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Enhancement and bilateral synchronization of ripples in atypical benign epilepsy of childhood with centrotemporal spikes

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HIGHLIGHTS

- Interictal epileptiform discharges (IED) with ripple co-occurrence were assessed in ABECTS.
- Ripple co-occurrence rates and peak power were higher in the secondary bilateral synchrony period.
- Bilaterally synchronized ripples may be helpful in distinguishing ABECTS from BECTS.

ABSTRACT

Objective: To determine whether the characteristics of scalp-recorded high frequency oscillations, especially ripples, can predict the "atypical forms" of benign epilepsy of childhood with centrotemporal spikes (ABECTS), in BECTS.
Methods: Seven patients with ABECTS and eighteen patients with BECTS underwent electroencephalography (EEG) in the secondary bilateral synchrony (SBS) and non-SBS periods for ABECTS patients. SBS period is that when more than 50% of the interictal epileptiform discharges (IEDs) are bilaterally synchronized. We determined the IED-ripple co-occurrence rate, performed time frequency analysis, and calculated the asymmetry index (AI).
Results: The IEDs-ripple co-occurrence rate increased in the SBS compared to the non-SBS period. Time frequency analysis showed higher high-frequency activity rate and peak power in the SBS than in the non-SBS period. The AI was lower in ABECTS than BECTS, both in the non-SBS and SBS periods.
Conclusions: Ripples were enhanced in the SBS period of ABECTS, and bilaterally synchronized both in the non-SBS and SBS periods, whereas ripples in BECTS were localized unilaterally.
Significance: Bilaterally synchronized ripples in the non-SBS period of ABECTS may distinguish ABECTS from BECTS in the non-SBS period of IEDs, and may be helpful for early detection of progressive neurophysiological regression leading to early intervention.

1. Introduction

Benign epilepsy in childhood with centrotemporal spikes (BECTS), or Rolandic epilepsy is the most common childhood epilepsy syndrome, and it is often described clinically as "benign" drug-sensitive epilepsy (Fejerman, 2008). The seizures occur during sleep in most children. Atypical clinical presentations of BECTS have been reported in some patients (Fejerman, 2009). One such presentation includes frequent drug-resistant seizures (Datta and Sinclair, 2007) that could result in permanent learning and behavioral disabilities (Hahn et al., 2001; Uliel-Sibony and

Abbreviations: ABECTS, atypical benign epilepsy of childhood with centrotemporal spikes; AED, antiepileptic drug; BECTS, benign epilepsy of childhood with centrotemporal spikes; EEG, electroencephalogram; ESES/CSWS, electrical status epilepticus during sleep/continuous spike-and-waves during slow sleep; HFA, high frequency activity; HFO, high-frequency oscillation; IED, interictal epileptiform discharge; MRI, magnetic resonance imaging; NREM, non-rapid eye movement; SBS, the secondary bilateral synchrony.

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Kramer, 2015); this presentation is termed "atypical forms" of BECTS (ABECTS, atypical Rolandic epilepsy; Fejerman 2009). Electroencephalogram (EEG) of ABECTS may reveal bilateral synchronous interictal epileptiform discharges (IEDs) or electrical status epilepticus during sleep/continuous spike-and-waves during slow sleep (ESES/CSWS; Tovia et al., 2011). According to the 2017 International League Against Epilepsy (ILAE) classification of the epilepsies (Scheffer et al., 2017), developmental and/or epileptic encephalopathy is defined as epileptic activity that contributes to severe cognitive and behavioral impairment above and beyond what is expected from the underlying pathology, and which can worsen over time. According to this definition, ABECTS could be considered as a form of epileptic encephalopathy.

It remains unknown whether the origin of ESES/CSWS is focal or generalized. Analysis of time differences of bilateral synchronous spike-wave bursts indicates that secondary bilateral synchrony (SBS), defined as "bilateral synchronous discharges arising from a unilateral cortical focus (Tukel and Jasper, 1952)," is one mechanism underlying ESES/CSWS pathophysiology (Kobayashi et al., 1994). ABECTS and epileptic encephalopathy with CSWS are considered as a spectrum of the epilepsy syndromes, because they are age dependent epileptic encephalopathy characterized by sleep induced continuous IEDs.

However, early discrimination, i.e. before the SBS period, of ABECTS from BECTS, is not always easy, and the distinction between these conditions is ambiguous despite the importance for future prognosis.

