


The First Unprovoked Seizure in Typically Developing Children: A Real-Life Setting in Southern Brazil

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Abstract

Aim. To describe the first unprovoked seizure in typically developing children, its clinical characteristics, recurrence rate, and possible risk factors in a real-life setting in Southern Brazil. **Method.** In this retrospective cohort study, medical records of typically developing children aged 28 days to 14 years who had a first unprovoked seizure in a single tertiary care center were reviewed, in a 10-year period (2006–2016). **Results.** Seventy-four children were included, 41 males and 33 females. The most frequent age group of the first seizure was 5 to 10 years and seizure main type was focal (50%). Most seizures occurred while children were awake (70%). All patients underwent an electroencephalogram (EEG), which was normal in 44.6%. Neuroimaging was performed in 81%, in 2 cases the etiology was considered structural, the remaining was classified as unknown. Median follow-up period was 32.5 months. Seizure recurrence rate was 56.7% and age younger than 5 years was a possible risk factor. **Interpretation.** In the subpopulation of Brazilian typically developing children with a first unprovoked epileptic seizure there is a high recurrence rate. An abnormal EEG was a common finding, although it was not associated with a higher risk of seizure recurrence. A possible risk factor was age younger than 5 years, which may suggest a more rigorous follow-up of these patients.

Keywords

seizures, child, recurrence, child development, epilepsy

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The first unprovoked seizure in childhood is a frequent event, with an estimated rate of up to 40 000 children presenting with 1 per year only in the United States and a worldwide incidence that ranges from 56.8 to 204 cases per 100 000 person-years.^{1–4}

In the literature, several risk factors for recurrence after the first seizure are described, and may include abnormal electroencephalogram (EEG) findings, symptomatic etiology, focal seizures, neurodevelopmental delay, intellectual disability, multiple seizures within 24 hours, seizures during sleep, history of febrile seizures, and family history of epilepsy. Nevertheless, the studies often include children with neurodisabilities that are associated with a known increased risk of seizures. In this regard, in typically developing children, namely, those without neurodevelopmental delay, these data become scarce. Moreover, these studies are usually done in developed countries, with a distinct approach regarding medical assistance when compared to developing countries, such as Brazil.

The purpose of this study is to describe the first unprovoked seizure in a subgroup of typically developing children attending a tertiary service in Southern Brazil and identify possible risk factors for its recurrence.

Method

This was a 10-year (between January 2006 and December 2016) retrospective study of typically developing pediatric patients aged 28 days to 14 years who had a first unprovoked seizure at the Center of Pediatric Neurology of the Federal University of Paraná, Southern Brazil, which is an academic and public tertiary hospital. All children were evaluated by a multiprofessional team, that included professionals of pediatric and pediatric neurology, nursing, psychology, and social assistance.

The medical records of 209 children were reviewed and a standardized protocol was used. Children with developmental

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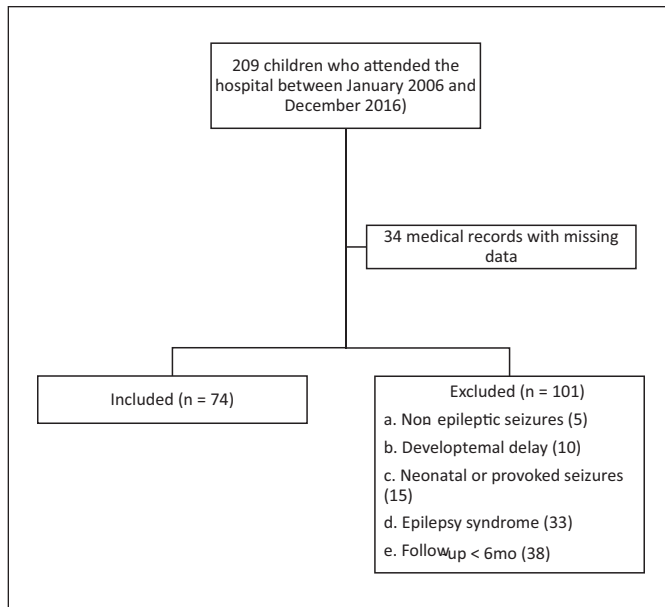


Figure 1. Summary of the inclusion and exclusion criteria.

delay, follow-up duration of less than 6 months, neonatal or provoked seizures, and a diagnosis of an epilepsy syndrome were excluded. Therefore, a total of 74 children were included in the study. This information is illustrated in Figure 1.

