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Original article

Factors associated with electroencephalographic and clinical remission of benign childhood epilepsy with centrotemporal spikes

Eun Hye Lee, Su-Jeong You *

Department of Pediatrics, Kyung Hee University, College of Medicine, Republic of Korea
Department of Pediatrics, Inje University College of Medicine, Sanggye Paik Hospital, Seoul, Republic of Korea

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Abstract

Purpose: Benign childhood epilepsy with centrotemporal spikes (BECTS) is strongly related to age, both to age at the time of seizure onset and to age at remission. However, the age of remission varies. The present study analyzed factors associated with remission of BECTS.

Methods: Sixty-nine children with BECTS were retrospectively analyzed. Thirty-eight (55.1%) were boys and 31 (44.9%) were girls. Mean age at seizure onset was 86.36 ± 24.55 months (range: 41–151 months).

Results: The mean age at the time of EEG improvement or remission was 138.31 ± 19.71 months. Of the 69 patients, 36 (52.2%) exhibited electroencephalography (EEG) improvement or remission before age 11.5 years, whereas 33 (47.8%) showed later improvement or remission. The two groups differed significantly in age at seizure onset. When patients were divided into groups using an age cutoff for last seizure of 9 years, the two groups differed significantly in age at seizure onset.

Conclusions: The most important predictor of early BECTS remission is age at seizure onset.

Keywords: Rolandic epilepsy; Childhood; Electroencephalography; Remission

1. Introduction

Benign childhood epilepsy with centrotemporal spikes (BECTS), also termed benign Rolandic epilepsy, is the most common benign focal epilepsy of childhood, found in 15–25% of epileptic children under age 15 years and with a male predominance [1–3]. Trials in small numbers of patients with short follow-up (1–2 years) have reported longitudinal changes in centrotemporal spike rates [4,5]. In addition, the effects of antiepileptic drugs (AEDs) on electroencephalography (EEG) profiles and seizure have been assessed in these patients [6–9]. However, these studies did not explore long-term seizure remission or EEG improvements. Furthermore, although AEDs reduce seizure frequency, their effects on the natural history of BECTS remain unclear.

Few studies to date have sought to identify factors associated with seizure remission and EEG improvements in patients with BECTS. This study therefore retrospectively analyzed factors associated with early clinical and EEG remission in patients with BECTS.

* Corresponding author at: Department of Pediatrics, Inje University College of Medicine, Sanggye Paik Hospital, 1342 Dongil-ro Nowon-gu, Seoul 01757, Republic of Korea.
E-mail address: su6236@naver.com (S.-J. You).

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2. Methods

2.1. Patients selection

This retrospective study included 69 children who were diagnosed with BECTS and started on AEDs in the pediatric neurology departments of two university hospitals (Sanggye Paik and Kyung Hee University Hospital, Seoul, Korea), with all patients followed up to the time of EEG remission or clinical improvement. All patients met both the clinical and EEG criteria for BECTS established by the International League Against Epilepsy (ILAE) in 2010 [10], and all except one were started on AEDs after at least two unprovoked seizures. Patients who did not exhibit improvement on EEG or remission at the last follow-up, those with obvious neurological deficits, those who experienced clinical or intellectual decline during follow-up, and those who exhibited atypical EEG characteristics and/or abnormal brain imaging findings were excluded.

2.2. Data collection

Data were collected retrospectively from patients' medical files. Factors recorded included patient age, sex, ages at seizure onset and last seizure, seizure time (awake or asleep), seizure frequency, EEG findings and treatment data.

Interictal EEG was performed using 18 electrodes (the 10–20 system) and during both wakefulness and sleep. Patients underwent EEG every 6–12 months until improvement was evident. Intermittent photic stimulation and hyperventilation were routinely applied. EEG results included location of rolandic spikes (unilateral or bilateral hemisphere). An EEG improvement was defined as a >50% reduction in the frequency of spike discharges, and a reduction in spike amplitude (spike fading). EEG normalization was defined as a normal EEG background activity with no spike discharges.

2.3. Analyses

Patients were divided into two groups based on age at EEG improvement or remission before (Group A) or after (Group B) 11.5 years. Patients were also divided based on whether their age at last seizure was <9 years (Group C) or ≥9 years (Group D). Clinical factors in these pairs of groups were compared. The study was approved by the medical ethics boards of both participating hospitals.