High-frequency oscillations (HFOs) were first detected in invasive intracranial EEGs as a biomarker for the identification of the epileptogenicity zone (Jacobs et al., 2009; Le Van Quyen et al., 2006; Ochi et al., 2007). HFOs are usually divided into two categories; ripples (80–200/250 Hz) and fast ripples (200/250–500 Hz). Additionally, physiological HFOs play an important role in higher brain functions such as sensory perception, memory, language, and cognitive functions (Herrmann and Demiralp, 2005). The differences between pathological and physiological HFOs remain unclear. In the last decade, HFOs have been detected in noninvasive scalp EEGs in several kinds of epilepsy syndromes such as Rolandic epilepsy (van Klink et al., 2016), Panayiotopoulos syndrome, (Shibata et al., 2016), epilepsy with ESES/CSWS (Kobayashi et al., 2010), and West syndrome (Kobayashi et al., 2015). With the progress in analytical methods, the time frequency analysis has made the quantitative evaluation of high frequency activities (HFA) possible. Therefore, we hypothesized that HFOs in ABECTS could serve as key findings for elucidating the pathophysiology of ABECTS and neuropsychological regression.

In this study, we investigated the characteristics of ripples in ABECTS, and BECTS patients, by focusing on the differences between SBS and non-SBS recordings using scalp-recorded EEG. In addition, we analyzed the differences in the power and distribution of ripples between the two epileptic syndromes.

2. Methods

2.1. Patients

A total of 25 patients (20 boys, 5 girls) were included in this study, and the characteristics of 7 patients with ABECTS are shown in Table 1. Scalp EEGs were recorded between January 2009 and May 2017 at the Saitama Children's Medical Center. Seven patients diagnosed with ABECTS and eighteen patients diagnosed with BECTS were enrolled, respectively. In this study, the presence of an SBS pattern was determined by two pediatric epileptologists blinded to the identity of the patients, as described in a previous study (Blume and Pillay, 1985). The diagnostic criteria for BECTS were as follows: mostly nocturnal focal motor and/or generalized seizures with age at onset ranging from 3 to 13 years and centrotemporal spikes with activation during sleep detected in EEG recordings (Commission on Classification and Terminology of the International League Against Epilepsy, 1989) without abnormalities on brain magnetic resonance imaging (MRI). ABECTS was defined as patients with focal seizures, no abnormalities on brain MRI, EEG abnormalities located in or near the Rolandic areas, and an atypical clinical course or atypical EEG pattern including the SBS pattern of IEDs (Fejerman, 2009).

We reviewed clinical records retrospectively and extracted the following data: age at onset of epilepsy, age at onset of SBS pattern in EEG, seizure types, seizure frequencies in the non-SBS and SBS periods, antiepileptic drugs (AEDs), comorbidities, and the presence or absence of intellectual disability. Informed consent was obtained from the parents or guardians of each patient. This study was approved by the Saitama Children's Medical Center Institutional Review Board.

2.2. EEG recording methods

Scalp EEG was recorded using a Nihon-Kohden Neurofax system with a sampling frequency of 500 Hz (Tokyo, Japan). Electrodes were placed according to the international 10–20 electrode system. Conventional 10-mm Ag-AgCl electrodes were used. Digital data were sampled through a low-cut 0.016-Hz filter.

2.3. EEG analysis

We analyzed the EEG data using an average montage. The EEG recordings analyzed in the present study were recorded during 10 min of non-rapid eye movement (NREM) (stages 2 or 3) sleep. We enrolled the last record before the onset of SBS as the non-SBS period, and the first SBS period record as SBS. IEDs were visually counted in EEG recordings with 10 s/page, 10–15 μV/mm, low frequency (LF) of 0.53 Hz, and high frequency (HF) of 120 Hz. IEDs were defined as paroxysmal discharges with sharp components that were clearly distinguishable from background activity.

Table 1
Clinical profiles of patients with ABECTS.

