






Time Interval between First and Last Epileptic Seizures and Electroencephalogram Normalization in Benign Childhood Epilepsy with Centrotemporal Spikes: Influencing Factors

Carmen Silvia Molleis Galego Miziara¹  Maria Laura Jorge Micheletto² 
 Virginia Aparecida Gelmeti Serrano³ Denise Harumi Nakanishi³ Mário Ivo Serinoli⁵ 
 Maria Luiza Giraldes de Manreza³  Umbertina Conti Reed³ 

¹ Department of Neurology, Faculdade de Medicina Hospital das Clínicas, Universidade de São Paulo, São Paulo, Brazil

² Department of Bioethics, Faculdade de Medicina do ABC, São Paulo, Brazil

³ Clinical Hospital of the University of São Paulo, São Paulo, São Paulo, Brazil

⁴ Nove de Julho University, São Paulo, Brazil

⁵ Department of Bioethics, Universidade Nove de Julho, São Paulo, Brazil

Address for correspondence Carmen Silvia Molleis Galego Miziara, PhD, Department of Neurology, Universidade de São Paulo Faculdade de Medicina Hospital das Clínicas, Rua Doutor Enéas de Carvalho Aguiar, 255, São Paulo, SP 05403-000, Brazil (e-mail: carmen.miziara@hc.fm.usp.br).

J Pediatr Epilepsy 2020;9:31–35.

Abstract

The aim of this study was to evaluate the interval between the first and last seizures, the normalization of the electroencephalogram (EEG), and to identify factors of influence. Medical records of children were analyzed with benign childhood epilepsy with centrotemporal spikes. Variables age at first and last seizure, gender, interval between the first and last seizure, the first seizure and EEG normalization, lateralization of the epileptiform discharges, and last epileptic seizure and EEG normalization. The mean time between the first and last seizure was 3.34 years. Early onset of seizures and unilateral discharges were factors that increased the interval between the first and last seizures ($p < 0.001$). Interval between the last seizure and EEG normalization was 2.40 years, without influence of age ($p = 0.986$). Interval was shorter in bilateral discharges ($p = 0.035$). The antiepileptic medicine did not alter the natural history of disease progression. In younger children, the interval between last seizure and normalization of the EEG is reduced compared to older children.

Keywords

- ▶ benign childhood epilepsy
- ▶ electroencephalography
- ▶ Rolandic epilepsy
- ▶ seizures

Introduction

Benign childhood epilepsy with centrotemporal spikes (BECTS), also called rolandic epilepsy (RE), is the most common self-limited focal epilepsy, with an estimated prevalence of 20 to 25% in school children with epilepsy.¹ Although the earliest reports of the disease date back to the 16th century, its syndromic components were only characterized by Nayrac and Beaussart (1958) in 1958.^{2,3} BECTS affects children between 6 and 9 years of age, but the

first seizure can occur between 3 and 12 years,⁴ with a slight predominance in males (1.5:1),⁵ and spontaneous resolution in adolescence, usually before 18 years of age, with a peak at 12 to 13 years, with or without medication^{6,7} usually before 18 years of age.

The symptoms observed during the seizures may vary considerably from child to child and, in some cases, from one episode to another.⁸ In most cases, seizures are infrequent, have a short duration, usually lasting only 2 to 3 minutes, and occur during sleep (nonrapid eye movement), without impaired

received

December 13, 2019

accepted after revision

March 4, 2020

published online

April 15, 2020

Copyright © 2020 by Georg Thieme Verlag KG, Stuttgart · New York

DOI <https://doi.org/>

10.1055/s-0040-1709187.