The study protocol comprised the following variables: age at the first seizure, gender, sociodemographic data, pregnancy history, classification and duration of the first seizure, number of seizures within the first 24 hours, sleep state, history of febrile seizures, family history of epilepsy, EEG and neuroimaging (brain computerized tomography and magnetic resonance imaging) findings, learning disabilities and formal neuropsychological evaluation with Wechsler Intelligence Scale for Children (WISC) III or IV, behavioral problems, treatment with antiepileptic drugs, etiology and recurrence. After analyzing these variables, possible risk factors for seizure recurrence were assessed.

Patients were divided into groups considering their age at the first seizure, as follows: (1) between 28 days and <1 year, (2) 1 to 3 years, (3) 3 to 5 years, (4) 5 to 10 years, and (5) 10 to 14 years.

In particular cases, antiepileptic treatment was offered after the first unprovoked seizure, that is, in those cases with multiple risk factors for recurrence previously reported in the literature, such as epileptiform discharges on EEG, family history of epilepsy and seizure during sleep, and also for participants with difficult access to medical care.

The EEG findings were categorized as (1) normal, (2) focal epileptic discharges, (3) generalized epileptic discharges, (4) focal background slowing, and (5) diffuse background slowing for age. Non-specific neuroimaging findings, such as discrete white matter hyperintensities, arachnoid cysts, ventricular asymmetries and hippocampal malrotations were not considered seizure causal factors.

Patients were followed-up every 3 to 6 months, or sooner if necessary, solely at clinic visits, with evaluation by the entire multiprofessional team.

Definitions and Classifications

This study used the new International League Against Epilepsy (ILAE) practical clinical definitions.^{5,6} The definition of an unprovoked seizure was one or more seizures within 24 hours and recovery of consciousness between episodes, without a temporary or reversible factor able to reduce the threshold for the occurrence of epileptic seizures, such as fever, concussion, or sleep deprivation. Seizure types were classified as focal, generalized, and unknown and etiology was divided into structural, genetic, infectious, metabolic, immune, and unknown.⁷ Epilepsy was diagnosed when (1) 2 or more seizures occurred more than 24 hours apart, (2) 1 unprovoked seizure and a high recurrence risk of at least 60%, and (3) clinical and EEG findings characterizing an epilepsy syndrome.

Statistical Analysis

The variables were analyzed using Student's *t* test, Fisher's exact test, and Pearson correlation. The level of statistical significance was established at $P < .05$.

Ethical Approval

The study protocol was approved by the Ethics Committee of the Clinical Hospital of the Federal University of Paraná, Brazil (CAAE 63661317.6.0000.0096).

Results

Epidemiology and Clinical Presentation

The study cohort included 74 typically developing children who had a first unprovoked seizure; 55.4% were male. The median follow-up period was 32.5 months (ranging from 6 to 132 months). Half of the participants (50.7%) lived in the metropolitan region or cities in the countryside of the state of Paraná and the other half was from Curitiba, the capital of Paraná. Parents' educational level was low, with virtually all respondents (a total of 131 parents) having incomplete elementary or high school education.

The most frequent age group of children who had the first unprovoked seizure was 5 to 10 years old (39.2%), followed by 10 to 14 years old (20.3%), as shown in Figure 2.

The first unprovoked seizure was classified as generalized in 17.6% of cases, focal in 9.5%, focal with evolution to bilateral tonic-clonic in 40.5%, and indeterminate in 32.4% (Figure 3). In 22% of the sample, multiple seizures occurred within the first 24 hours and, in most cases, the seizure occurred during wakefulness (70%). A history of previous febrile seizures was positive in 8.5% and in 52% of the cases there was a family history of epilepsy in first- or second-degree relatives.

