

Serial changes in the paroxysmal discharges in rolandic epilepsy may predict seizure recurrence: A retrospective 3-year follow-up study

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ABSTRACT

Objective: The aim of this study was to assess the electrographic criteria related to seizure recurrence and determine age-related seizure recurrence in children with rolandic epilepsy under long-term follow-up.

Methods: We retrospectively analyzed the data belonging to 109 patients with rolandic epilepsy with sufficient information regarding disease course and follow-up duration longer than 3 years. Patients were divided into two categories: Group A (n: 75), comprised of “patients having fewer than four seizures”, and Group B (n: 34), the “recurrence group comprised of patients having more than four seizures in the first three months”. The number of spikes per minute during both wakefulness and sleep, the localization of spikes other than centroparietal region, and the duration of spike-wave activity were evaluated longitudinally, with repeated electroencephalogram (EEG) recordings every 6 months.

Results: The appearance of rolandic spikes in awake EEGs tended to be more prevalent in Group B than Group A. In Group B, spike rates significantly increased in the 12 and 18 months after onset whereas spike rates increased significantly only 6 months after onset in Group A. Seizure recurrence is mostly seen at 6–8 years, and improvement becomes evident by age 12. The mean number of paroxysmal rolandic discharges during sleep was significantly higher in the younger age groups (3–5, 6–8), and the mean number of spikes per minute significantly decreased at ages 9–11 and over 12.

Conclusion: Our study demonstrates that extended periods of high frequency of paroxysmal discharges, initial frontal EEG focus, and persistence of awake interictal abnormalities are highly effective in predicting seizure recurrence in patients with rolandic epilepsy (RE).

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1. Introduction

Rolandic epilepsy (RE) is the most frequent epilepsy syndrome in school-aged children, accounting for 20–25% of all childhood epilepsies [1,2]. Low seizure frequency with infrequent nocturnal seizures and good seizure control is the characteristic finding that has led to the nomenclature of “benign” rolandic epilepsy. About 10% of the cases have only one isolated seizure with an onset just before or after the child starts school [2]. Decision on starting continuous treatment with antiepileptic drugs (AEDs) is often difficult since AEDs have worrisome side effects on cognition and unclear factors about seizure recurrence in these children.

Although the name “benign rolandic epilepsy” and its early descriptions suggested a benign course, there is now substantial evidence for neuropsychological impairment and cognitive and academic problems in affected children. Numerous literature data have shown language defects, impaired reading performance and auditory discrimination, and memory impairment in rolandic epilepsy [3–11]. Several factors could

account for the atypical evolution in these children. Literature studies on neuropsychological impairments in atypical rolandic epilepsy have shown that interictal epileptiform discharges on electroencephalogram (EEG) may be responsible for disrupting brain function and leading to atypical evolutions [9,12–15].

Most children have only rare seizures and, when treated, their seizures respond well to AEDs. However, in a poorly identified subset of children with rolandic epilepsy, more than one AED is required for effective control of recurrent seizures without any atypical evolution. Extensive information on EEG criteria for seizure recurrence in these patients is still lacking, and there is still a need for clinical and EEG markers that predict seizure recurrence in rolandic epilepsy. Thus, there is a continuing debate about the effect of EEG spike-wave activity in children with seizure recurrence without any atypical evolution. There is only one recent study regarding the frequency of paroxysmal EEG discharges and its correlation with seizure recurrence in rolandic epilepsy. Kanemura et al. showed a significant correlation between seizure recurrence and extended periods of paroxysmal EEG abnormalities in their study [16].

This is the first study to assess the EEG criteria related to seizure recurrence in a large group of children with rolandic epilepsy without atypical evolution under long-term follow-up. This study also

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represents the first attempt to account for the impact of age on seizure recurrence and their significance in relation to paroxysmal discharges.