ISSN 2146-457X.

awareness. The main clinical manifestations of seizures consist of unilateral facial sensory (numbness) and/or motor (clonic contractions) symptoms, involvement of the oropharyngeal-laryngeal, including dysarthria (due to loss of the power and coordination of the musculature responsible for the articulation of words) and sialorrhea (autonomic manifestation).⁹

With regard to its electroencephalographic features, BECTS is characterized by normal background activity, with sudden, high-voltage centrotemporal spikes, often followed by sleep-activated slow waves tending to spread out or shift from side to side. These spikes are unilateral in approximately 60% of cases and bilateral in approximately 40%; they may be mono- or multifocal.^{10,11} Study showed correlation between the number of ripples and the number of seizures.¹²

In BECTS, the epileptogenic zone involves a neuronal network of the rolandic cortex surrounding the central sulcus bilaterally (somatosensory cortex) that represents the face and oropharynx and reflects the maturation instability of the age-related lower rolandic region.^{5,13} Although BECTS is one of the most common types of childhood focal epilepsies, clinical, and electroencephalographic factors that may influence the time between cessation of epileptic seizures and normalization of the electroencephalogram (EEG) have not been well studied, a fact that justifies this research.

Methods

This study retrospectively analyzed medical records of children with both clinical and electroencephalographic criteria for BECTS in the Neurology Department of Hospital das Clínicas, Universidade de São Paulo. The variables studied were age of the child at the time of the first and last seizure, gender, time interval between the first and last seizure, between the first seizure and EEG normalization, and also the last epileptic seizure and EEG normalization lateralization of the epileptiform discharges, and treatment with antiepileptic medications (AEMs). The inclusion criteria applied were medical records detailing the clinical and EEG criteria, according to the International League against Epilepsy, after being seizure free for 2 years; at least two consecutive normal EEGs with intervals of at least 2 years between them; medical follow-up for at least 2 years after normalization of the EEG; and at least one normal neuroimaging (brain computed tomography or MRI). Exclusion criteria were children with abnormal neurological examination, severe chronic or psychiatric comorbidities, and EEG without epileptiform discharges generalized discharges at 3 Hz continuous discharges and generalized polyspike. EEGs were performed in sleepiness, sleep, and wakefulness with electrodes distributed according to the international system 10 to 20 and under sleep deprivation. Since many children had epileptiform discharges to the right, to the left, or bilaterally, their lateralization was considered to be the area of predominance of discharges.

Statement of Ethics

This study was analyzed and approved by the Ethics and Research Committee of the Hospital das Clínicas of the Faculty

of Medicine of the University of São Paulo. The research was approved by the Ethics and Research Committee of the Hospital das Clínicas of the Faculty of Medicine of the University of São Paulo. All data were analyzed anonymously. It was a study based on data collection of medical records.

Statistical Analyses

All analyses were performed using Stata software. The level of statistical significance was set at $p < 0.05$. Categorical variables, including sex and lateralization of discharges (uni or bilateral), were compared using Chi-squared tests and continuous variables, including age at seizure onset, age at last seizure, and age at EEG normalization 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. The Shapiro–Wilk’s test was used to verify the normality of the continuous variables (age of the child at first seizure, last seizure, and EEG normalization, interval I (between the first and last seizure), interval II (between the first seizure and EEG normalization), and interval III (between the last seizure and EEG normalization)). The hypothesis H0 was rejected, and the hypothesis of normality could not be excluded, resulting in *p*-values of $p = 0.644$, $p = 0.349$, $p = 0.616$, $p = 0.069$, $p = 0.784$, and $p = 0.134$, respectively.

Results

A total of 274 medical records were evaluated, 58 of which were selected after applying the inclusion and exclusion criteria. The majority of unselected cases were due to the patient’s abandonment of outpatient follow-up. The group consisted of 31 (53.45%) boys and 27 (46.55%) girls.

The average age of the children in the first seizure was 6.35 years (SD: 2.431 from 1.2 to 11.5 years) in the last 9.65 years (SD: 2.16; 4.9–15 years), and at the time of EEG normalization 11.92 years (SD: 2.35; 6.8–16 years; ▶ **Table 1**). EEG normalization was defined as a normal EEG background activity with no spike discharges. In 14 (24.14%) cases, epileptiform discharges were bilateral and 44 unilateral (75.86%), 24 (41.38%) on the left, and 20 (34.48%) on the right.

