Delayed cortical maturation at the centrotemporal brain regions in patients with benign childhood epilepsy with centrotemporal spikes (BCECTS)

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ABSTRACT

Benign childhood epilepsy with centrotemporal spikes (BCECTS) is an epilepsy syndrome commonly found in child and adolescent. Although the prognosis is mostly favorable as long as the seizure is well controlled. However, they are often suffering from the cognitive and behavioral problems which might be the consequences of the initial insults. It is still not clear whether the initial epileptiform discharges has long term impact on the resting-state brain activities at later ages. This study investigated the resting-state brain activities in BCECTS patients with clinical seizure remission stage (n = 16; 11 males) and compared with the non-epileptic, age-matched control subjects.

Quantitative electroencephalography (qEEG) revealed a significantly higher absolute power of the theta and alpha waves in BCECTS patients with clinical seizure remission as compared with the non-epileptic control subjects. Interestingly, the differences were observed mainly over the centrotemporal electrodes which are the common sites of the initial epileptiform discharges. The differences were more significant in patients with bilateral epileptiform discharges than those with the unilateral epileptic activities. Typically, the brain wave power continuously decreases with increasing ages. Therefore, higher absolute powers of the brain waves indicate more delayed in cortical maturation compared with the non-epileptic control group. These findings indicated that BCECTS patients have delay cortical maturation at the centrotemporal brain regions even at the clinical seizure remission phase.

1. Introduction

Benign childhood epilepsy with centrotemporal spikes (BCECTS) or benign rolandic epilepsy (BRE) is the most common localization-related (focal) epilepsy in children. Usually, it can be founded in the typically-developed children with a routine neurological examination. There are growing pieces of evidence reported that the BCECTS might not benign. Even though there is no specific anatomical lesion when observing with neuroimaging techniques, however, a minimal and non-specific brain dysfunction has been reported in the BCECTS patients (Boxerman et al., 2007). Several lines of evidence revealed that BCECTS patients exhibit various neuropsychological dysfunctions, mainly affecting non-verbal cognition and executive function (Filippini et al., 2016; Fonseca et al., 2007; Pinton et al., 2006).

Electroencephalography (EEG) is commonly used in the clinical practice to classify a specific epileptic syndrome by observed the presence of epileptiform discharges, a hallmark for diagnosis of epilepsy.

Typically, EEG characteristic of the BCECTS patients is the centrotemporal spikes or Rolandic spikes (usually located at the C3, C4, T3, and T4 electrodes). Different characteristics of the centrotemporal spikes are associated with poor cognitive functions, e.g., sites (Metz-Lutz et al., 1999), frequency (Ebus et al., 2012; Metz-Lutz et al., 1999), distribution (Metz-Lutz et al., 1999), and the absence of dipole (Vinayan et al., 2005), etc.

Beside the epileptic discharge, the background EEG activity is another parameter for determining the patient's brain functions. For example, in patients with symptomatic epilepsy, the abnormal EEG background activities (e.g., the presence of slow activities or a burst suppression pattern) indicate an impairment of neural processing that might associate with the cognitive problems and developmental delay. The background EEG signal can be further investigated by the quantitative EEG (qEEG) analysis. The qEEG is a procedure that processes the EEG data from the time domain to the frequency domain by a Fast Fourier Transform (FFT). The FFT provides numerical information

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presenting as the absolute power and the relative power (power ratio) of the brain waves. Using the qEEG analysis, the abnormalities of background EEG activity have been reported in various neurological and psychiatric disorders such as; schizophrenia (Gross et al., 2006), attention deficit hyperactivity disorder (Barry et al., 2003; Markovska-Simoska and Pop-Jordanova, 2017), autism spectrum disorder (Wang et al., 2013), and learning disabilities (Fonseca et al., 2006), etc.

Currently, a study examining long term effects of the epileptiform discharges on the background EEG activity in the BCECTS patients with clinical remission is scared. We hypothesized that the BCECTS patients might have an alteration in the background neural activities despite the absence of a clinical seizure. Therefore, the present study aims to investigate the resting-state brain activities using the qEEG analysis and compared among the BCECTS patients with clinical remission and the healthy age-matched, non-epileptic control subjects.

2. Materials and methods

2.1. Participants

Participants are BCECTS patients (N = 16; 11 males) age between 8–17 year-olds with clinical seizure remission. The mean age at the time of first diagnosis (T0) was 7.78 year olds (SD = 2.09). The mean age at the time of the study (T1) was 13.0 year olds (SD = 2.80). Overall, the means duration of the disease was around 5.29 (SD = 2.24) years after the initial diagnosis. They were recruited from the Pediatric Neurology Clinic of the Faculty of Medicine, Ramathibodi Hospital and the Queen Sirikit National Institute of Child Health. The diagnosis of the BCECTS is based on the criteria of the International League Against Epilepsy (ILAE) (Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009) (Berg et al., 2010). For the history of drugs treatment; fifteen patients were treated with various antiepileptic drugs, while one patient did not receive any medical treatment. The participant's demographic, the comorbid condition, types of antiepileptic drugs used and the initial EEG finding were shown in Table 1. The control group was the healthy, age-matched participants who never have the history of seizure (N = 111, mean age 14.2 year-olds). All subjects and their parents had to sign an informed consent before participating in this study. They were informed about the experimental procedures and their right to leave the study at any time. All experimental procedures were performed according to the Helsinki Declaration, and the protocol was approved by the Mahidol University Central Institutional Review Board.