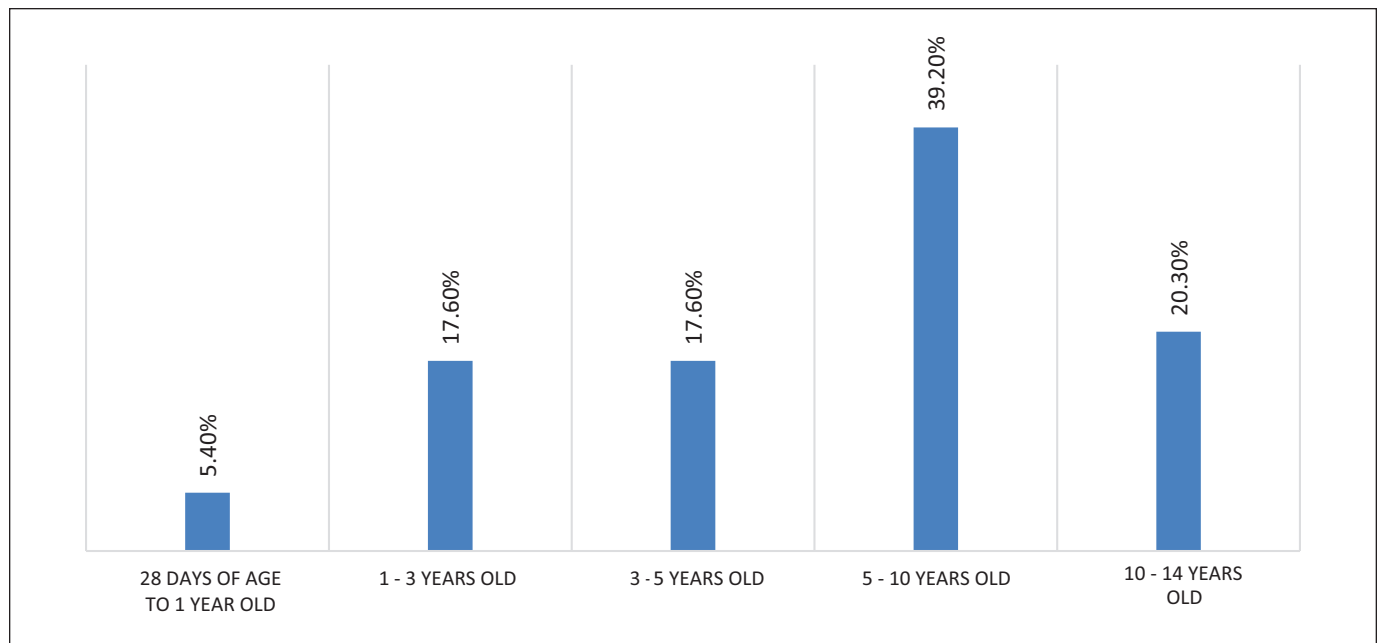


Figure 2. Percentage of children who had the first seizure according to age groups.

