3D) head model, which was built based on standard MRI data (MNI152 T1 data associated with FSL [http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/]). As in our previous studies employing a realistic head model with estimated electrode locations,[15,16] the head model was composed of triangular meshes of three surfaces: the scalp, skull (the outer surface of the skull), and brain (actually the inner surface of the skull). The conductivity ratio was 1:0.025:1,[17] and brain conductivity was set as 0.33/Ωm.[18] The potential field generated by a dipole source was computed using the boundary element method.[19] We used the same 19 electrodes of the 10–20 system for dipole analysis in spectral analysis, and a mean correction was performed that had the same effect as using an average reference.

In this algorithm of dipole modeling, the residual variance (RV) indicates the proportion of EEG data that cannot be explained by the dipole source model. The dipole fitting was computed for the 5 points separated with 4-ms intervals at the peak of averaged spikes. The dipole with the largest goodness of fit (GOF) (GOF % = 100 − RV %), which should be ≥90%, was selected. The locations of estimated dipoles were determined according to the cortical parcellations of MNI152 T1 data performed with FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). The anatomical localizations of the dipoles were used for the subsequent statistical analysis.

Computation was performed using a program written in-house for MATLAB (version 6.5.1; MathWorks Inc., Natick, MA, U.S.A.).

Statistical analysis

First, the proportion of spike clusters that had associated HFA in at least one channel was compared between BECTS and PS by Fisher's exact test. In spike clusters with HFA, the peak frequency and peak power of the high-frequency spectral blob with the largest power were compared between BECTS and PS using the Mann-Whitney *U* test because of the possibility of their non-Gaussian distributions.

For dipole analysis, the estimated dipoles of spike clusters were divided into one group with associated HFA and another group without associated HFA. The relationship between the anatomical localizations of selected dipoles and the presence or absence of spike-associated HFA was investigated for both BECTS and PS.

Similar analysis was performed with respect to visually identified HFOs. The relationship between the number of clinical seizures and each of these parameters was also investigated.

Statistical analysis, including Fisher's exact test and Mann-Whitney *U* test, was performed using SPSS (Japanese ver. 23; IBM Japan, Ltd., Tokyo, Japan). Relationships were considered statistically significant if $p < 0.05$.

Results

Demographic data of the patients are shown in Table 1. The mean age of seizure onset was 81.2 and 48.4 months in BECTS and PS, respectively. The mean number of seizures was 12.4 and 9.4. The mean age of the time of EEG recording was 100.1 and 53.6 months. The mean time from the most recent seizure to EEG recording was 1.34 and 1.10 months in BECTS and PS, respectively. The age at seizure onset and the time of EEG recording tended to be younger in PS than in BECTS, but the latency from the most recent seizure to EEG recording was similar in both groups. The numbers of patients receiving antiepileptic treatment at the time of EEG recording were 20 (57.1%) and 22 (75.9%) in BECTS and PS, respectively, with no statistically significant difference ($p = 0.19$). A total of 159 spike clusters were analyzed (96 in BECTS and 63 in PS).

Time-frequency analysis

The results for HFA associated with spike clusters are presented in Table 2. HFA was detected in 73 spike clusters

Table 1. Patient demographic data

	BECTS	PS
Patients	35	29
Analyzed spike clusters	96	63
Age at SZ onset in months	81.2 ± 22.9 (30–136)	48.4 ± 15.2 (22–89)
Number of seizures	12.4 ± 14.3 (1–70)	9.4 ± 7.8 (1–30)
Age at the time of EEG recording in months	100.1 ± 23.8 (48–146)	53.6 ± 23.8 (24–128)
Latency from the most recent seizure to EEG recording in months	1.34 ± 1.85 (0–6)	1.10 ± 1.40 (0–5)
Antiepileptic treatment at the time of EEG recording[a]		
Yes	20	22
No	15	7

BECTS, benign epilepsy with centrotemporal spikes; EEG, electroencephalogram; PS, Panayiotopoulos syndrome; SZ, seizure.
[a]p = 0.19 by Fisher's exact test; (), ranges are enclosed in parentheses.