Patient no./sex	Age at epilepsy onset	Age at SBS onset	Seizure type	Seizure frequency		Treatment at EEG	Comorbidity	Intellectual disability
				Non-SBS period	SBS period			
1/M	6y 7 m	9y 11 m	FIAS	1/2–3 months	1/2–3 months	VPA	Autistic behaviors	Mild
2/M	2y 4 m	7y 1 m	FBTCS, FIAS	1/month	1/month	CBZ, CLB	Autistic behaviors	Mild
3/M	5y 7 m	7y 5 m	FBTCS, FIAS	1/2–3 months	1/month	VPA, ESM	Autistic behaviors	No
4/M	6y 11 m	7y 7 m	FBTCS	1/month	2/month	LEV	Dysarthria	No
5/F	3y 3 m	5y 3 m	FIAS	1/month	1/month	CBZ	Dysarthria	No
6/M	7y 10 m	9y 1 m	FBTCS	1/3–4 months	1/3–4 months	LEV		No
7/F	8y 11 m	10y 1 m	FBTCS	1/month	1/month	LEV		No

ABECTS, atypical benign epilepsy of childhood with centrotemporal spikes; AED, antiepileptic drug; CBZ, carbamazepine; CLB, clobazam, EEG, electroencephalogram; ESM, ethosuximide; FBTCS, focal to bilateral tonic-clonic seizure; FIAS, focal impaired awareness seizure; LEV, levetiracetam; m, month; SBS, secondary bilateral synchrony; VPA, valproic acid; y, year.

Ripples related to IEDs were counted in the 100 ms (ms) signal before and after each IED. Ripples were defined as at least four oscillations that were clearly distinguishable from the background (Andrade-Valenca et al., 2011). We assessed oscillations under the following conditions; sensitivity 5 μV/mm, paper speed 1 s/page, LF: 53 Hz (Fig. 1A, B). We then calculated the number of IED–ripple co-occurrences and the IED–ripple co-occurrence rate in the EEG recordings from 10 min of NREM (stages 2 or 3) sleep. The IED–ripple co-occurrence rate was calculated using the following formula;

$$\text{IED} - \text{rippleco} - \text{occurrencerate}\ (\%) = \frac{\text{number of IEDs with ripples}}{\text{total number of IEDs}} \times 100$$

2.4. Time frequency analysis

Time frequency analysis was performed using a Nihon-Kohden Neurofax system (Nihon Kohden Corporation, Tokyo, Japan). Wavelet analysis was performed with the following settings; minimum analyzed frequency 10.0 Hz, sampling time interval 2 ms, and sampling frequency interval 20 Hz. The spectrum of each channel was visually inspected (Fig. 1C). HFA was defined as distinct spectral blobs >80 Hz in the 50 ms before or after spike peaks, as described previously (Shibata et al., 2016). Time frequency analysis was performed for each of the following channels: Fp1, Fp2, F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, and T6. The frequency range was 20–200 Hz. The analysis was performed for 30 IEDs in NREM sleep EEG recordings, and the peak frequency (Hz) and peak power (μV^2) were calculated if distinct spectral blobs were discovered. We then calculated the HFA rate with the following formula.

$$\text{HFArate}\ (\%) = \frac{\text{number of IEDs with HFA}}{\text{total number of IEDs}} \times 100$$

To assess the bilateral synchronization of HFA, we used the asymmetry index (AI). We performed time frequency analysis of 30 IEDs in all channels for all patients in the non-SBS and SBS periods. IEDs with HFA in electrodes from each hemisphere were counted and the ratio of the numbers of IEDs with HFA on each electrode corresponding to contralateral hemisphere was calculated as the AI. The AI of HFA was calculated with the following formula.

$$\text{Asymmetry index (AI) of HFA} = \frac{|L - R|}{(L + R)/2}$$

L: number of IEDs with HFA of electrodes in left hemisphere (Fp1, F3, C3, P3, O1, F7, T3, and T5), R: number of IEDs with HFA of electrodes in right hemisphere (Fp2, F4, C4, P4, O2, F8, and T4).

2.5. Statistical analysis

Data were analyzed using SPSS (SPSS Inc., Chicago, IL, USA) software for statistical analysis. Continuous variables were compared using the Mann–Whitney *U* test and categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Differences were defined as significant at a probability level of $p < 0.05$.