2.2. EEG recording

For the initial EEG data collecting at T0, the EEG recording system is Nihon Kohden with 19 standard electrodes placing on scalp according to the international 10–20 system. The standard clinical EEG recording including FP1, FP2, FZ, F3, F4, F7, F8, T3, T4, T5, T6, C3, C4, CZ, P3, P4, PZ, O1, and O2 sites. Two reference electrodes were placed on both mastoid regions. The qEEG data were collected again at T1, using the Neuroscan recording system version 4.3 (Compumedics Neuroscan, USA). The Electro-Cap attached with a set of 30 Ag/AgCl electrodes were placed according to the international 10–20 system (Klem et al., 1999). At T1, the recording electrode were FP1, FP2, FZ, F3, F4, F7, F8, FT7, FC3, FCZ, FC4, FT8, T3, T4, T5, T6, TP7, TP8, C3, CP3, C4, CZ, CPZ, CP4, P3, P4, PZ, O1, O2, and OZ sites. Therefore, there are 19 overlapping electrode sites among the initial clinical EEG data and the current EEG recording, particularly the centrotemporal electrodes (C and T electrodes). The reference electrodes were placed on both mastoid regions. Also, four electrodes for electrooculography (EOG) were placed over both orbits to detect the eye's movement. EEG gel was applied to all electrodes to keep the skin impedance less than 5 kOhms. Analog-to-digital (A/D) rate was set at 500 Hz. The pre-recording filter was set at the bandpass between 0.1–60 Hz, and the notch was opened at 50 Hz. The resting-state brain activities were recorded over 10–15 minutes.

2.3. EEG analysis

The EEG data were analyzed in two steps; 1) visual inspection of the clinical EEG assessment and 2) the quantitative EEG analysis. Visual inspection of the raw EEG data was performed by experienced Pediatric Neurologist who was blinded for patient's information. The clinical EEG results were interpreted as normal or abnormal EEG; then, the abnormal EEG waveforms were classified as epileptiform discharges, slow activities, or other EEG abnormalities.

The quantitative EEG analysis was performed using the Neuroscan software. First, the continuous EEG data was cut into the EEG segments of 2,000 ms. Artifact rejection was manually performed by the experimenter and then followed by the EEG software assigned at ± 80 Hz. Post-recording filter was set at 0.3–30 Hz. EEG data from each subject were averaged in the frequency domain, and the results were presented as the absolute power (μV^2). The brainwaves were analyzed for the

Table 1
The table shows the demographic data, the initial EEG data at the onset of epilepsy and the clinical characteristics of the BCECTS patients (N = 16) at T0. (CBZ, Carbamazepine; CNZ, Clonazepam; PHT, Phenytoin; TPM, Topiramate; VPA, Valproic acid).

Patients	Age (yrs)	Age at seizure onset (yrs)	Gender	Handedness	Initial EEG data		Antiepileptic drugs			Comorbid conditions
					Result	Sites of epileptiform discharges	Drug Types	Total No.of AED	Response	
Case 1	9	5	F	Rt.	Abnormal	Centrotemporal (Lf.)	VPA	1	Good	–
Case 2	13	8	M	Rt.	Abnormal	Centrotemporal (Lf.)	PHT	1	Good	–
Case 3	13	5	M	Rt.	Abnormal	Centrotemporal (Lf.)	PHT	1	Good	–
Case 4	15	10	M	Lf.	Abnormal	Centrotemporal (Rt.)	PHT	1	Good	–
Case 5	16	10	M	Rt.	Abnormal	Centrotemporal (Rt. > Lf.)	VPA	2	Fair	–
Case 6	16	8.5	F	Rt.	Abnormal	Centrotemporal (Rt. > Lf.)	CBZ	1	Good	ADHD, LD
Case 7	12	10	M	Rt.	Abnormal	Centrotemporal (Rt. > Lf.)	VPA	1	Good	–
Case 8	17	7	M	Rt.	Abnormal	Centrotemporal (Rt. > Lf.)	CBZ	1	Good	–
Case 9	13	7	F	Rt.	Abnormal	Centrotemporal (Lf. > Rt)	–	–	–	–
Case 10	17	10	M	Rt.	Abnormal	Centrotemporal (Rt.)	PHT	1	Good	–
Case 11	15	8	M	Lf.	Normal	–	TPM	> 2	Fair	–
Case 12	10	8	F	Rt.	Abnormal	Centrotemporal (Lf. > Rt)	TPM	1	Good	–
Case 13	9	4	M	Rt.	Abnormal	Centrotemporal (Rt. > Lf.)	VPA	1	Fair	–
Case 14	8	4.5	F	Lf.	Abnormal	Centrotemporal (Rt.)	VPA + CNZ	> 2	Fair	–
Case 15	12.5	9.5	M	Rt.	Abnormal	Centrotemporal (Rt.)	VPA	1	Fair	–
Case 16	12.5	10	M	Rt.	Normal	–	TPM	2	Fair	ADHD, Tics

power spectrum of four common frequency bands: delta (0.5–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), and beta waves (13–30 Hz).