(76.0%) in BECTS and 37 (58.7%) in PS; this proportion was significantly higher in the former than in the latter (p = 0.024). The peak frequencies of the high-frequency spectral blobs in time-frequency spectra ranged from 101.6 to 146.5 Hz (median 128.9 Hz) in BECTS and from 93.8 to 146.5 Hz (median 125.0 Hz) in PS with no statistical difference. The peak-power values of the high-frequency spectral blobs ranged from 0.012 to 0.356 μV^2 (median 0.033 μV^2) in BECTS and from 0.011 to 0.423 μV^2 (median 0.048 μV^2) in PS with no statistical difference.

In PS, we further divided the spike clusters into two groups based on the visually identified spike foci: one group included spikes over the occipital region, which was the main spike focus in PS, and the other group was composed of spikes over the remaining regions. The proportion of spike clusters with associated HFA was 23 of 32 (71.9%) in the group of occipital spikes, and it was significantly higher than the corresponding proportion (14 of 31, 45.2%) in the group of other spikes (p = 0.042). The proportion of spike clusters with associated HFA in occipital spikes in PS was similar to that in BECTS with no statistically significant difference (p = 0.64).

In all spike clusters, the electrode of the greatest high-frequency peak power was the same or was adjacent to that of the visually identified spike focus.

Visually identified HFOs

The number of spike clusters that included one or more spikes with associated morphologically identified ripples was 27 in BECTS (27 of 96) and 13 in PS (5 of 32 in the group of occipital spikes, 8 of 31 in the group of other spikes). In this number of spike clusters, including at least one spike with visually identified HFOs, there was no statistically significant difference between BECTS and PS (p = 0.35) or between occipital spikes and other spikes in PS (p = 0.36; Table S1).

Dipole analysis

Eighty-five and 59 dipoles with GOF ≥90% were estimated in 96 and 63 spike clusters in BECTS and PS, respectively. The dipoles are plotted on the standard brain MRI (Fig. 2 for BECTS; Fig. 3 for PS). The details of the dipole locations are presented in Table 3. We divided the spike clusters into two groups based on the dipole locations. In

Table 2. High-frequency activity detected in associations with spike clusters

	HFA (+)	HFA (−)	p Value
No. of spike clusters			
BECTS	73	23	0.024[a]
PS	37	26	
Occipital[b]	23	9	0.042[a]
Of other foci	14	17	
Peak frequency of HFA (Hz)			
BECTS	Median 128.9 (range: 101.6–146.5; mean 130.0 ± 10.46)	N/A	0.053[c]
PS	Median 125.0 (range: 93.8–146.5; mean 126.2 ± 10.22)	N/A	
Peak power of HFA (μV^2)			
BECTS	Median 0.033 (range: 0.012–0.356; mean 0.070 ± 0.085)	N/A	0.25[c]
PS	Median 0.048 (range: 0.011–0.423; mean 0.091 ± 0.104)	N/A	

BECTS, benign epilepsy with centrotemporal spikes; HFA, high-frequency activity; N/A, not applicable; PS, Panayiotopoulos syndrome.
[a]Fisher's exact test.
[b]p = 0.64 when comparing the number of occipital spike clusters in PS and the number of spike clusters in BECTS by Fisher's exact test.
[c]Mann-Whitney *U* test.