3. Results

3.1. Clinical profiles

Clinical data of all subjects are shown in Table 1. The median age at onset of epilepsy in ABECTS and BECTS patients was 6 years, 7 months (range 2 years, 4 months–8 years, 11 months) and 7 years, 6 months (range 3 years, 1 months–9 years, 11 months), respectively. The median age at onset of SBS in patients with ABECTS was 7 years, 7 months (range 5 years, 3 months–10 years, 1 month). As for comorbidities in ABECTS patients, behavior abnormalities (autistic behaviors) were present in 3 patients, and dysarthria in 2 patients and intellectual disability were present in 2 patients. However, there were no comorbidities in patients with BECTS. All patients with ABECTS showed SBS patterns in EEG

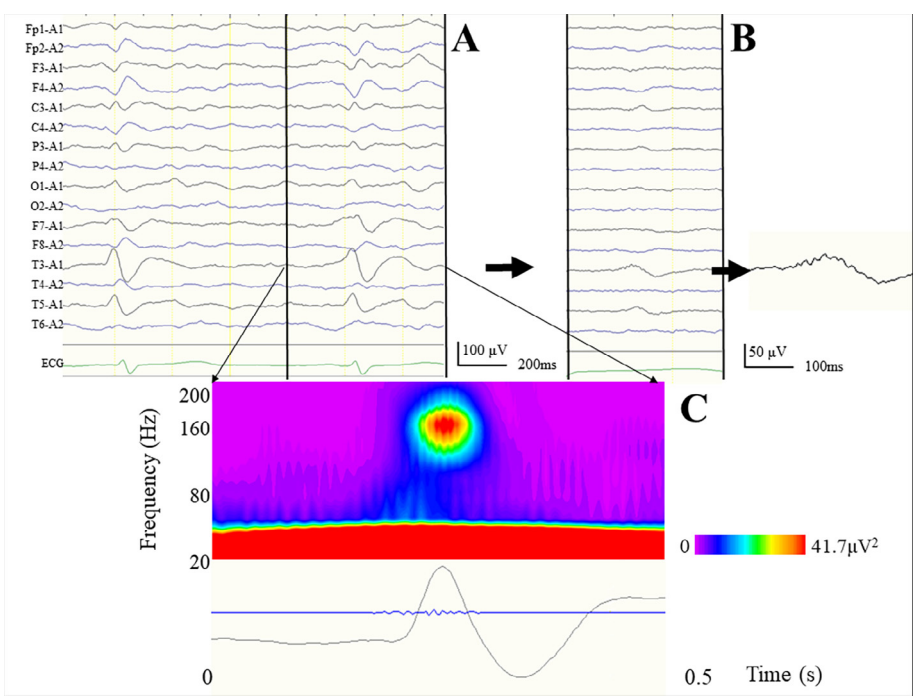

Fig. 1. Representative EEG trace and result of time frequency analysis in a patient with BECTS. (A) EEG setting; paper speed 2 s/page, 10 μV/mm, low frequency (LF) of 0.53 Hz, and high frequency (HF) of 120 Hz. (B) EEG setting; paper speed 1 s/page, 5 μV/mm, LF of 53 Hz HF of 120 Hz. (C) The time frequency analysis showed a spectral blob above 80 Hz.

recordings during the clinical course. Most of the patients with ABECTS presented seizures in same frequency between the non-SBS and SBS period (Table 1). The first AED was ineffective in all patients with ABECTS (7/7), whereas seizures resolved in all patients with BECTS (18/18) with either the first AED treatment or without any AED.

3.2. Visually identified IEDs and IEDs with ripple co-occurrence

The average number of IEDs, and IEDs with ripple co-occurrences are shown in Table 2. The IED-ripple co-occurrences rate (number of IEDs with ripples/total number of IEDs (%)) was higher in the SBS period (40.7%) than in the non-SBS period (10.2%, $p < 0.01$), and was not significantly different in the non-SBS period, and in patients with BECTS (12.7%, p 0.97). There was no significant difference in the total number of IEDs in the non-SBS periods in patients with ABECTS and BECTS ($p = 0.66$).

3.3. HFA in time frequency analysis

The results of the time frequency analysis are shown in Table 3. The HFA rate, peak frequency, and peak power were calculated in patients with ABECTS and BECTS during the non-SBS and SBS periods. The HFA rate (number of IEDs with HFA/total number of IEDs) was higher in the SBS period (58.6%) than in the non-SBS period (21.9%, $p < 0.01$). However, the HFA rate in the non-SBS period in ABECTS patients and patients with BECTS (41.3%) were not significantly different ($p = 0.10$). There was no difference in peak frequency of spectral blobs between the non-SBS and SBS periods in patients with ABECTS ($p = 0.14$). The peak power of spectral blobs was higher in the SBS period than in the non-SBS period in patients with ABECTS (15.6 μV^2 vs 5.8 μV^2, respectively, $p < 0.001$), and there were no differences in the non-SBS period of patients with ABECTS and BECTS ($p = 0.19$).