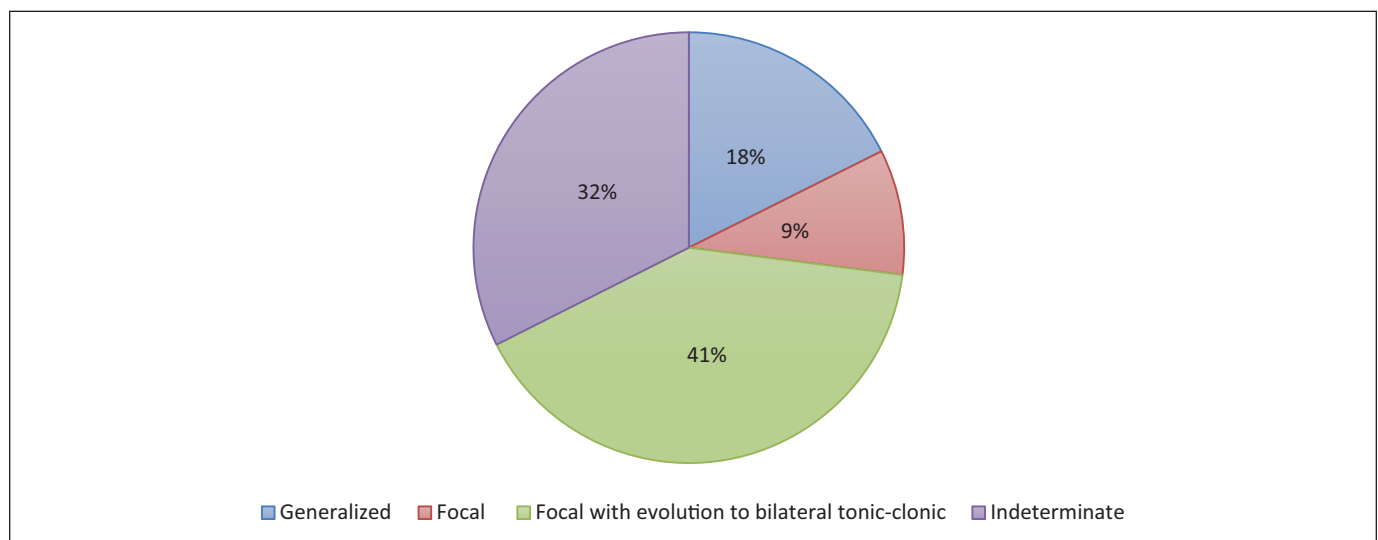


Figure 3. Clinical characteristics of the first seizure.

The general clinical characteristics of the participants are summarized in Table 1.

EEG and Neuroimaging Results

EEG was performed in every participant, as literature recommends. EEG was normal in 44.6% cases. In 27% there was focal epileptiform activity; in 6.7% generalized epileptiform activity; focal background slowing in 13.5% and diffuse background slowing in 8.1%. Therefore, the most frequent abnormal finding was the occurrence of focal epileptiform activity. A new EEG was requested for 60 participants during the

follow-up, and only 20% had focal or generalized epileptiform activity. The data related to the first EEG are summarized in Figure 4.

Structural neuroimaging was available in 81% (61 out of 74) of the sample, cranial computed tomography (CT) scan was performed in 29 patients and magnetic resonance imaging (MRI) in 46 patients, and both modalities were performed in 14 participants. Only 2 cases had a well-defined structural etiology—1 participant with multiple calcifications on CT secondary to congenital toxoplasmosis and one case of periventricular leukomalacia, both, however, with typical neurodevelopment. The etiology of the other participants was classified as

Table 1. General Clinical Characteristics of the Participants (n = 74).

Most frequent age group	5-10 years
Gender, n	41 male, 33 female
Family history of epilepsy, n (%)	38 (52)
History of febrile seizures, n (%)	6 (8.5)
Classification of the first seizure, n (%)	
Generalized	13 (17.6)
Focal	7 (9.5)
Focal with evolution to bilateral tonic-clonic	30 (40.5)
Indeterminate	24 (32.4)
Duration of the first seizure, n (%)	
More than 5 minutes	45 (63.4)
Less than 5 minutes	26 (36.6)
Number of seizures within the first 24 hours, n (%)	
One	57 (78)
Multiple episodes	16 (22)
Sleep state, n (%)	
Awake	21 (30)
Sleep	49 (70)
EEG, n (%)	
Normal	33 (44.6)
Focal epileptic discharges	20 (27)
Generalized epileptic discharges	5 (6.7)
Focal background slowing for age	10 (13.5)
Diffuse background slowing for age	6 (8.1)

unknown, according to the new classification of epilepsy by ILAE.

Pregnancy History

About a quarter of pregnancies (18 out of 71 with available data) had clinical complications, such as prematurity, hypertensive disorders, treated congenital toxoplasmosis, gestational diabetes mellitus, among others. Birth weight was considered normal in most cases (87.7%), and vaginal delivery accounted for 64% of births. The Apgar scale was available to 35 participants, and only 1 case scored less than 7 at the 5-minute mark.

Comorbidities

Clinical comorbidities were assessed from the medical records and learning disabilities was the most identified (31%), followed by behavioral problems, that included irritability, aggressiveness, and psychomotor agitation, accounting for 23% of the sample. Tension headache, attention deficit hyperactivity disorder (ADHD) and mood disorders were also found. Table 2 lists all identified comorbidities.

Cognitive Assessment

A formal neuropsychological evaluation was performed in 35 out of 74 participants by qualified psychologists, divided in multiple sessions depending mainly on the child's cooperation.

The test used was WISC-III and -IV), which is the most frequently used test to evaluate the intelligence quotient in the pediatric population. Most of our sample (51.4%) had total IQ classified as average, 31.4% as low average, and 14.3% were classified as superior. One participant was considered borderline. More than half of the participants (65.7%) were using an antiepileptic drug at the time of the evaluation.