2.4. Statistical analyses

All analyses were performed using SPSS software ver. 24.0. The level of statistical significance was set at $p < 0.05$. Categorical variables, including sex, seizure time (awake or asleep), and spike lateralization (unilateral or bilateral), were compared using chi-squared tests. Continuous variables, including age at seizure onset, total number of seizures, and age at last seizure, were compared using *t*-tests. Multivariate logistic regression analysis was performed to adjust for possible correlations between factors independently predicting remission, employing variables that differed significantly on univariate analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated.

3. Results

Sixty-nine children with BECTS, 38 (55.1%) boys and 31 (44.9%) girls, were retrospectively analyzed. Mean age at seizure onset was 86.36 ± 24.55 months (range: 41–151 months), mean age at the time of the last seizure was 108.22 ± 24.19 months (range: 54–158 months) and mean interval from the first to the last seizure was 21.80 ± 20.66 months (range: 0–78 months) (Table 1). No patient experienced a seizure after EEG improvement/normalization.

In total, 12 (21.8%) of 55 patients had seizures during wakefulness; data for the other 14 patients were missing. No patient exhibited only simple partial seizures or waking seizures. All children underwent full-lead EEG at presentation, and all underwent sleep EEG. Spike foci were bilateral in 41 (59.4%) of the 69 patients and unilateral in the other 28 (40.6%). Only five patients (7.2%) exhibited generalization on EEG; this parameter was not included in comparisons.

Overall, the mean age at the time of EEG improvement or remission was 138.31 ± 19.71 months. Of the 69 patients, 36 (52.2%) experienced EEG resolution before age 11.5 years (Group A), whereas 33 (47.8%) showed later improvement or remission (Group B). These groups differed significantly in age at seizure onset (Table 2) (76.69 ± 16.41 vs. 96.91 ± 27.69 months, *t*-test $P < 0.05$), with younger age at seizure onset associated with earlier EEG improvement. When patients were divided into two groups based on age at last seizure of 9 years (Table 3), we found significant differences in age at seizure onset between Groups C and D (74.92 ± 16.05 vs. 98.85 ± 26.29 months, *t*-test $P < 0.05$). Early seizure remission was also associated with early age at seizure onset.

On binary multivariate logistic regression analysis, age at seizure onset was the only factor affecting early EEG remission (odds ratio [OR] 1.060, $P = 0.002$, Table 2) and early clinical remission (OR, 1.179, $P = 0.001$, Table 3). Waking seizure status, seizure frequency, and EEG lateralization were unrelated to age at remission. On multivariate regression analysis, age at the time of EEG improvement or normalization and age at last seizure also correlated with age at seizure onset (all $P < 0.05$).

Table 1
Patient characteristics.

Number of seizures (n = 69)	7.32 ± 11.70 (1–87) months
Age at seizure onset (n = 69)	86.36 ± 24.55 (41–151) months
Age at last seizure (n = 69)	108.22 ± 24.19 (54–158) months
Interval between first seizure and start of treatment	6.78 ± 11.66 (0–57) months
Age at EEG normalization (n = 48)	139.41 ± 20.42 (96–184) months
Age at EEG improvement (n = 38)	144.13 ± 19.90 (114–183) months
Interval between first seizure and last follow-up	70.06 ± 34.02 months
Male:female	38:31
Age at EEG improvement or remission	138.32 ± 19.71 (96–183) months
Time between the last seizure and EEG improvement	30.10 ± 19.84 (1–129) months
Interval from first to last seizure	21.80 ± 20.66 (0–78) months
Waking seizures (n = 55)	
Present	12
Absent	43
Lateralization (hemispheric data) evident on EEG	
Bilateral	41
Unilateral	28

EEG, electroencephalography.

Table 2
Comparison of early and late EEG remission or improvement (cutoff: age of 11.5 years).

Parameter		Group A (n = 36)	Group B (n = 33)	Comparison	Binary logistic test
Number of seizures		5.22 ± 3.72	9.58 ± 16.30	P > 0.05	
Duration of epilepsy (months)		18.03 ± 19.28	27.91 ± 21.60	P > 0.05	
Age at seizure onset (months)		76.69 ± 16.41	96.91 ± 27.68	P = 0.001	P = 0.002 Exp (B)1.063 (1.024–1.104)
Waking seizures	Present	5	7	P > 0.05 chi-squared	
	Absent	26	17		
Lateralization (hemispheric) on EEG	Bilateral	21	20	P > 0.05 chi-squared	
	Unilateral	15	13		

EEG, electroencephalography.
Group A: Improvement or remission as shown by EEG before 11.5 years of age.
Group B: Improvement or remission as shown by EEG after 11.5 years of age.

Table 3
Comparison of early and late seizure remission using a cutoff of 9 years of age.