A total of 17 (29.31%) children received AEM during the period of outpatient follow-up, and treatment time ranged from 2 months to 2 years (mean of 15 months).

Table 1 Time evolution between the onset and end of epileptic seizures, and normalization of the electroencephalogram tracing

	Average time (y)	Standard deviation	95% CI
Interval I	3.34	2.066	2.801–3.888
Interval II	5.53	2.209	4.953–6.115
Interval III	2.40	1.475	2.017–2.793

Abbreviation: CI, confidence interval.

Table 2 Statistical significance between the dependent variable (range) and independent variables (sex, age at onset of seizures, laterality of epileptiform discharges, and antiepileptic medication [regression model])

	Sex	Age (first seizure)	Bilateral discharges	AEM
Interval I	$p = 0.592$	$p < 0.001$	$p = 0.024$	$p = 0.352$
Interval II	$p = 0.547$	$p < 0.001$	$p = 0.670$	$p = 0.308$
Interval III	$p = 0.938$	$p = 0.986$	$p = 0.035$	$p = 0.559$

Abbreviation: AEM, antiepileptic medication.

The medications given were oxcarbazepine (8), sulthiame (6), and valproic acid (3), all in monotherapy. There was no difference between the treated and untreated groups in relation to the average age of the child in the first seizure (t -test: $p = 0.5229$), and the same was true in relation to sex of patients (Fisher's exact test: $p = 0.260$), and between the laterality of epileptiform discharges and administration or not of AEM (Fisher's exact test: $p = 0.767$).

The laterality of the discharge also showed no association with the average age of the child at the time of EEG normalization (analysis of variance: $p = 0.7495$).

According to the t -test, child's sex did not influence the mean age of the child at the first seizure ($p = 0.905$).

Analysis of Intervals

The mean time between the first and the last seizure (interval I) was 3.34 years (SD: 2,066), the mean time between the first seizure and EEG normalization (interval II) was 5.53 years, and between the last seizure and EEG normalization (interval III) was 2.40 years (–Table 1).

Influence of the independent variables sex, age, laterality of epileptiform discharges in EEG, and use of AEM on the intervals studied (–Table 2).

Interval I (between the First and Last Seizure) in Relation to Sex, Age, Laterality, and Antiepileptic Medication

The regression model included as a dependent variable interval I and the independent variables (predictors) sex, age at first seizure, and laterality of epileptiform discharges (bilateral or unilateral), and AEM explains 37.99% = adjusted R2 33.31% of the range variance, having moderate to strong influence; it is a model with statistical significance, $F(4.53) = 8.12$; $p < 0.001$.

The sex and AEM had no statistically significant effect on interval I ($p = 0.592$ and $p = 0.352$, respectively); however, the variables age at the first seizure and bilateral epileptiform discharges showed significance of $p < 0.001$ and $p = 0.024$, respectively.

In these cases, the size of the β effect was strong and moderate with $\beta =$ minus 0.550, and minus 0.251, respectively. There was no multicollinearity problem calculated by the mean variation inflation factor (VIF) 1.02, being close to 1 for all variables. Therefore, the model shows that for an increase of 1 month in the age of the child at the first seizure, the interval I decreases by 0.43 months. In the same way, the

occurrence of bilateral discharges decreases the interval I by 13.15 months.

Interval II (between the First Seizure and Normalization of the EEG) in Relation to Sex, Age, Antiepileptic Medication, and Bilaterality of EEG Discharges

The regression model included interval II as the dependent variable and sex, medication, and age of the child at the first seizure as independent variables (predictors), and epileptic discharge bilaterality explains 25.53% (adjusted R2 = 19.91%) of the variance of the interval, having a moderate to strong relationship and model with statistical significance, $F(4.53) = 4.54$ $p = 0.003$.