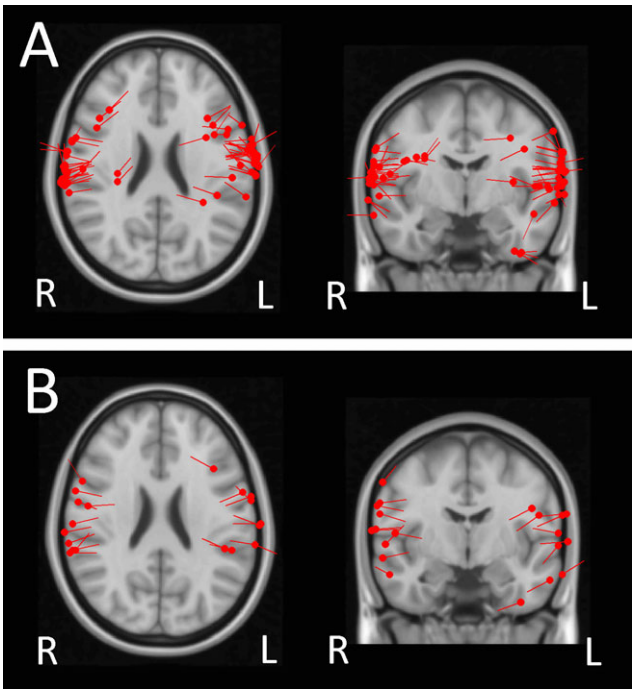

Figure 2.
Dipole locations of the spike clusters in BECTS. (**A**) Spikes with associated high-frequency activity (HFA). (**B**) Spikes without associated HFA. The distributions are similar in both groups.
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BECTS, one group (Group A_{BECTS}) included spikes with dipoles in the perirolandic area (i.e., a combination of the precentral and postcentral gyri) and the other group (Group B_{BECTS}) was composed of spikes with dipoles outside of the perirolandic area. The proportion of spikes with associated HFA was significantly higher in Group A_{BECTS} (42 of 49) than in Group B_{BECTS} in BECTS (23 of 36, $p = 0.037$).

In PS, one group (Group A_{PS}) included spikes with dipoles in the occipital lobes and the other (Group B_{PS}) was composed of spikes with dipoles outside of the occipital lobes. The proportion of spikes with associated HFA was significantly higher in Group A_{PS} (20 of 26) than in Group B_{PS} in PS (13 of 33, $p = 0.020$).

In the morphological examination, the proportion of spikes with visually identified ripples was significantly higher in Group A_{BECTS} (20 of 49) than in Group B_{BECTS} in BECTS (6 of 36, $p = 0.019$). In contrast, there was no statistically significant difference between Group A_{PS} (9 of 26) and Group B_{PS} (4 of 33) for the similar proportion in PS ($p = 0.06$; Table S2).

Relationship between number of seizures and HFA/HFOs

The median number of seizures was 10 (range 1–70) in BECTS and 7 (range 1–30) in PS. In patients who had many seizures with uncertain exact numbers, we indicated the approximate number of seizures. For patients whose seizures were still active as of March 31, 2016, we indicated the number of seizures until this date (Table 1).

Patients who had at least one spike cluster with associated HFA were defined as having HFA. There were 30 patients with HFA and 5 without HFA in BECTS. The median number of seizures was 10 (range 1–70) in patients with HFA and 3 (range 1–5) in those without HFA. There was a statistically significant difference between these two groups ($p = 0.048$) in BECTS. In contrast, there were 20 patients with HFA and 9 without HFA in PS. The median number of seizures was 4.5 (range 1–30) in patients with HFA and 10 (range 2–30) in those without HFA. There was no statistically significant difference between the two groups ($p = 0.27$) in PS.

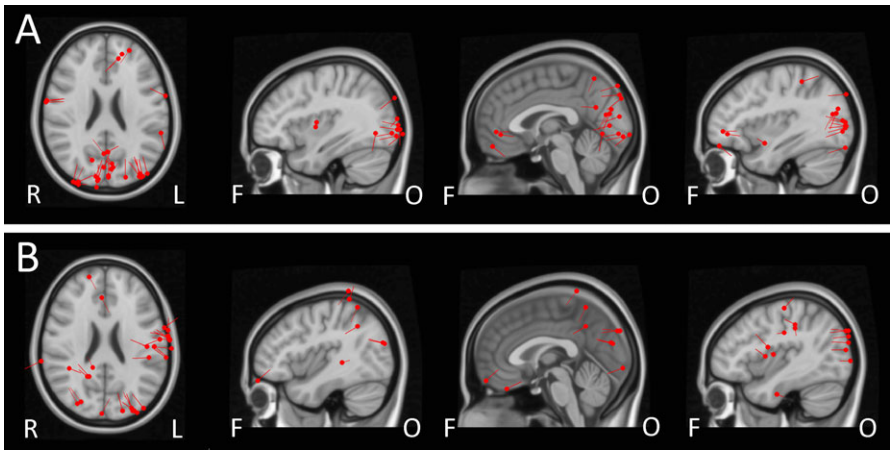

Figure 3.
Dipole locations of the spike clusters in Panayiotopoulos syndrome (PS). (**A**) Spikes with associated HFA. (**B**) Spikes without associated HFA. Spikes with HFA tend to be distributed in the occipital lobes and, in contrast, spikes without HFA in the other lobes.
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Table 3. Relationship between spike-associated HFA and dipole locations