3.4. Asymmetry index (AI) of HFA

The results for the AI of HFA are shown in Fig. 2. There was no significant difference in the AI between the non-SBS and SBS periods in patients with ABECTS ($p = 0.79$). The AI was significantly lower in the non-SBS and SBS periods of patients with ABECTS compared to patients with BECTS ($p < 0.01$). This indicates that HFA was displayed in both hemispheres bilaterally not only in the SBS period, but also in the non-SBS in patients with ABECTS, while HFA appeared commonly only unilaterally in patients with BECTS.

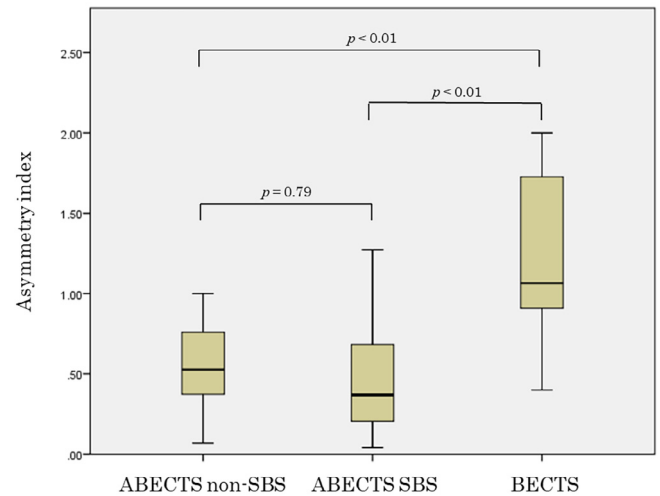

Fig. 2. Asymmetry index (AI) in the secondary bilateral synchrony (SBS) and non-SBS periods of patients with ABECTS, and patients with BECTS.

4. Discussion

This is the first study that effected a comparison between the characteristics of scalp recorded ripple between the early stage (before SBS period) and SBS period in the "atypical form" of BECTS patients and BECTS patients. In this study, we found that ripples were enhanced when IEDs were bilaterally synchronized in patients with ABECTS. We compared ripples between the non-SBS and SBS periods and found that the ripple power and the

Table 2
Visually identified IEDs and IEDs with ripple co-occurrence.

	ABECTS		p-value	BECTS	p-value vs. non-SBS
	non-SBS period	SBS period			
Total number of IEDs	346 (391.6 ± 186.0)	706 (741.6 ± 217.9)	0.01[a]	306 (355.0 ± 196.5)	0.66[a]
Number of IEDs ripple co-occurrence	9 (39.9 ± 45.5)	356 (301.9 ± 149.9)	0.002[a]	21 (44.9 ± 66.4)	0.97[a]
IED-ripple co-occurrence rate (%)	10.2	40.7	<0.01[b]	12.7	0.70[b]

Median (mean ± standard deviation).
ABECTS, atypical benign epilepsy of childhood with centrotemporal spikes; BECTS, benign epilepsy of childhood with centrotemporal spikes, IEDs, interictal epileptiform discharges; SBS, secondary bilateral synchrony.
[a] Mann–Whitney U test.
[b] Fisher's exact test.

Table 3
HFA in the time frequency analysis.

	ABECTS		p-value	BECTS	p-value vs. non-SBS
	non-SBS period	SBS period			
HFA rate (%)	21.9	58.6	<0.01[a]	35.6	0.10[a]
Peak frequency (Hz)	142.1 (140.8 ± 22.3)	138.0 (133.6 ± 18.9)	0.14[b]	140.3 (141.6 ± 16.5)	0.17[b]
Peak power (μV^2)	5.8 (5.4 ± 3.2)	15.6 (21.1 ± 13.8)	< 0.001[b]	5.6 (7.1 ± 4.4)	0.19[b]

Median (mean ± standard deviation).
ABECTS, atypical benign epilepsy of childhood with centrotemporal spikes; BECTS, benign epilepsy of childhood with centrotemporal spikes, SBS, secondary bilateral synchrony.
[a] Fisher's exact test.
[b] Mann–Whitney U test.

IED-ripple co-occurrence rate increased in the SBS period. We also found that the ripple power during the non-SBS period was similar in patients with ABECTS and BECTS. Thus, we were not able to distinguish ABECTS from BECTS in the non-SBS period on the basis of ripple power alone. This result is consistent with the clinical course of ABECTS, in which neurophysiological regression occurs mainly after initiation of SBS in the ESES/CSWS pattern.