Treatment

Antiepileptic drugs were offered to 62.2% of the participants after the first unprovoked seizure, and carbamazepine was the most used (32.4%), followed by valproic acid and phenobarbital (both 12.2%). About 30% of these participants experienced side effects from medication, including irritability, weight gain, drowsiness, skin rash, and gastric intolerance.

Seizure Recurrence

Of the 74 participants, 42 (56.7%) experienced seizure recurrence during the study period. In 80.9% of the participants with seizure recurrence, the relapse occurred within the first year after the first unprovoked seizure. Of the 39 participants who experienced relapses, 33 (84.6%) had a single recurrence, 4 (10.2%) had between 10 and 20 seizures, and 2 (0.05%) had more than 20 episodes.

There was no statistically significant association between seizure recurrence and follow-up period, treatment with antiepileptic drugs, family history of epilepsy, history of febrile seizure, classification and duration of the first seizure, number of seizures within the first 24 hours, sleep state, and EEG or neuroimaging findings ($P > .05$).

Among children who recurred, those younger than 5 years had a risk of recurrence 2.5 greater than those aged 5 years or older (odds ratio 2.55; 95% CI [0.95–6.80]). Also, the cesarean section was associated with an increased risk of recurrence, being 3.6 greater when compared with vaginal delivery.

Discussion

Despite widespread knowledge about the first unprovoked seizure in childhood, in the subgroup of typically developing children the natural history of the event is still unclear as few studies have focused exclusively on them.⁸⁻¹⁰ Hence, our study provides information regarding the clinical presentation and evolution of these patients at an uncontrolled environment, which is, in fact, the closest to the reality of these patients' daily care in developing countries, such as Brazil. Understanding the natural history of an unprovoked first seizure in typically developing children can not only facilitate the management of these patients, but also reduce its psychosocial impact.

In this cohort, there was no statistically significant difference between genders (41 males and 33 females) and the most frequent age group who had a first unprovoked seizure was 5 to 10 years, which is in agreement with literature data.⁹⁻¹⁴ The main seizure type was focal, making up 50% of the sample,