The variables sex ($p = 0.547$), AEM ($p = 0.308$), and bilateral EEG discharges ($p = 0.670$) were not statistically significant. However, the variable age of the child at the time of the first seizure was found to have a statistically significant effect, $p < 0.001$.

The age variable at the first seizure has a strong predictor effect with $\beta = -0.47$. The model has no multicollinearity problem calculated by the mean VIF = 1.02, being close to one for all variables. Therefore, the model shows that for an increase of 1 month in the age of the child at the first seizure, interval II decreases by 0.43 months, with statistical difference ($p < 0.001$).

Interval III (between Last Seizure and Normalization of EEG) in Relation to Sex, Age at the First Seizure, and Bilaterality of Epileptiform Discharges

The regression model, including interval III as the dependent variable and sex, medication, age at first seizure, and bilateral EEG discharges independent (predictor) variables, explains 8.77% (adjusted R2 = 1.88%) of the variance of the interval having weak relation and a model without statistical significance, $F(4.53) = 1.27$ and $p = 0.2921$. The variables sex ($p = 0.938$), age at first seizure ($p = 0.986$), and AEM ($p = 0.559$) had no effect with statistical significance. However, the bilateral discharges variable has a statistically significant effect ($p = 0.035$) and moderate predisposition effect of $\beta = 0.28$. Thus, bilaterally epileptiform discharges on EEG increased interval III by 11.60 months.

Discussion

BECTS is the most common form occurring in childhood, with an incidence of around 10 to 20/100,000 children aged 0 to 15 years,¹⁴ accounting for 25% of all nonfebrile seizures (incidence around 2.8 per 100,000 person years).¹⁵ Spontaneous complete remission during or near adolescence is one of the most striking aspects of this epileptic syndrome and occurs in 95.2% of cases.¹⁶ AEMs do not seem to be favorable prognostic factors concerning the duration of the disease and the frequency of focal epileptic seizures.¹⁷

The mean age at onset of epileptic seizures was 6.35 years, a slightly lower age than that found in the literature, showing variation between 3 and 14 years, with a peak between 8 and 9 years of age^{18–20} The remission of epileptic seizures was at 9.65 years on average, an earlier age than that described by

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.

Bouma et al,⁷ who reported the occurrence of remission around 12 years of age. As for EEG normalization, the mean age was around 11 years, a result similar to that described by Lee and You (2018).²¹

The mean time between the first and the last seizure was 3.34 years, similar to those observed by other authors.²² EEG normalization occurred, on average 2 years after the last seizure, data in agreement with that described by other authors.¹⁵ There is a greater chance of remission when epilepsy starts within 5 to 10 years of age, a fact that was observed in the present study.^{19,20} Therefore, our study showed, in agreement with the literature, that the onset of BECTS seizures occurs at preschool age and remission occurs at the onset of puberty, most often regardless of whether AEMs have been used. These data are in line with the self-limited term used for this form of epilepsy, which can be attributed to the genetically determined abnormality of the systemic functional maturation of the developing brain.¹⁴

The normal maturation of the brain allows the gradual increase in the correlation of structural and functional connectivity; however, some situations may alter the normal trajectory of cerebral development, including the epileptic discharges. Besseling et al showed that children with BECTS, when compared with control children, present maturational delay causing reduction in the correlation between structural connectivity and functional connectivity, a fact that improves with age.²³ The disappearance of the spikes, although later than the remission of seizures, is complete and definitive. In our study, the EEG normalization was not influenced by AEM. This differs from the study of Kim et al, in which the AEM significantly reduced the time to EEG normalization. This disagreement can be explained by the disproportion of children treated by those authors (73% of the children were treated) in relation to our study, in which only 29.31% of patients received medication. In both studies, the most commonly used medication was oxcarbazepine since this is the first choice medication in cases of focal epilepsy in children.²⁴