Parameter		Group C (n = 36)	Group D (n = 33)	Comparison	Binary logistic test
Number of seizures frequency		4.97 ± 3.468	9.85 ± 16.283	P > 0.05	
Duration of epilepsy (months)		14.14 ± 19.288	30.15 ± 23.462	P = 0.001	
Age at seizure onset (months)		74.92 ± 16.049	98.85 ± 26.291	P = 0.001	P = 0.001 Exp(B)1.129 (1.054–1.210)
Waking seizures	Present	4	8	P > 0.05 chi-squared	
	Absent	27	16		
Lateralization (hemispheric) on EEG	Bilateral	23	18	P > 0.05 chi-squared	
	Unilateral	13	15		

EEG, electroencephalography.
Group C: Seizure remission before the age of 9 years.
Group D: Seizure remission after the age of 9 years.

During follow-up, all patients were treated with AEDs; 38 (55.1%) were started on oxcarbazepine, 18 (26.1%) on topiramate, six (8.7%) on lamotrigine, three (4.3%) on valproic acid, and one each (1.4%) on levetiracetam, zonisamide, carbamazepine, and phenytoin. Seven children received polytherapy at times. Medication history did not correlate with clinical or EEG remission.

4. Discussion

BECTS is the most common age-related focal epilepsy, being present in 15–23% of children with epilepsy syndromes [11]. BECTS is strongly associated with age, both to age at seizure onset and to age at remission. Studies exploring the prognosis and natural course of BECTS have found that this condition usually commences between 3 and 13 years of age [1,12–14], with most patients experiencing their first seizure at age 7–8 years and recovering by age 16 years [15]. A meta-analysis reported that 50% of patients with BECTS experienced remission by age 6 years, 92% by age 12 years, and 99.8% by age 18 years, with a marked peak in remission at age 13 years [1]. The present study found that 48 patients (69.6%) exhibited EEG normalization at a mean age of 139.41 ± 20.42 months (range: 96–184 months), and 38 (55.1%) showed EEG improvement at a mean age of 144.13 ± 19.90 months (range: 114–183 months). Overall, the mean age at the time of EEG improvement or remission was 138.32 ± 19.71 months (range: 96–183 months), and the mean age at seizure remission was 108.22 ± 24.19 months (range: 54–158 months), with EEG tracings improving later than clinical remission, as in a previous study [16].

The age-specific onset and remission of BECTS is likely due to brain maturation. Idiopathic focal epilepsies including BECTS constitute a spectrum of syndromes with no underlying structural brain lesion or attendant neurological signs or symptoms, and are likely genetically linked and associated with derangement of age-related, systemic brain maturation [15,17].

Structural and functional magnetoencephalography (MEG) analysis has shown that, at the time of epilepsy onset, children with BECTS exhibited significantly thicker cortices in the right superior frontal, right superior, middle temporal, and left pars triangularis gyrus regions than controls [18]. In addition, children with BECTS were found to have significant putamen hypertrophy and deformities, and increases in bilateral fronto-temporal surfaces and volumes [19,20]. Voxel-based morphometry of children with BECTS by age group showed that their levels of cortical gray matter were higher than normal, primarily in the frontal, and to a lesser extent, the insular and parietal regions, but approached normal values after epilepsy ceased [20]. Such structural alterations in the brain, followed by normalization with increasing age, indicate an association between altered brain maturation associated with interictal epileptic activity and age-related remission of the condition. The time interval between BECTS onset and remission may reflect similar age-related gene expression or the involvement of epigenetic factors.

Previous studies focused on the age-dependent features of BECTS and factors prognostic of this condition found that early age at seizure onset, more frequent seizures, and bilateral EEG foci were associated with AED treatment failure and cognitive deficits. However, relationship between these factors and BECTS remission has not been determined [12,14]. This study comparing groups of children with early and late remission found that earlier age at onset was associated with earlier improvement in EEG status and clinical remission. Seizure frequency, waking seizure status, EEG lateralization, and treatment were not associated with EEG improvement or remission. AED treatment failure was irrelevant in this context. Therefore, it is suggested that AED discontinuation should reflect patient age, and especially EEG status, not the time elapsed since the last seizure.

Given the age-related brain maturation described above, our findings suggest that a certain fixed period allowing for such maturation may be required for recovery. Thus, early seizure onset may reflect an early altered, epileptic brain maturation in patients with BECTS.

The retrospective design of our study was a major limitation. Seizure types were not analyzed in all patients. Patients who did not receive AEDs or who improved on EEG after successful withdrawal of AEDs were not included. Thus, our results may not be representative of all children with BECTS. However, unlike most previous studies, which assessed atypical features of BECTS or failure of AED treatment, it is noteworthy that our study assessed remission or improvement in these patients.