2. Patient selection and protocol design

The hospital medical records were searched for all children who were diagnosed with rolandic epilepsy. Data belonging to the patients with rolandic epilepsy with sufficient information regarding disease course and follow-up duration longer than 3 years at Gazi University Faculty of Medicine Pediatric Neurology Department outpatient clinic recruited from March 15, 2006 to December 31, 2013 were included in the study. All patients had their first seizure between March 2006 and December 2013. Patients who had their seizure onset ranging from 3 to 14 years of age with normal neurological examination and magnetic resonance imaging were included in the study. Patients who were not regularly followed, who had a concomitant neurological and psychiatric disorder, and who had received a neurological drug other than an AED were not included in the study. The diagnosis was made on characteristic focal clonic seizure manifestation but may be secondarily generalized and a typical EEG with spikes and sharp waves in either of the centrottemporal region.

The information on each patient included the family history of epilepsy; febrile convulsion history; age at onset; the duration, frequency, and number of seizures; and the seizure semiology. According to the clinical presentation, patients were divided into two categories: Group A, comprised of “patients having fewer than four seizures”, and Group B, the “recurrence group comprised of patients having more than four seizures in the first three months”. These groups were determined based on the clinical data of the patients.

- Group A This group consisted of 75 patients who had their first seizures at the age of 4 to 8. All patients had the abovementioned criteria of rolandic epilepsy. They had four or fewer seizures at follow-up.
- Group B This group consisted of 34 patients who first had their seizure at the age of 3 to 7. All patients fulfilled the typical electroclinical characteristics of rolandic epilepsy. Because of seizure recurrence, routine laboratory examination and routine metabolic disorder screening were performed on all these patients. None of these patients had a seizure other than a rolandic or a secondarily generalized seizure.

Carbamazepine (CBZ, 15 mg/kg/day) was the first choice, and sodium valproate (VPA, 20 mg/kg/day) was prescribed if CBZ did not control the seizures.

3. Assessment of interictal EEG findings

We evaluated the serial EEGs of the patients from the onset of the seizures. Interictal EEG was recorded using a digital system with 18 electrodes according to the International 10–20 system during both wakefulness and sleep without sedation. Intermittent photic stimulation and hyperventilation were performed routinely in each patient. Two electroencephalographers (EA, AS) who were blinded to the clinical details and the grouping of the patients analyzed the EEG according to the below mentioned analysis. The dominant region was defined as the localization where spikes are most frequent and higher in amplitude. The readers analyzed the following:

- the number of spikes per minute
- the localization of spikes, unilateral or bilateral centrottemporal
- the localization of spikes other than the centrottemporal region
- the duration of spike-wave activity

The number of spikes was computed during both wakefulness and NREM sleep stages 1 and 2.

The number of spikes was expressed as the number of discharges per minute. These evaluations were made by visual inspection by each reader separately. Interobserver agreement was high ($\kappa = 0.91$).

Initial EEG recordings were performed within 7–10 days after the initial seizure of all patients. In the recurrence group, EEG obtained just before AED administration was selected as the first EEG for evaluation. Repeated EEG recordings were obtained for all patients every 6 months. Electroencephalogram was made at least 3 years for every patient. All EEG recordings from all patients were analyzed in order.

The patients were evaluated in relation to age at first occurrence for each group. First, age at seizure onset was noted for each group. Second, from this pool, the age at which the most frequent seizure recurrence occurred and the number of spikes per minute during both sleep and wakefulness in Group B was evaluated. These data were evaluated on the basis of 4 stages of development. Those age groups were 3–5, 6–8, 9–11, and over 12 years.

3.1. Cognitive function assessment

At onset, all patients were evaluated using the Wechsler Intelligence Scale for Children version II (WISC-II). However, cognitive functions were not evaluated by neuropsychological assessments but only through parental and teacher reports. Families were contacted by phone and if they agreed to participate in the study, questions were then asked about school performance and behavioral aspects of the patient at that time. Therefore, a longitudinal follow-up for cognitive functions could not be evaluated.