The epileptic discharges present in self-limited epilepsies are the result of spikes of excitation (spikes) and inhibition (slow waves) that occur during a period of excessive activity of excitatory and inhibitory pathways, necessary to brain development. Cortical maturation involves regression of axonal collateral and synapses, both excitatory and inhibitory concomitantly,²⁵ to compensate for this excessive number of synapses that were formed in the early stages of brain development.²⁶ The genetically determined (gene susceptibility)²⁷ delay of brain maturation explains well-established pattern of BECTS onset of childhood seizures and clinical remission and EEG normalization near puberty, with focal spikes in the centrotemporal region being the result of increased focal excitability with possibility for regression.²⁸ Otherwise, epileptogenic process may also be associated with delaying the normal cortical maturation process.²⁹

The consideration above agrees with our findings regarding the influence of the age of onset of crises over the interval between the first and last seizure, since the younger the child at the first seizure, the longer this interval will be, so that for

each month of increase in the age of the child at the first seizure occurrence, the interval is reduced by 0.43 months. Likewise, age also had a strong impact on EEG normalization.

Our results showed that unilateral epileptiform discharges, regardless of whether left or right, were associated with the longest time between the first and last seizures.

In conclusion, our results showed that the age at onset of epileptic seizures is a determining factor for the time of duration of epileptic seizures and for the maintenance of the EEG abnormality. The early onset of epilepsy implies a longer time between the first and last seizure and between the first EEG normalization, but does not influence the interval between the last seizure and EEG normalization.

Conflict of Interest

None declared.

References

- Fejerman N. Benign childhood epilepsy with centrotemporal spikes. In: Engel J Jr, Pedley TA, eds. *Epilepsy: A Comprehensive Textbook*. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:2369–2377
- Nayrac P, Beaussart M. [Pre-rolandic spike-waves: a very peculiar EEG reading; electroclinical study of 21 cases]. *Rev Neurol (Paris)* 1958;99(01):201–206
- Gregory DL, Wong PK. Topographical analysis of the centrotemporal discharges in benign rolandic epilepsy of childhood. *Epilepsia* 1984;25(06):705–711
- Zhao X, Chi Z, Chi L, Shang W, Liu X. Clinical and EEG characteristics of benign rolandic epilepsy in Chinese patients. *Brain Dev* 2007;29(01):13–18
- Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutroumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. *Brain* 2008;131(Pt 9):2264–2286
- Loiseau P, Duché B, Cohadon S. The prognosis of benign localized epilepsy in early childhood. *Epilepsy Res Suppl* 1992;6(Suppl):75–81
- Bouma PAD, Bovenkerk AC, Westendorp RGJ, Brouwer OF. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. *Neurology* 1997;48(02):430–437
- Miziara CSMG, Manreza ML. Benign focal epilepsy of childhood with centrotemporal spikes (BECTS): clinical characteristics of seizures according to age at first seizure. *Arq Neuropsiquiatr* 2002;60(2-B):390–394
- Loiseau P, Duché B, Cordova S, Dartigues JF, Cohadon S. Prognosis of benign childhood epilepsy with centrotemporal spikes: a follow-up study of 168 patients. *Epilepsia* 1988;29(03):229–235
- Dravet C. Benign epilepsy with centrotemporal spikes: do we know all about it? In: Wolf P, ed. *Epileptic Seizures and Syndromes*. London: John Libbey; 1994:231
- Lerman P. Benign childhood epilepsy with centro-temporal spikes (BECT). In: Engel J Jr, Pedley TA, ed. *Epilepsy: A Comprehensive Textbook*. Philadelphia: Lippincott-Raven Publishers; 1997:2307–2014
- van Klink NE, van 't Klooster MA, Leijten FS, Jacobs J, Braun KP, Zijlmans M. Ripples on rolandic spikes: a marker of epilepsy severity. *Epilepsia* 2016;57(07):1179–1189
- Panayiotopoulos CP, Bureau M, Caraballo RH, Dalla Bernardina B, Valeta T. Idiopathic focal epilepsies in Childhood. In: Bureau M, Genton P, Dravet C, Tassinari CA, Thomas P, Wolf P, eds. *Epileptic Syndrome in Infancy, Childhood and Adolescence*. 5th ed. John Libbey Eurotext Ltd; 2012:217–254
- Koutroumanidis M, Panayiotopoulos C. The incidence and prevalence of epilepsy. In: F.J. Rugg-Gunn and HB Stapley, eds. *Epilepsy 2017 From Bench to Bedside: A Practical Guide to Epilepsy*. Oxford: University of Oxford Mathematical Institute; 2017:119