We surveyed the co-occurrence of HFA in bilateral hemispheres using the AI. We found that ripple synchronization to the contralateral hemisphere preceding IEDs were bilaterally synchronized in ABECTS. Pizzo et al. reported that ripples were not bilateral when IEDs were synchronized bilaterally in generalized and focal epilepsy patients (Pizzo et al., 2016). They suggested that ripples might indicate the origin of the epileptic focus even when IEDs are bilateral. We speculated that the discrepancy between the previous report and our results of ripple propagation were possibly due to variation in the epilepsy syndromes. Bilateral ripple propagation in the non-SBS period of IEDs may be a specific finding in ABECTS, and may be associated with cognitive deterioration.

The co-occurrence of HFA to both hemispheres preceding the IEDs were bilaterally synchronized in ABECTS, whereas HFA in BECTS was localized to only one hemisphere. ABECTS is thought to be a form of epileptic encephalopathy wherein IEDs themselves can cause neurophysiological regression and behavioral disorders (Scheffer et al., 2017). Considering a possible relationship between neurophysiological regression in ABECTS and ripple power enhancement, early detection of the co-occurrence of HFA to both hemispheres preceding the synchronization of IEDs might be essential for preventing neurophysiological regression before ripple power enhancement.

Although the mechanism underlying the bilateral synchrony of ripples preceding IEDs in ABECTS has been unclear, the thalamus and GABAergic system may play a critical role. A previous functional-MRI study revealed that BOLD changes in the thalamus in epileptic encephalopathy with CSWS indicated changes in the activity in the cortico-thalamic network (Fahoum et al., 2014). Other reports have shown that neonatal thalamic hemorrhage (Kersbergen et al., 2013) and polymycrogyria with thalamic hypoplasia (Bartolini et al., 2016) were related to the pathogenesis of CSWS. The mechanism underlying secondary bilateral synchronous IEDs is thought to involve the thalamus (Kanemura et al., 2012) and/or corpus callosum (Spencer et al., 1985). Additionally, the thalamus has an important role in the generation of physiologic sleep oscillations and propagation of spike and wave discharges (Meeren et al., 2002). Carbamazepine (CBZ) acted at the thalamus to aggravate absence seizures through activation of the $GABA_A$ receptor in absence model rats (Liu et al., 2006). Generation of pathologic HFOs was under the control of the $GABA_A$ receptor antagonist (Bragin et al., 2002). These reports suggest that the cortico-thalamic network and GABAergic system may involve generation and bilateral synchrony of IEDs and ripples in ABECTS and BECTS.

Epilepsy and migraine are both recurrent neurological disorders. EEG signals of patients with both these disorders exhibit ripples (Wu et al., 2016). The difference is that the EEG signals occur in the beta bands for migraine patients, but in the low frequency bands for epilepsy patients (Akben et al., 2011). The subjects of this study were diagnosed with an absence migraine. In addition, we surveyed ripple bands in this study. Thus, the ripples in this study were not related to migraine.

Finally, our results should be interpreted with caution. Melani et al. (2013) reported that a higher spiking rate increased the rate of ripple occurrence. This indicates that the high IED prevalence possibly reflected the high number of IEDs with ripple co-occurrence and high HFA rate. We therefore surveyed HFA power as another parameter. The co-occurrence of HFA to both hemispheres preceding the propagation of IEDs, which were bilaterally synchronized in ABECTS, whereas HFA in BECTS was localized to only one hemisphere. These findings indicate that distinctive ripple/HFA patterns may be present in ABECTS, and this could be a way to distinguish ABECTS from BECTS. Because of the relatively small number of patients in the present study, and as the characteristics of the patients were not controlled, for example duration of epilepsy, the number of antiepileptic drugs administered, and the timing of EEG recordings were varied. These factors may have influenced the results. Further studies are necessary for clarifying the significance of enhancement and bilaterally synchronized ripple/HFA in ABECTS.

In conclusion, distinguishing ABECTS from BECTS with ripple distribution in the non-SBS period may be helpful for early detection of progressive neurophysiological regression, and may lead to early intervention. Moreover, in future, ripple power and distribution can also be used as a marker for treatment response. However, further studies are required to determine this.

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Declarations of Interest

None.

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