4. Statistical analysis

The following parameters were included in the statistical evaluation: the age at onset, gender, family history of epilepsy, and history of febrile seizure. All data are expressed as means of each measure. Continuous variables are expressed as means $\pm$ SD, and categorical variables are presented as frequencies and percentages. Fisher's test, McNemar's test, repeated analysis of variance (ANOVA), Dunnett's test, and Student's *t*-test were used to compare the differences in categorical variables among the two groups, as appropriate. For statistical analysis, SPSS 20.0 statistical software (SPSS, Chicago, IL, USA) was used. In all analyses, $p < 0.05$ was taken to indicate statistical significance. This study was approved by the Ethics Committee of Gazi University Medical Faculty, Turkey.

5. Results

A total of 109 patients with rolandic epilepsy were included in this study. The study population consisted of 59 males (54.1%) and 50 females (45.9%) with a mean follow-up duration of 48.7 ± 18.1 months (3–10 years). The first three-year follow-ups were evaluated, and all assessments were performed during this period. The number of patients as distributed to the groups according to the clinical presentation was as follows: Group A, $n = 75$ (68.8%), and Group B, $n = 34$ (31.2%) (Table 1). The clinical profiles of Groups A and B are given in Table 1. Neurologically, they all appeared to have normal development. There were no differences between the two groups in age at seizure onset, history of neonatal seizure, previous febrile seizure, and laterality of spike foci. Family history of epilepsy ($p = 0.041$) and the number of males were significantly higher in Group B when compared with Group A (Table 1). None of the patients in either of the groups had atypical seizures including atypical absences, negative myoclonus, or oromotor symptoms. There was no difference in seizure semiology between the two groups. Carbamazepine was initiated after two or more seizures. In Group A, the mean seizure frequency was 1.5 seizures, and the mean interval between the first and the second seizure was 1.2 months for patients who had more than one seizure. In Group B, the mean

Table 1
Clinical and demographic features of Groups A and B.

	Group A (n: 75)	Group B (n: 34)	p
Gender	M/F = 35/40	M/F = 24/10	0.02
Age at onset of seizure	7.7	7.8	0.82
Family history of epilepsy	11/75	11/34	0.04
Previous febrile seizure	2/75	0	0.88
Seizure type	FS:SG = 64:11	FS:SG = 29:5	0.67
Seizure lateralization	R:L:BL = 33:35:7	R:L:BL = 17:13:4	0.34
Spike foci side	R:L:BL = 46:29:0	R:L:BL = 17:16:1	0.21

Abbreviations: M: male, F: female, FS: focal seizure, SG: secondarily generalized, R: right, L: left, BL: bilateral.

Statistical significance level was $p < 0.05$

seizure frequency was 3.4 seizures, and the mean interval between the first and the second seizure was 2.8 months. Twenty-two patients received CBZ therapy whereas 12 children were given VPA because of CBZ failure. Seizures disappeared after VPA therapy in all children. The mean duration of treatment is 3.6 years.

The background activities were normal in all children during serial EEGs. The number of spikes were evaluated during both wakefulness and sleep stages 1–2. The appearance of rolandic spikes in initial EEGs in the awake recordings differed between Groups A and B. Spikes were recorded in 18.6% (14/75) of Group A and 79.4% (27/34) of Group B (Table 1). The rate of rolandic spikes in serial awake recordings were significantly higher in Group B ($p = 0.002$). The appearance of rolandic spikes in awake EEGs tended to be more prevalent in Group B than Group A (OR: 4.234, CI: 0.402–324.56). The mean number of spikes per minute in the awake state in Groups A and B was 3.5 and 4.5, respectively. Serial changes of spike frequency were fewer in the awake state than in the sleep state.

In sleep stages 1 and 2, the appearance of spikes in Group B was initially 24 times/min on average whereas the average spike frequency rate in Group A was 17/min. In Group B, a significant increase in the spike frequency rate was observed in the first year. Spike rates increased from 24/min to 44/min. In contrast, interictal abnormalities slightly increased during the first six months in Group A, and spike frequency rate increased from 17 to 24. (Fig. 1). In Group B, spike rates significantly increased in the 12 and 18 months after onset (Dunnett's test; $p < 0.05$ vs initial). In Group A, spike rates increased significantly only 6 months after onset (Dunnett's test; $p < 0.01$ vs initial). Interictal EEG abnormalities persisted longer in Group B than in Group A. Spike rates for the follow-up period was significantly higher in Group B than in Group A (repeated ANOVA, $p < 0.001$).