- 15 Neligan A, Sander JW. The incidence and prevalence of epilepsy. In: Rugg-Gunn FJ, Stapley HB, eds. *Epilepsy 2017 From bench to bedside: A Practical Guide to Epilepsy*. ILAE British Chapter; 2017: 3–10
- 16 Berg AT, Rychlik K, Levy SR, Testa FM. Complete remission of childhood-onset epilepsy: stability and prediction over two decades. *Brain* 2014;137(Pt 12):3213–3222
- 17 Peters JM, Camfield CS, Camfield PR. Population study of benign rolandic epilepsy: is treatment needed? *Neurology* 2001;57(03): 537–539
- 18 Callenbach PMC, Bouma PAD, Geerts AT, et al. Long term outcome of benign childhood epilepsy with centrotemporal spikes: Dutch Study of Epilepsy in Childhood. *Seizure* 2010;19(08):501–506
- 19 Mellish LC, Dunkley C, Ferrie CD, Pal DK. Antiepileptic drug treatment of rolandic epilepsy and panayiotopoulos syndrome: clinical practice survey and clinical trial feasibility. *Arch Dis Child* 2015;100(01):62–67
- 20 Kim H, Kim SY, Lim BC, et al. Spike persistence and normalization in benign epilepsy with centrotemporal spikes - Implications for management. *Brain Dev* 2018;40(08):693–698
- 21 Lee EH, You SJ. Factors associated with electroencephalographic and clinical remission of benign childhood epilepsy with centrotemporal spikes. *Brain Dev* 2019;41(02):158–162
- 22 Lerman P, Kivity S. Benign focal epilepsy of childhood. A follow-up study of 100 recovered patients. *Arch Neurol* 1975;32(04): 261–264
- 23 Besseling RMH, Jansen JFA, Overvliet GM, et al. Delayed convergence between brain network structure and function in rolandic epilepsy. *Front Hum Neurosci* 2014;8(704):704
- 24 Franzoni E, Gentile V, Pellicciari A, et al. Prospective study on long-term treatment with oxcarbazepine in pediatric epilepsy. *J Neurol* 2009;256(09):1527–1532
- 25 Dulac O, Milh M, Holmes GL. Brain maturation and epilepsy. *Handb Clin Neurol* 2013;111:441–446
- 26 Swann JW, Smith KL, Brady RJ. Age-dependent alterations in the operations of hippocampal neural networks. *Ann N Y Acad Sci* 1991;627:264–276
- 27 Doose H, Baier WK. Benign partial epilepsy and related conditions: multifactorial pathogenesis with hereditary impairment of brain maturation. *Eur J Pediatr* 1989;149(03):152–158
- 28 Halász P, Kelemen A, Rosdy B, Rásonyi G, Clemens B, Szűcs A. Perisylvian epileptic network revisited. *Seizure* 2019;65:31–41
- 29 Bourel-Ponchel E, Mahmoudzadeh M, Adebimpe A, Wallois F. Functional and structural network disorganizations in typical epilepsy with centro-temporal spikes and impact on cognitive neurodevelopment. *Front Neurol* 2019;10:809