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software version 18. The descriptive analysis was used to explain the demographic background of participants and the mean values of the absolute power of each brain wave spectrum. The power of theta, alpha and beta waves were statistically investigated for normality using the Kolmogorov-Smirnov test with the $p > .05$ indicate the data are normally distributed. Normality test revealed that the data were skewed or non-normally distributed ($p < 0.05$); therefore, the log transformation was applied to reduce the skewness or to make the data distributed normally as possible. Normality test was rechecked using the Kolmogorov-Smirnov test to make sure that the log-transformed data are normally distributed (p > .05). Then, the means and SD of the log-transformed data were used for further statistical analysis. The hypothesis of significant differences between the brain waves power between the BCECTS patients and the control group at T1 was tested using an independent t-test, and the hypothesis of significant differences between the brain wave power within the BCECTS group (unilateral- & bilateral epileptic activities) was tested using the Mann-Whitney U test. Pearson's correlation was utilized to examine the correlation between the age of seizure onset and the power of brain waves within the BCECTS group. The significant value was set at an alpha level of 0.05 ($p < .05$).

3. Results

3.1. Quantitative EEG analysis in BCECTS patients with clinical seizure remission

Visual inspection of the raw EEG data was done to examine the background activities as well as the sites and distribution of the epileptic brain activities in the BCECTS patients with clinical seizure remission and the control group. Neither epileptiform discharges nor the abnormal slow wave activities were detected in children from both groups.

We further investigated the qEEG data to find out whether there is a difference in the resting state EEG activities between the two groups. However, due to the absence of delta activities from the EEG raw data, therefore, the qEEG were analyzed only for the theta, alpha, and beta waves. Besides, one patient was excluded from this study due to the excessive artifacts. Therefore, the EEG profiles from only 15 BCECTS cases were analyzed. The qEEG analysis revealed the significant differences in the resting-state brain activities among the BCECTS patients and the control group. The differences in resting brain waves were observed mainly over the theta range (4–8 Hz). BCECTS patients showed a significant greater in the means log theta power than the control group over the C3 electrode (BCECTS = 0.78 ± 0.29 μV^2, control = 0.63 ± 0.27 μV^2; t = 1.961, $p < .05$), CP3 electrode (BCECTS = 0.79 ± 0.33 μV^2, control = 0.62 ± 0.28 μV^2; t = 2.029, $p < .05$), CPZ electrode (BCECTS = 0.93 ± 0.29 μV^2, control = 0.76 ± 0.29 μV^2; t = 2.159, $p < .05$), T3 electrode (BCECTS = 0.44 ± 0.26 μV^2, control = 0.25 ± 0.26 μV^2; t = 2.608, $p < .01$), T4 electrode (BCECTS = 0.44 ± 0.27 μV2, control = 0.27 ± 0.26 μV2; t = 2.274, $p < .05$) and TP7 electrode (BCECTS = 0.35 ± 0.27 μV^2, control = 0.17 ± 0.27 μV^2; t = 2.443, $p < .05$), the results were shown in Table 2. The finding indicate that the BCECTS group had a significantly greater means log theta power than the control group mostly at the centrotemporal electrodes (C3, CP3, CPZ, T3, T4 and TP7) which are the similar sites of the initial epileptiform discharges (the centrotemporal electrodes or C3, C4, T3 and T4) observed at the time of seizure onset Fig.1.

BCECTS patients also showed a significant greater means log alpha power than the control group over the T3 electrodes

(BCECTS = 0.62 ± 0.27 μV^2, control = 0.40 ± 0.33 μV^2; t = 2.409, $p < .05$); T4 electrodes (BCECTS = 0.68 ± 0.27 μV^2, control = 0.45 ± 0.34 μV^2; t = 2.472, $p < .05$) and TP7 electrode (BCECTS = 0.56 ± 0.30 μV^2, control = 0.33 ± 0.34 μV^2; t = 2.429, $p < .05$), the results were shown in Table 3. The finding indicates that BCECTS patients have a significantly greater means log alpha power than the control group over both temporal regions (T3, T4, and TP7) which are the common sites of initial epileptiform discharges. Regarding the beta power, there is no significant difference in the means log beta power over all electrode sites when compared between the two groups (Table 4).

In summary, the BCECTS patients exhibited the significant greater in the means log theta- powers mainly over the centrotemporal electrodes and a significantly higher in the means log alpha- powers mainly over both temporal regions as compared to the non-epileptic control group.