	HFA (+)	HFA (−)	p Value
BECTS (n = 85)			
Perirolandic area[a]	42	7	0.037[b]
Other locations[c]	23	13	
PS (n = 59)			
Occipital lobes	20	6	0.020[b]
Other locations	13	20	
Perirolandic area[a]	3	7	
Frontal lobes	3	2	
Temporal lobes	1	6	
Parietal lobes	6	5	

BECTS, benign epilepsy with centrotemporal spikes; PS, Panayiotopoulos syndrome.
[a]Including the precentral and postcentral gyri.
[b]Fisher's exact test.
[c]Mostly including the temporal lobe and the supramarginal gyrus.

Similar comparisons were performed regarding visually detected spike-associated HFOs. There were 13 patients with HFOs and 22 without HFOs in BECTS. The median number of seizures was 10 (range 1–30) in patients with HFOs and 9 (range 1–70) in those without HFOs. There was no statistically significant difference between the two groups ($p = 0.72$) in BECTS. In contrast, there were 6 patients with HFOs and 23 without HFOs in PS. The median number of seizures was 14.5 (range 3–30) in patients with HFOs and 5 (range 5–30) in those without HFO. There was a statistically significant difference between the two groups ($p = 0.047$) in PS (Table S3).

Discussion

In the present study, HFA/HFOs were detected from scalp-recorded spikes in both BECTS and PS with a reconfirmation of the previous observation that spikes in idiopathic focal epilepsy of childhood are accompanied by HFOs. In addition, we explored the differences between spikes with and without HFA/HFOs, because we could not fully elucidate these differences in our previous study.[8]

The proportion of spikes with associated HFA was higher in BECTS than in PS. In BECTS, it is known that dipoles of rolandic spikes generally cluster in the rolandic area and have relatively uniform distributions with stable sources.[20] In the present study, we found that rolandic spikes in BECTS do not constitute a uniform group and that the spikes emanating from the perirolandic area are more often accompanied by HFA with greater pathophysiological meaning in terms of a possible relation to epileptic activity than the spikes from the surrounding cortex.

In PS, the proportion of spike clusters with associated HFA was lower in total than in BECTS, though this was not the case when the investigation was limited to the occipital spikes in PS. In dipole analysis, the dipoles located in the occipital lobes had a higher rate of association with HFA and may thus have greater pathophysiological meaning than those in the extraoccipital area.

PS was originally reported as a type of benign childhood epilepsy with occipital paroxysms.[21] It was later clarified that the foci are multiple in both ictal and interictal recordings.[22] It was suggested that there is no actual focus in a certain region and that spikes only indicate extensive cortical excitability.[23] In addition, the ictal semiology of PS does not include visual symptoms, which are common among occipital lobe epilepsies, but mainly include autonomic symptoms such as nausea and vomiting. For all of these reasons, there is some doubt as to whether PS should be included in the group of occipital lobe epilepsies.

We found that the proportion of spikes with associated HFA was significantly different between the occipital lobes and the other regions in PS. Given the relationship between HFA and epileptic activity, spikes generated in the occipital lobes may indicate greater epileptic activity than other spikes in this disorder. However, this is not a denial of multifocality in PS. HFA/HFOs were also detected from outside the occipital lobes, and therefore we think that the present results indicated the gradient of intensity of epileptic activity in PS. In other words, even when spikes are multifocal, the occipital lobes may play a crucial role in PS. As for why PS is characterized by autonomic seizures even though they originate from the occipital lobes, it is speculated that autonomic symptoms, including vomiting, may be attributed to the involvement of the limbic and insular regions, to which occipital seizures originating below the calcarine fissure may spread.[22] High sensitivity of the autonomic center unique to young children may be related to these symptoms.

