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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.