3.2. The lateralization of the initial epileptiform discharges and the abnormal background EEG activities in the BCECTS patients with clinical seizure remission

We further investigate whether the distribution of epileptic activities at the initial stage affects the background EEG activities at later age. From the total of 16 BCECTS cases, the initial EEG data at the time of diagnosis (T0) found the abnormal epileptic discharges in 14 cases includes; 7 unilateral- and 7 bilateral epileptics distribution. Interestingly, the BCECTS cases with bilateral epileptic activities at the initial EEG recording show a significantly higher in the mean log theta power over the frontal (F3, Fz, F4), frontocentral (FC3, FCZ, FC4), and the central (CZ) electrodes, than the cases with unilateral epileptic focus, despite no epileptiform discharges (Table 5). Besides this, patients with the initial bilateral epileptiform discharges had a significantly greater means log beta power over the frontal (F4), frontocentral (FC3, FCZ), central (CZ), and the temporal (T3, T4, TP7) electrode, as compared to the cases with unilateral epileptic focus (Table 6). In contrast, there is no significant difference in the means log alpha power when compared between the bilateral and unilateral epileptic focus (Table 7).

3.3. Correlation between the age of seizure onset and the qEEG data in the BCECTS patients with clinical seizure remission

The age of seizure onset is one of the crucial factors for determining seizure and cognitive outcomes in children and adolescents with epilepsy. In this study, we found the negative correlation between age of seizure onset and the theta power over the CPz electrode (r = -0.53, $p < .05$). However, no such correlation was found when observed over the alpha and beta frequencies.

4. Discussion

Benign childhood epilepsy with centrotemporal spikes (BCECTS) accounts for about 10–20% of childhood epilepsy. It can be occurring as a result of various etiologies, especially the genetic disturbances of neurotransmission and neurodevelopment processes, which can contribute to the aberrant network alteration and hyperexcitability (Pitkanen et al., 2015; Xiong and Zhou, 2017). The genetic basis of BCECTS is polygenic and complex, probably highly interact with many genes or environmental factors (Schulze-Bonhage, 2017). Another essential factor is the alteration in epigenetic mechanisms which have been reported to play roles in etiology of epilepsy by exerting important influences on gene networks involved with the epileptogenesis (Hauser et al., 2018; Henshall, 2018).

In the present study, BCECTS patients are in the clinical remission period and did not show any characteristics of the epileptiform discharges. One possibility is may be due to the effect of antiepileptic drugs which control the abnormal electrical brain activity that causes

Table 2

The log theta power compared between the BCECTS group (N = 16) and the control group (N = 111). Values represent means and SD.

log Theta power (μV2)	BCECT group		Control group		Stat		Normality test	
	Mean	SD	Mean	SD	t	*p*-value	Stat	*p*-value
Frontal electrodes								
F3 (left)	0.76	0.27	0.71	0.25	0.813	0.418	0.043	0.200
Fz (midline	0.88	0.30	0.79	0.23	1.296	0.197	0.050	0.200
F4 (right)	0.84	0.30	0.73	0.24	1.646	0.102	0.055	0.200
Frontocentral electrodes								
FC3 (left)	0.67	0.39	0.68	0.27	− 0.088	0.931	0.031	0.200
FCz (midline)	0.88	0.31	0.81	0.24	1.077	0.284	0.056	0.200
FC4 (right)	0.81	0.30	0.70	0.25	1.573	0.118	0.067	0.200
Central electrodes								
C3 (left)	0.78	0.29	0.63	0.27	1.961	0.050*	0.070	0.200
Cz (midline)	0.87	0.31	0.78	0.26	1.236	0.219	0.063	0.200
C4 (right)	0.80	0.30	0.65	0.28	1.851	0.067	0.066	0.200
Centroparietal electrodes								
CP3 (left)	0.79	0.33	0.62	0.28	2.029	0.045[*]	0.063	0.200
CPz (midline)	0.93	0.29	0.76	0.29	2.159	0.033[*]	0.047	0.200
CP4 (right)	0.76	0.31	0.63	0.30	1.569	0.120	0.053	0.200
Parietal electrodes								
P3 (left)	0.72	0.39	0.62	0.30	1.235	0.219	0.050	0.200
Pz (midline)	0.84	0.40	0.73	0.33	1.207	0.230	0.050	0.200
P4 (right)	0.82	0.36	0.70	0.35	1.217	0.226	0.051	0.200
Temporal electrodes								
T3 (left)	0.44	0.26	0.25	0.26	2.608	0.010[**]	0.035	0.200
T4 (right)	0.44	0.27	0.27	0.26	2.274	0.025[*]	0.050	0.200
TP7 (left)	0.35	0.27	0.17	0.27	2.443	0.016[*]	0.053	0.200
TP8 (right)	0.33	0.24	0.28	0.37	0.450	0.653	0.083	0.540

$^*p \le .05$, $^{**}p \le .01$.

seizures. Another explanation is may be due to the EEG recording in our study was done during awake. Therefore, we cannot observe the epileptic activities in BCECTS children because the epileptiform discharges usually occur during sleep or drowsiness stages. Despite no epileptiform discharges, we found a significantly higher absolute theta and alpha power at the centrotemporal electrode as compared with the control children. Several lines of evidence consistently reported that children with epileptic activities had a general increment in the absolute power of brain waves overall electrode sites. For examples, children 7–9 and 10–12 year-olds with Rolandic spike, had a significantly higher absolute delta and theta powers over all electrode sites regardless of the seizure symptoms (Braga et al., 2000). Other studies also reported that the children with BCECTS had a significantly higher absolute theta and delta powers (Tedrus et al., 2006), greater absolute alpha and beta powers, in most of all electrode sites as compared with the control group (Fonseca et al., 2004).