In conclusion, age was the most important factor associated with BECTS remission, as assessed by EEG or seizure remission, irrespective of EEG findings, AED treatment, or seizure frequency. However, further prospective studies on the natural course of BECTS should evaluate patients not treated with AEDs as well as children exhibiting only BECTS spikes on EEG.

5. Ethics statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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References

[1] Bouma PA, Bovenkerk AC, Westendorp RG, Brouwer OF. The course of benign partial epilepsy of childhood with centrotemporal spikes. A meta-analysis. Neurology 1997;48:430–7.
[2] Shields DW, Snead III C. Benign epilepsy with centrotemporal spikes. Epilepsia 2009;50:10–5.
[3] Wirrell EC. Benign epilepsy of childhood with centrotemporal spikes. Epilepsia 1998;39.
[4] Kanemura H, Sano F, Ohyama T, Sugita K, Aihara M. Sequential EEG characteristics may predict seizure recurrence in rolandic epilepsy. Seizure-Eur J Epilepsy 2014;23:646–50.
[5] Kellaway P. The electroencephalographic features of benign centrotemporal (rolandic) epilepsy of childhood. Epilepsia 2000;41:1053–6.
[6] Bast T, Völp A, Wolf C, Rating D, Group SS. The influence of sulthiame on EEG in children with benign childhood epilepsy with centrotemporal spikes (BECTS). Epilepsia 2003;44:215–20.
[7] Mitsudome A, Ohfu M, Yasumoto S, Ogawa A, Hirosea S, Ogata H, et al. The effectiveness of clonazepam on the Rolandic discharges. Brain Dev 1997;19:274–8.
[8] Tacke M, Borggraefe I, Gerstl L, Heinen F, Vill K, Bonfert M, et al. Effects of Levetiracetam and Sulthiame on EEG in benign epilepsy with centrotemporal spikes: a randomized controlled trial. Seizure-Eur J Epilepsy 2018;56:115–20.
[9] Tzitiridou M, Panou T, Ramantani G, Kambas A, Spyroglou K, Panteliadis C. Oxcarbazepine monotherapy in benign childhood epilepsy with centrotemporal spikes: a clinical and cognitive evaluation. Epilepsy Behav 2005;7:458–67.
[10] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia 2010;51:676–85.
[11] Cavazzuti G. Epidemiology of different types of epilepsy in school age children of Modena, Italy. Epilepsia 1980;21:57–62.
[12] Incecik F, Altunbasak S, Herguner OM, Mert G, Sahan D. Prognostic significance of failure of the initial antiepileptic drug in children with benign childhood epilepsy with centrotemporal spikes. Brain Dev 2015;37:66–70.
[13] Massa R, de Saint–Martin A, Carcangiu R, Rudolf G, Seegmuller C, Kleitz C, et al. EEG criteria predictive of complicated evolution in idiopathic rolandic epilepsy. Neurology 2001;57:1071–9.
[14] You SJ, Kim D-S, Ko T-S. Benign childhood epilepsy with centro-temporal spikes (BCECTS): early onset of seizures is associated with poorer response to initial treatment. Epileptic Disorders 2006;8:285–8.
[15] Panayiotopoulos C. Epileptic seizures and their classification. In: A Clinical Guide to Epileptic Syndromes and their Treatment. Springer; 2010. p. 21–63.
[16] Arzimanoglou A, Guerrini R, Aicardi J. Epilepsies with predominantly myoclonic seizures. Aicardi's Epilepsy Children 2004;3:58–80.
[17] Panayiotopoulos C. Benign childhood partial epilepsies: benign childhood seizure susceptibility syndromes. J Neurol Neurosurg Psychiatry 1993;56:2.
[18] Kim E-H, Yum M-S, Shim W-H, Yoon H-K, Lee Y-J, Ko T-S. Structural abnormalities in benign childhood epilepsy with centrotemporal spikes (BCECTS). Seizure-Eur J Epilepsy 2015;27:40–6.
[19] Lin JJ, Riley JD, Hsu DA, Stafstrom CE, Dabbs K, Becker T, et al. Striatal hypertrophy and its cognitive effects in new-onset benign epilepsy with centrotemporal spikes. Epilepsia 2012;53:677–85.
[20] Pardoe HR, Berg AT, Archer JS, Fulbright RK, Jackson GD. A neurodevelopmental basis for BECTS: evidence from structural MRI. Epilepsy Res 2013;105:133–9.