While none of the patients in Group A showed frontal or occipital foci at seizure onset, thirteen patients (38.2%) had a frontal focus and

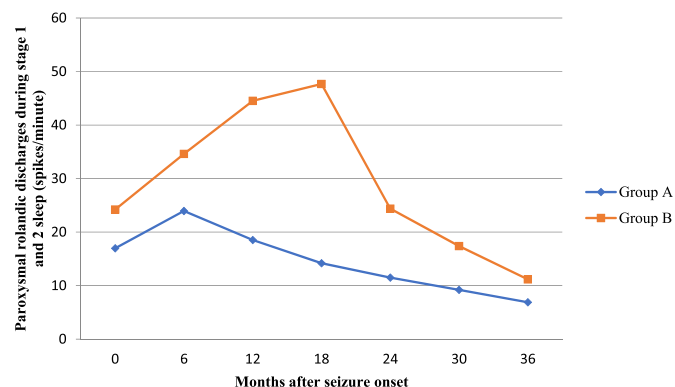


Fig. 1. Sequential paroxysmal rolandic discharges in sleep stages 1 and 2 in both groups. The mean frequency of rolandic discharges (spikes/minute) are shown for Group A (blue diamond) and Group B (orange square).

two patients (5.8%) had an occipital focus at seizure onset in Group B. In serial EEGs, a frontal EEG focus (a spike focus separate from the typical centrotemporal focus in rolandic epilepsy) was observed in 64.7% (22/34) and an occipital EEG focus (occipital EEG focus having a separate occipital spike) in 11.7% (4/34) of the patients in Group B whereas 14.6% (11/75) patients in Group A had a frontal focus. The frontal EEG focus was more prevalent in Group B than in Group A (McNemar's test, $p < 0.001$). The mean duration of frontal EEG focus in Groups A and B was 6 and 12 months, respectively, and showed a significant difference in duration (t -test, $p = 0.02$).

Of the 34 patients who were administered AEDs in Group B, 22 were treated successfully with CBZ, and 12 were treated with VPA. Although there was a risk for CBZ to induce EEG worsening, none of the EEGs evolved to an atypical pattern such as electrical status epilepticus during sleep (ESES) during the follow-up period. However, spike rates increased in 8 patients in Group B during follow-up. This effect was thought to be a consequence of CBZ treatment. These patients also had a seizure recurrence despite CBZ treatment so CBZ was switched to VPA in these patients.

The intelligence quotients (IQs) of the 75 patients in Group A ranged from 91 to 118 (mean: 99.23, SD: 18.45) while those of the 34 patients in Group B ranged from 84 to 112 (mean 97.12, SD: 16.54). There were no significant differences between the two groups ($p = 0.298$). Cognitive functions were not evaluated by formal tests longitudinally in these patients; therefore, we do not have the final IQ levels of the patients. We know only from the parent and teacher reports that no patients showed any neurophysiological problem during the follow-up period in both groups.

The topical distribution of seizure recurrence in different age groups in Group B is shown in Fig. 2. The seizure recurrence is mostly seen at 6–8 years, and improvement becomes evident by age 12. The mean number of paroxysmal rolandic discharges during sleep was significantly higher in the younger age groups (3–5, 6–8), and the mean number of spikes per minute significantly decreased at ages 9–11 and over 12, when more than half of the EEGs became normal. The seizure recurrence and the mean number of spikes in relation to age groups were found to be statistically significant ($p < 0.0001$) (Fig. 3).