In contrast, our results showed that the BCECTS patients had a significant increase in the absolute theta and alpha power that mainly occur at the centrotemporal electrodes together with few adjacent brain regions, rather than the widespread abnormalities commonly found in
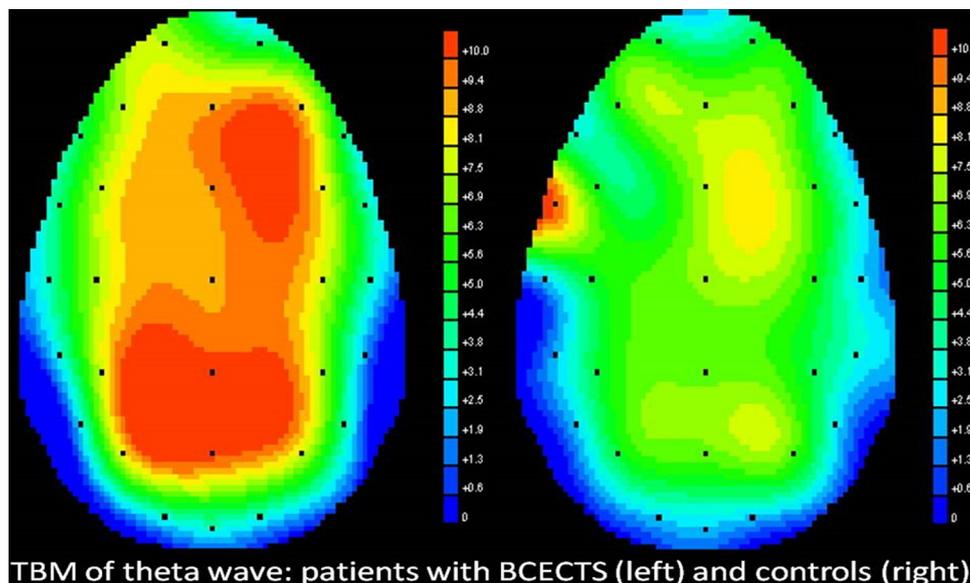

Fig. 1. The topographic brain mapping shows the theta power compared between the BCECTS group (Left) and the control group (Right).

Table 3
The log Alpha power compared between the BCECTS group (N = 16) and the control group (N = 111). Values represent means and SD.

log Alpha power (µV2)	BCECT group		Control group		Stat		Normality test	
	Mean	SD	Mean	SD	t	p-value	Stat	p-value
Frontal electrodes								
F3 (left)	0.96	0.27	0.86	0.35	1.123	0.264	0.054	0.200
Fz (midline	1.04	0.27	0.92	0.34	1.294	0.198	0.041	0.200
F4 (right)	1.03	0.27	0.89	0.34	1.545	0.125	0.051	0.200
Frontocentral electrodes								
FC3 (left)	0.99	0.31	0.87	0.35	1.142	0.256	0.044	0.200
FCz (midline)	1.07	0.28	0.97	0.34	1.090	0.278	0.063	0.200
FC4 (right)	1.03	0.26	0.93	0.36	1.069	0.287	0.066	0.200
Central electrodes								
C3 (left)	1.04	0.27	0.90	0.36	1.476	0.143	0.058	0.200
Cz (midline)	1.11	0.29	1.02	0.36	0.874	0.384	0.073	0.098
C4 (right)	1.07	0.28	0.93	0.37	1.376	0.171	0.061	0.200
Centroparietal electrodes								
CP3 (left)	1.10	0.32	0.92	0.38	1.690	0.094	0.102	0.079
CPz (midline)	1.29	0.31	1.11	0.39	1.714	0.089	0.068	0.200
CP4 (right)	1.09	0.33	1.00	0.41	0.841	0.402	0.076	0.154
Parietal electrodes								
P3 (left)	1.11	0.49	1.06	0.41	0.370	0.712	0.081	0.056
Pz (midline)	1.31	0.37	1.17	0.39	1.303	0.195	0.061	0.200
P4 (right)	1.27	0.46	1.23	0.42	0.371	0.711	0.077	0.067
Temporal electrodes								
T3 (left)	0.62	0.27	0.40	0.33	2.409	0.017[*]	0.104	0.200
T4 (right)	0.68	0.27	0.45	0.34	2.472	0.015[*]	0.080	0.064
TP7 (left)	0.56	0.30	0.33	0.34	2.429	0.017[*]	0.098	0.084
TP8 (right)	0.65	0.32	0.54	0.41	0.904	0.368	0.098	0.071

[*] $p \leq .05$.