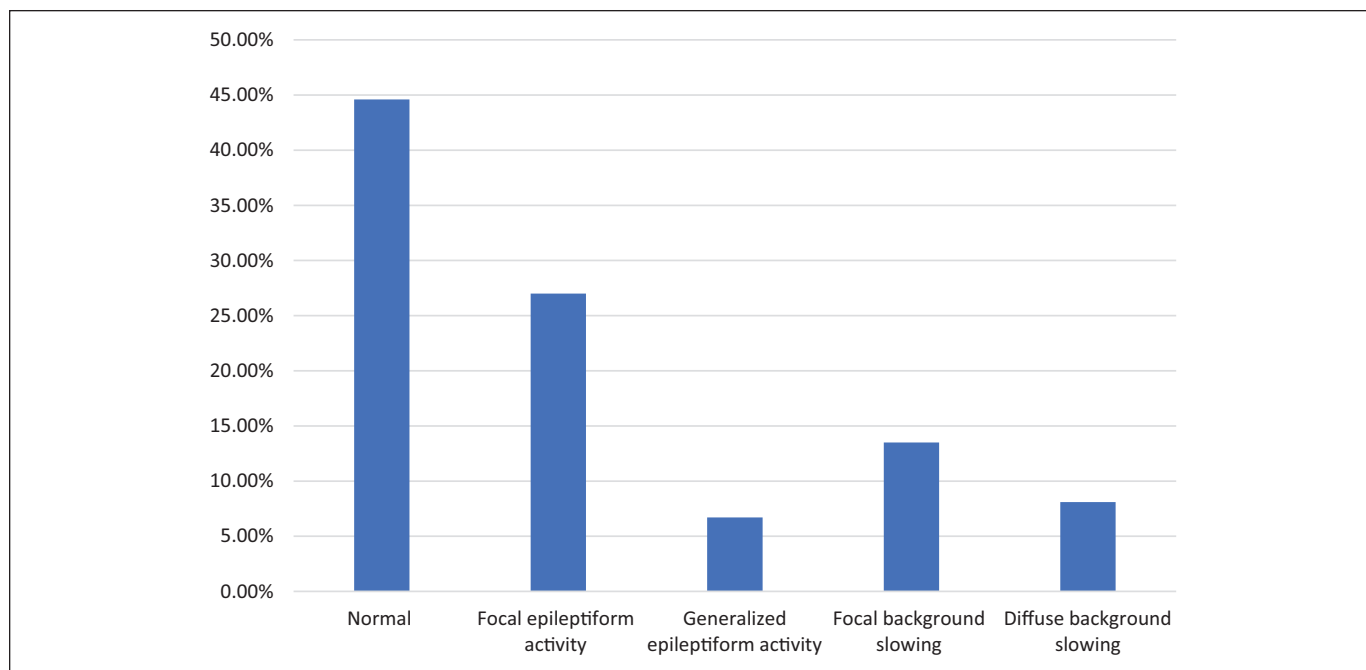


Figure 4. Data from patients' first EEGs.

Table 2. Participants' Clinical Comorbidities (n).

Tension headache	10
Attention deficit hyperactivity disorder	6
Prematurity	3
Mood disorders	3
Migraine	2
Sleep disorder	1
Breath-holding spells	1
Congenital hip dislocation	1
Prurigo strophulus	1
Asthma	1
Essential tremor	1
α-thalassemia	1
Micropenis	1

with or without evolution to bilateral tonic-clonic. We also found a high frequency of indeterminate seizures, accounting for 32.4%, although this can be explained by the difficulty in properly obtaining data characterizing the seizure in the pediatric population. Generalized onset seizure corresponded to a minority of 17.6%.

In Brazil, Scotoni et al¹⁴ conducted a prospective study with 213 children who had a first unprovoked seizure classified as cryptogenic/idiopathic. The study average follow-up time was 25.7 months and no participant received antiepileptic treatment after the first seizure. The most frequent seizure type was focal, which is similar to our results, which also showed a higher frequency of focal seizures, and this might be due to common ethnic, genetic, and clinical characteristics between the 2 Brazilian groups. However, it is worth noting that this study

does not mention the neurological development of these children and it has a prospective design, which may impair the parallel with our results.

Conversely, Kim et al⁹ reviewed retrospectively 152 medical records of solely typically developing children aged 5 months to 17.5 years with a first unprovoked seizure. They reported a much higher frequency of generalized seizures in their study comparing to ours. Despite these differences in seizure semiology, the Kim et al⁹ study corroborates our findings, that is, in their study the type of seizure was not considered a risk factor for recurrence in typically developing children as well.

Seizures occurred in 49 (70%) children during sleep and in 21 (30%) children while awake and family history of epilepsy was positive in 38 cases (52%), both with no statistically significant association with seizure recurrence. That finding is consistent with the results of Kim et al,⁹ who also studied the subgroup of typically developing children. Prior febrile seizures were seen in less than 10% of our sample and it was not associated with a higher risk of seizure recurrence, in accordance to previous studies.^{9,12-14}

Neuroimaging studies were obtained in 61 patients and in virtually all the children the etiology was considered indeterminate. However, prior studies have identified a higher frequency of structural etiologies (about 16%) in typically developing children.^{9,10} This can be explained by the design of our study. First, not all participants underwent a neuroimaging study since, as in most developing countries, our institution also endures significant financial restraints. Second, these studies included only MRI scans, with a known superior sensitivity and specificity for the identification of certain brain lesions,

such as malformations of cortical development, when comparing to CT scans, included in our study. Thus, the high frequency of unknown etiology most likely represents these limitations.

Our study did not find a statistical significance between an abnormal EEG and seizure recurrence, although it has been considered a main risk factor by other authors.¹¹⁻¹⁷ However, our results are similar to studies that included only typically developing children,^{8,9} which may demonstrate that this specifically subgroup of children might have distinctive risk factors for seizure recurrence. Nevertheless, for a better understanding of the EEG role as a risk factor in this specific population, prospective studies are needed.