6. Discussion

Rolandic epilepsy is a common childhood epilepsy syndrome, usually having benign prognosis and considered under the topic of “benign childhood epilepsies”; since it has both age-related and age-limited characteristics, most patients show spontaneous resolution before or around puberty, sometimes with solely one seizure. Although these features do exist in RE, some patients may develop atypical evolution with a poor outcome, or some may show seizure recurrence without any atypical progression [3,4]. Although few clinical or EEG similarities exist between either atypical evolution and seizure recurrence without

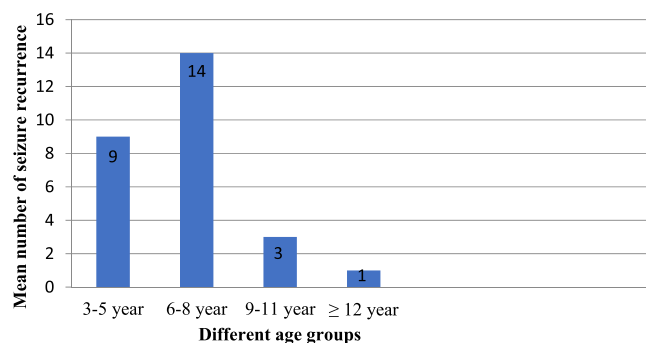


Fig. 2. The distribution of seizure recurrence in different age groups in group B, showing that seizure recurrence is mostly seen at 6–8 years, and improvement becomes evident by age 12.

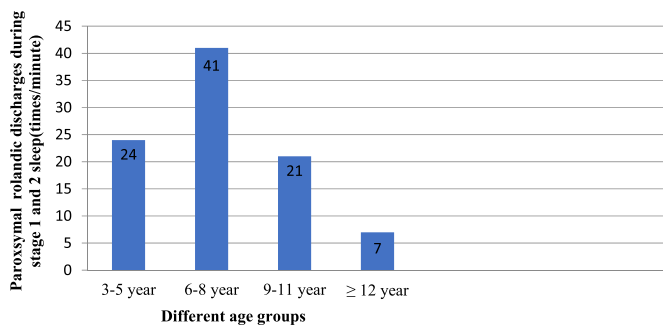


Fig. 3. Age-related sequential paroxysmal rolandic discharges in sleep stages 1 and 2 in Group B.

atypical evolution, the data pertaining to the paroxysmal EEG discharges in patients with seizure recurrence still remain unknown. In our study, we found a significant correlation between seizure recurrence and high frequency of paroxysmal EEG discharges. The results of the present study also support the age-related characteristics of both the seizure recurrence and these high frequency paroxysmal discharges in EEG in RE.

To the best of our knowledge, our study is the first to investigate the impact of change in serial interictal paroxysmal discharges on the seizure recurrence and age-related changes in the largest group of RE patients without any atypical evolution.

Analyses conducted in our population revealed that the rate of rolandic spikes in initial and serial awake recordings was more frequent in the recurrence group. This is an important practical finding since frequent awake rolandic spikes may suggest seizure recurrence without an atypical evolution in these children. Studies performed in atypical cases have also shown that the abundance of awake interictal paroxysmal discharges explain the high risk for developing atypical features like frequent seizures [13]. Confirming previous studies, this finding suggests that the presence and abundance of paroxysmal discharges in the awake state may be correlated with seizure recurrence [16,17].

We also found that rolandic spike rates were higher, and this high frequency persists over long periods in the recurrence group than in the other group. Although comparison is difficult, Verrotti et al. have shown more persistent EEG abnormalities in children with atypical RE than in those with typical RE [17]. Along with our findings, Kanemura et al. have previously demonstrated a high degree of correlation between spike rates and persistence of interictal discharges [16]. This finding reinforces the idea that seizure recurrence may be associated with a combination of high spike rate and extended periods of high frequency paroxysmal discharges. Still, this finding highlights the need for long-lasting studies with more patients.