Table 4
The log Beta power compared between the BCECTS group (N = 16) and the control group (N = 111). Values represent means and SD.

log Beta power (µV2)	BCECT group		Control group		Stat		Normality test	
	Mean	SD	Mean	SD	t	p-value	Stat	p-value
Frontal electrodes								
F3 (left)	−0.19	0.24	−0.17	0.18	−0.337	0.737	0.054	0.200
Fz (midline	−0.14	0.21	−0.17	0.17	0.663	0.509	0.041	0.200
F4 (right)	−0.13	0.19	−0.16	0.17	0.649	0.517	0.051	0.200
Frontocentral electrodes								
FC3 (left)	−0.18	0.22	−0.19	0.19	0.288	0.774	0.044	0.200
FCz (midline)	−0.14	0.19	−0.16	0.17	0.506	0.614	0.063	0.200
FC4 (right)	−0.15	0.19	−0.17	0.20	0.352	0.725	0.066	0.200
Central electrodes								
C3 (left)	−0.15	0.21	−0.19	0.21	0.723	0.471	0.058	0.200
Cz (midline)	−0.15	0.18	−0.16	0.17	0.326	0.745	0.073	0.098
C4 (right)	−0.13	0.20	−0.17	0.20	0.706	0.481	0.061	0.200
Centroparietal electrodes								
CP3 (left)	−0.11	0.24	−0.18	0.21	1.225	0.223	0.102	0.007
CPz (midline)	−0.04	0.20	−0.14	0.19	1.896	0.060	0.068	0.200
CP4 (right)	−0.13	0.20	−0.16	0.20	0.564	0.574	0.076	0.154
Parietal electrodes								
P3 (left)	−0.08	0.26	−0.14	0.22	0.810	0.420	0.081	0.056
Pz (midline)	0.00	0.22	−0.07	0.20	1.235	0.220	0.061	0.200
P4 (right)	−0.02	0.27	−0.03	0.23	0.174	0.862	0.077	0.067
Temporal electrodes								
T3 (left)	−0.40	0.24	−0.40	0.30	−0.014	0.989	0.104	0.002
T4 (right)	−0.39	0.15	−0.40	0.26	0.096	0.924	0.080	0.044
TP7 (left)	−0.52	0.17	−0.51	0.25	−0.199	0.842	0.098	0.004
TP8 (right)	−0.48	0.15	−0.43	0.27	−0.571	0.569	0.098	0.011

the early stage of the disease. Typically, the brain wave power decreases with increasing ages that appear together with more organized functional networks as the children growing up (Anderson and Perone, 2018; Miskovic et al., 2015; Whitford et al., 2007). A greater power of the low-frequency brain waves with increasing age (e.g., the theta and delta power), indicate the delayed cortical maturation (Anderson and Perone, 2018; Benninger et al., 1984; Gmehlin et al., 2011; Miskovic et al., 2015; Whitford et al., 2007). Therefore, a significant increase in the mean log theta power over the centrotemporal regions in BCECTS patients indicate the delayed cortical maturation as compared with

Table 5
The log theta power within the BCECTS group, compared between the unilateral (N = 7) and bilateral (N = 7) epileptic activities. Values represent mean (SD).

log Theta power (µV2)	Unilateral epileptic Activities		Bilateral epileptic Activities		Mann-Whitney U test	
	Mean	SD	Mean	SD	Stat	p-value
Frontal electrodes						
F3 (left)	0.60	0.21	0.92	0.26	0.035	0.038*
Fz (midline	0.71	0.28	1.05	0.26	0.035	0.038*
F4 (right)	0.67	0.26	1.01	0.27	0.018	0.017*
Frontocentral electrodes						
FC3 (left)	0.38	0.32	0.95	0.26	0.009	0.007**
FCz (midline)	0.71	0.28	1.06	0.26	0.025	0.026*
FC4 (right)	0.65	0.27	0.98	0.27	0.018	0.017*
Central electrodes						
C3 (left)	0.65	0.28	0.93	0.27	0.064	0.073
Cz (midline)	0.71	0.28	1.05	0.28	0.025	0.026*
C4 (right)	0.66	0.28	0.95	0.27	0.085	0.097
Centroparietal electrodes						
CP3 (left)	0.68	0.40	0.90	0.27	0.391	0.445
CPz (midline)	0.87	0.29	1.03	0.30	0.338	0.383
CP4 (right)	0.62	0.31	0.91	0.28	0.116	0.138
Parietal electrodes						
P3 (left)	0.55	0.44	0.91	0.29	0.142	0.165
Pz (midline)	0.70	0.47	1.00	0.31	0.180	0.209
P4 (right)	0.78	0.42	0.88	0.35	0.749	0.805
Temporal electrodes						
T3 (left)	0.30	0.22	0.59	0.24	0.064	0.073
T4 (right)	0.35	0.26	0.54	0.29	0.277	0.318
TP7 (left)	0.22	0.26	0.49	0.23	0.048	0.053
TP8 (right)	0.30	0.31	0.36	0.15	0.685	0.755

$^{*}p \leq .05$, $^{**}p \leq .01$.

control children. Also, the results indicate that the epileptogenesis might have long term negative impact on cortical maturation, especially at the centrotemporal brain regions which may underlie the cognitive and behavioral problems in children with BECTS even at the seizure remission stage.