The brain regions that epileptic discharges are prone to involve change according to age, especially in idiopathic epilepsies.[24–27] Occipital foci are most common in preschool-aged patients, and centrotemporal foci predominate in school-aged patients. Therefore, it is possible to speculate that patients with PS may show occipital spikes in early childhood, when they are likely to have seizures, and that the epileptogenicity might decline by the time the spike foci move to other regions. In the present study, however, the ages were similar between the 17 PS patients with spike dipoles in the occipital lobes (mean age: 69 ± 21.7 months) and the 16 patients with spike dipoles in other areas (mean age: 64.5 ± 27.2 months) (including 4 overlapping patients). This finding indicates that the present result was not caused by age differences.

It is known that the primary sensory area and the occipital cortex generate physiological HFOs.[28,29] Therefore, it is possible that epileptic HFA/HFOs are prone to be detected from these regions as in the case of physiological ones. However, in the present results regarding spikes with dipoles in the perirolandic area, 42 out of 49 spike clusters had associated HFA in BECTS, but only 3 of 10 spike clusters had associated HFA in PS ($p = 0.0008$, by Fisher's exact test). This finding conflicted with the possibility that

every spike originating from a physiological HFO-rich area is evenly loaded with epileptic HFA. As van Klink et al. mentioned, "Physiologic ripples have not (yet) been found in scalp recordings." Epileptic and physiological HFA/HFOs may differ on the scalp, and the generation of epileptic HFA/HFOs associated with scalp spikes might not be directly linked to the generation of physiological HFOs.

As conclusions of the present study, the origins of spikes in the perirolandic area were probably closely related to epileptic activity with the generation of spike-associated HFA in BECTS. In contrast, in PS, even when the spikes were multifocal, the greatest epileptic activity was related to spikes originating from the occipital lobes with the generation of HFA.

The relationship between HFA/HFOs and number of seizures is another important issue. In the present study in BECTS, patients with HFA had more seizures than those without HFA, but there was no relationship between the presence or absence of visually detected HFOs and the number of seizures. In PS, on the other hand, there was no relationship between the presence or absence of HFA and the number of seizures, but patients with visually detected HFOs had more seizures than those without visually detected HFOs. van Klink et al.[6] reported that the number of visually detected ripples showed a significantly positive correlation with the number of seizures in children with rolandic spikes. In our study, visually detected HFOs did not have a consistent relation with the number of seizures. van Klink et al. categorized patients into three groups (i.e., [1] patients with rolandic spikes but no epilepsy, [2] those with typical rolandic epilepsy, and [3] those with atypical and symptomatic rolandic epilepsy) and investigated among these three groups, whereas we investigated only typical BECTS. This difference might have caused different results. Visually detected HFOs are indicated as useful for detecting atypical cases or patients who have more seizures. In this study, because the number of patients was not very large, it is difficult to make a conclusion regarding the relationship between HFA/HFOs and number of seizures in typical BECTS or PS.

The present study is limited because the estimated dipole locations might differ from the actual source locations because we used a standard brain image for the head model in place of the real brain of each patient for dipole analysis. In addition, the study subjects may be biased to include children with relatively complex epilepsy with frequent and/or uncontrollable seizures because all participants visited Okayama University Hospital, a tertiary epilepsy center.

In the future, based on the present conclusion that indicates the occipital lobes have relatively high epileptic activity in PS, we hope to elucidate the functional mechanisms of the occipital lobes that cause autonomic seizures. The reason why the foci differ between BECTS and PS should also be addressed. In addition, because we only investigated the EEGs recorded during the active phase of seizure occurrence in each patient, further study of the prognostic implications of HFA/HFOs associated with spikes in idiopathic focal epilepsy is needed.

The results of this study help elucidate the pathophysiology of idiopathic focal epilepsy of childhood.

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Disclosure

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

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Supporting Information

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

Figure S1. Spike detection and clustering analysis in BECTS.

Figure S2. Representative EEG data recorded from a patient with Panayiotopoulos syndrome (PS).

Table S1. HFOs visually detected in association with spike clusters.

Table S2. Relationship between visually detected spike-associated HFOs and dipole locations.

Table S3. Relationship between number of seizures and spike-associated HFA/HFOs.