The results demonstrate a high risk for seizure recurrence in patients with initial frontal EEG focus and extended periods of frontal EEG focus. Studies performed in atypical cases of RE, complicated by neurophysiological features, suggest that frontal EEG focus could lead to both cognitive and behavioral impairments [13]. Similarly, Kanemura et al. showed no difference in the periods of frontal EEG focus between the recurrence and isolated group [16]. None of our patients showed cognitive or behavioral deficits. This level of cause and effect is not easily determined. On the basis of the findings of this study, it is recommended that the extended periods of frontal EEG focus mainly affect cognitive and behavioral development. However, the occurrence of frontal EEG focus in the initial EEG may predict seizure recurrence in children with RE. In a previous study, the presence of a frontal paroxysmal EEG abnormality has been found to be correlated with subsequent development of epilepsy in febrile seizures [18]. In our group of children with recurrent seizures, frontal disturbance may similarly be assumed to be the cause of seizure recurrence. Frontal disturbance cannot be entirely attributed to cognitive or behavioral impairment. According to the nocturnal ictal EEG of patients with RE, seizures frequently start from the

centrotemporoparietal region but sometimes from the frontal area. Interictal spikes often predominate over the centrotemporoparietal regions, but EEG foci frequently shift, multiply, and propagate to more anterior brain structures. Thus, a centrotemporal-to-frontal profile of interictal epileptic activity may occur. Frontal spikes are described as the most typical secondary propagation of epileptic activation triggered by an earlier centrotemporal discharge. Therefore, disturbance in frontal functioning may be more predictable in case of seizure recurrence in RE. Unfortunately, we cannot provide very precise information about the pathophysiology of a frontal EEG focus. Additional explanations are offered to clarify this point.

Concerning the impact of age on seizure recurrence and rate of paroxysmal discharges, seizure recurrence was mostly seen at 6–8 years, and the rate of paroxysmal rolandic discharges during sleep was significantly higher in the younger age groups while showing a significant decrease at older ages. There are few reports regarding the age at seizure onset and the course or the outcomes of RE [19–21]. This is the first study to evaluate the age-related seizure recurrence rate and the rate of paroxysmal rolandic discharges in RE. Most studies recognize that age 5–6 years is the “critical point” up to which the plasticity of the developing brain affected by injury allows the transfer of spike-wave activity, both in adults with partial epilepsy and in children [22,23]. Thus, it seems that brain injury at an early age might have better outcomes because of the ongoing active network reorganization processes. However, this may seem to be in conflict with our findings. How can our findings be explained in the context of the fact that the brain is capable of reorganizing its networks and regaining the lost function in the case of early damage? It is now accepted that patients with epilepsy develop structurally disorganized networks [24]. We speculate that in case of a “static” lesion occurring early in life (before the “critical period”), adjacent brain areas can reorganize the cortical networks and overtake the impaired function. In cases of epilepsy, the process of functional cortical reorganization may be impaired as part (if not most) of the cortex is continuously or intermittently disrupted by epileptic discharges, especially during sleep. Our study does not allow differentiation among the significance of these possibilities. Whatever the mechanisms may be, there are important practical implications: early recognition of risk of seizure recurrence in children with RE may enable timely interventions and prevention of long-term consequences. This puts the question of the need for medical treatment without delay in young children with epilepsy, even if RE is most likely.

A few limitations should be noted in this study. First, the possibility of interictal epileptic discharges may influence the cognitive and behavioral aspects of the patients. Therefore, a longitudinal neuropsychological evaluation to assess the attention, language, reading and auditory performance, and memory should be performed in these patients. Second, the current study is retrospectively designed. More patients with RE should be recruited prospectively to determine the results of the study in the future. In our future work, we plan to overcome these limitations through a long-term prospective study by following the electroclinical and neurophysiological features of the patients. When compared with past studies, the larger sample size is the strength of the present study.

7. Conclusion

The results of the present study provide support for the prediction of seizure recurrence in patients with RE with extended periods of high frequency of paroxysmal discharges, initial frontal EEG focus and persistence of awake interictal abnormalities. Acknowledgment of those phenomena may improve the clinician's ability to manage RE and estimate prognosis in individual cases.

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Conflict of interest

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