Besides, it is possible that the oscillatory abnormality of the

Table 6
The log Beta power within the BCECTS group, compared between the unilateral (N = 7) and bilateral (N = 7) epileptic activities. Values represent mean (SD).

log Beta power (µV2)	Unilateral epileptic Activities		Bilateral epileptic Activities		Mann-Whitney U test	
	Mean	SD	Mean	SD	Stat	p-value
Frontal electrodes						
F3 (left)	−0.27	0.25	−0.09	0.22	−1.725	0.085
Fz (midline	−0.22	0.22	−0.03	0.17	−1.725	0.085
F4 (right)	−0.21	0.17	−0.02	0.17	−1.981	0.048*
Frontocentral electrodes						
FC3 (left)	−0.34	0.18	−0.04	0.18	−2.192	0.028*
FCz (midline)	−0.23	0.17	−0.02	0.17	−2.108	0.035*
FC4 (right)	−0.22	0.18	−0.06	0.17	−1.597	0.110
Central electrodes						
C3 (left)	−0.22	0.22	−0.06	0.17	−1.086	0.277
Cz (midline)	−0.24	0.16	−0.04	0.16	−1.981	0.048*
C4 (right)	−0.21	0.19	−0.04	0.19	−1.342	0.180
Centroparietal electrodes						
CP3 (left)	−0.15	0.33	−0.06	0.17	−0.286	0.775
CPz (midline)	−0.02	0.26	−0.04	0.15	−0.447	0.655
CP4 (right)	−0.18	0.24	−0.07	0.17	−0.714	0.475
Parietal electrodes						
P3 (left)	−0.17	0.36	−0.02	0.18	−0.857	0.391
Pz (midline)	0.04	0.31	−0.03	0.14	−0.857	0.391
P4 (right)	−0.05	0.37	0.00	0.18	−0.064	0.949
Temporal electrodes						
T3 (left)	−0.54	0.15	−0.34	0.17	−1.981	0.048*
T4 (right)	−0.43	0.14	−0.38	0.15	−0.575	0.565
TP7 (left)	−0.61	0.17	−0.42	0.13	−2.108	0.035*
TP8 (right)	−0.48	0.20	−0.47	0.09	−0.568	0.570

* $p \leq .05$.

Table 7
The log Alpha power within the BCECTS group, compared between the unilateral (N = 7) and bilateral (N = 7) epileptic activities. Values represent mean (SD).

log Alpha power (μV2)	Unilateral epileptic Activities (N = 7)		Bilateral epileptic Activities (N = 7)		Mann-Whitney U test	
	Mean	SD	Mean	SD	Stat	p-value
Frontal electrodes						
F3 (left)	0.91	0.34	0.99	0.22	− 0.192	0.848
Fz (midline	1.01	0.35	1.06	0.21	− 0.064	0.949
F4 (right)	0.98	0.32	1.06	0.23	− 0.447	0.655
Frontocentral electrodes						
FC3 (left)	0.85	0.33	1.07	0.32	− 0.893	0.372
FCz (midline)	1.02	0.34	1.10	0.24	− 0.064	0.949
FC4 (right)	0.99	0.31	1.05	0.23	− 0.064	0.949
Central electrodes						
C3 (left)	1.01	0.30	1.06	0.28	− 0.064	0.949
Cz (midline)	1.04	0.34	1.17	0.27	− 0.447	0.655
C4 (right)	1.05	0.33	1.07	0.26	− 0.192	0.848
Centroparietal electrodes						
CP3 (left)	1.11	0.40	1.09	0.30	− 0.429	0.668
CPz (midline)	1.36	0.35	1.23	0.31	− 0.703	0.482
CP4 (right)	1.08	0.44	1.09	0.26	− 0.143	0.886
Parietal electrodes						
P3 (left)	0.99	0.65	1.19	0.32	− 0.447	0.655
Pz (midline)	1.36	0.47	1.27	0.32	− 0.286	0.775
P4 (right)	1.23	0.61	1.27	0.38	0.000	1.000
Temporal electrodes						
T3 (left)	0.55	0.29	0.67	0.27	− 0.319	0.749
T4 (right)	0.67	0.31	0.69	0.27	− 0.064	0.949
TP7 (left)	0.45	0.34	0.68	0.24	− 0.958	0.338
TP8 (right)	0.69	0.43	0.57	0.17	− 0.731	0.465

background EEG activities found in our study might be the consequences of the previous seizers (Sutula et al., 2003). Several lines of evidence demonstrated that even the single or repeated brief minimal seizures could produce the long-term adverse consequences on neuronal damage and death (Kotloski et al., 2002) or loss of interneuron subclasses (Sayin et al., 2003; Silva et al., 2002). Loss of GABAergic interneuron function is an important factor for the pathogenesis of repeated epilepsy. Therefore, seizure induces loss or dysfunction of interneurons can further contribute to an imbalance between excitatory and inhibitory function in the cortex which might underlie the oscillatory abnormality of the background EEG activities at later ages.

The occurrence of epileptic activities, either with or without a seizure, can disturb normal brain development and later impair cognitive functions. In fact, the centrotemporal discharges (or Rolandic spikes) do not only occur in the BCECTS and other epilepsy syndromes (Braga et al., 2000) but can also found in various neurological and neurodevelopmental disorders; e.g., migraine (Nejad Biglari et al., 2012), autistic spectrum disorders (Boutros et al., 2015), and the siblings of BCECTS patients (Verrotti et al., 2013). The previous study also reported a relationship between the alterations in background brain activities and lower academic performance in children with BECTS (Hommet et al., 2001; Tedrus et al., 2009; Vannest et al., 2015). Therefore, our finding provides further evidence that cortical delay maturation may underlie the effect of seizure on cognitive development and functions in BECTS patients with clinical seizure remission.

The lateralization of the Rolandic spikes is somehow associated with poor cognitive functions in the BCECTS patients at later ages. Previous studied reported the significant correlation between the lateralization of the epileptic focus and the difficulties in non-verbal functions in the BCECTS children at 18 months follow up (Metz-Lutz et al., 1999). However, an influence of the lateralization of the epileptic discharges on the cortical maturation is not well understood. In the present study, we found that BCECTS patients with the initial bilateral distribution of epileptic discharges had a significantly higher in the log- theta and beta powers than the patients with the initial unilateral epileptic activities. Our results indicate that the BCECTS

patients with initial bilateral epileptiform discharges exhibit more delay in cortical maturation than the BCECTS cases with the initial unilateral epileptic activities. Therefore, our results provide needed evidence underlying long term effects of the lateralization of the initial epileptiform discharges on the background EEG activities at later age. Another interesting finding from the lateralization studied is the qEEG differences were observed mainly over the frontal, frontocentral, and central electrodes, which indicate functional impairment of the frontal lobe in the BCECTS cases with bilateral centrotemporal spikes. Our finding corresponded to the previous report that frontal lobe functions were impaired in the BCECTS cases (Baglietto et al., 2001). Altogether, the findings suggest that the BCECTS cases with bilateral epileptiform discharges have a higher chance of cognitive impairment than the unilateral cases which may be due to the epileptogenesis induces delay maturation in the frontal cortex. Although the present studied did not found a significant correlation between the qEEG data and other clinical parameters (e.g., the numbers of antiepileptic drug used and the treatment response). However, the significant correlation was found between the age of seizure onset and the abnormal qEEG data. Our result indicates that the younger age of seizure onset significantly correlates with a poorer brain maturation which in line with the previous reports that early seizure onset has the negative impact on children's cognitive functions at the school age (Deltour et al., 2007; Fonseca et al., 2007).

There are some limitations to this work. First, there was no qEEG data of BCECTS patients at the time of seizure onset that might limit the interpretation of current qEEG finding which done at the remission phase. Therefore, the future study may need to analyze whether the oscillatory abnormalities defined at the follow up occur in the same region as the epileptic discharges in the initial EEG finding. Second, the sample size is quite small, and the age range of the BCECTS group was rather wide (8–17 year-olds). Although the background brain activities are somewhat stable from late childhood to adolescence, however, the qEEG profile obtained from children at the narrow age range would provide a more precise interpretation of the cortical maturation. Third, participants in this study consisted of mix-handedness (13 Right-Handed and 2 Left-handed). Thus, it may also affect the interpretation

of background brain activities in each cerebral hemisphere. Finally, even the BCECTS commonly occurs in male; this work includes both male (N = 15) and female patients (N = 5). Therefore, sex different might also have some effects on the resting-state brain activities. Future studies are needed to follow-up the qEEG from the onset, on a larger scale, and should control for age and sex of the participants.

5. Conclusions

In conclusion, our results have shown a significant increase in the absolute theta and alpha brain wave powers in BCECTS patients with clinical remission stage. The significant greater mainly occur over the centrotemporal electrodes. In normal development, the brain waves' power usually decreases with increasing ages that appear together with more organized functional networks. Therefore, the increments of brain waves power in the BCECTS group indicate the delayed maturation of the centrotemporal brain regions.

Moreover, BCECTS cases with bilateral epileptiform discharges have a significantly higher absolute theta and beta powers than the cases with unilateral epileptic activities. The results suggest that the sites and distribution of the abnormal electrical activities at the initial EEG recording are critical for determined long term outcome of the BCECTS on brain development and maturation. Further study needs to explore more on the event-related potentials (ERP) and neuropsychological tests to elucidate the influence of epileptiform discharges on the cognitive profile in the BCECTS patients at later ages.

Acknowledgment

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