Our seizure recurrence rate was 56.7%, slightly higher than what has been reported on literature,^{8,11-14,17} even when compared specifically with the Brazilian study,¹⁴ which had a recurrence rate of 34%. Yet most studies include children with intellectual disability or global developmental delay. When we narrow the study population to children with typical development, we find rates closer to those found in our study,^{9,10} namely, Kim et al⁹ reported 63.7% of seizure recurrence in their sample and Arthur et al¹⁰ found a seizure recurrence rate of 66.4%. Therefore, one hypothesis that should be questioned is whether this specific study population does not have a distinct behavior regarding recurrence, which would have direct implication in its treatment. Most seizure recurrences (80%) occurred within the first year after the first episode, a fact that has been previously described in literature.^{11,13,14,16}

In this regard, there was no statistically significant association between seizure recurrence and family history of epilepsy, history of febrile seizure, sleep state, duration or number of seizures, seizure classification, abnormal EEG or neuroimaging, and antiepileptic treatment after the first episode. Although we did not find a statistically significant association between seizure recurrence and antiepileptic treatment, it is important to emphasize that it has been described that the antiepileptic treatment can reduce the risk of relapse after a first seizure when compared to placebo, but it does not modify the long-term prognosis of epilepsy.¹⁸ The treatment can also increase the incidence of adverse effects and we did find a high proportion of adverse effects in our sample.

However, a statistically significant association was found between cesarean section and an age less than 5 years at the time of the first unprovoked seizure.

The association between the cesarean section and the first seizure has been described before², but not its association with seizure recurrences. In our study, participants delivered by cesarean section had a 3.6 times higher risk of recurrence compared to those born by vaginal delivery (odds ratio 3.63, 95% CI [1,23-10,71]). However, this finding was considered a fortuitous association since the cesarean section has precise indications related to both maternal and fetal distress and might be masking unidentified pre- and perinatal risk factors.

A statistically significant association was found between seizure recurrence and the first seizure occurring in typically developing children younger than 5 years ($P = .01$). This

finding, in particular, is not confirmed by recent studies. One possible explanation would be brain immaturity, already known in these children, reducing the threshold of epileptic seizures due to the imbalance between excitatory and inhibitory mechanisms.¹⁹

Limitations and Conclusion

Some pertinent considerations should be made concerning the present study. First, it is a retrospective study based on medical records, which may alter the results found, especially due to lack of data. Additionally, this methodological design might falsely select the study sample, notably by excluding patients who did not present with a second seizure and, therefore, lost follow-up. That possible bias can artificially increase the seizure recurrence rate observed in the present study. On the contrary, precisely because its retrospective design, it is possible to perform a new analysis of the available information, reclassifying them according to the new operational definitions, reducing the risk of semiological classification bias. In addition, to reduce a possible selection bias, strict inclusion and exclusion criteria were used, in order to homogenize the group to be studied. This decision has not only positive points, such as the increase in internal validity, but also negative points, such as the reduction of external validity, reducing the capability to generalize our results to other segments of the population. With strict inclusion and exclusion criteria, there was also a reduction in sample size. One positive point of this study is that it approaches the reality of medical care provided for these children in Brazil.

In conclusion, typically developing Brazilian children often present a first unprovoked seizure between 5 and 10 years old, particularly while awake, and in the majority of cases the EEG is abnormal. In our sample, the antiepileptic treatment did not alter the risk of recurrence, which was close to 60%. The only statistically significant risk factor was age less than 5 years, which may suggest that these specific children should undergo a more strictly surveillance. However, prospective studies that specifically follow typically developing children after a first unprovoked seizure will be essential to corroborate these findings.

Author Contributions

Mayara de Rezende Machado substantially contributed to the study conception, acquisition and interpretation of data and drafted the manuscript.

Isac Bruck contributed to the study conception and acquisition of data and critically revised the manuscript.

Luciano de Paola contributed to the study interpretation and critically revised the manuscript.

Mônica Nunes Lima Cat contributed to analysis and interpretation of data and critically revised the manuscript.

Sérgio Antonio Antoniuk contributed to the study conception and interpretation and critically revised the manuscript.

Carlos Eduardo Soares Silvado contributed to analysis and interpretation of the data and critically revised the manuscript.

All authors gave final approval.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study protocol was approved by the Ethics Committee of the Clinical Hospital of the Federal University of Paraná, Brazil (CAAE 63661317.6.0000.0096).

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Supplemental material

Supplemental material for this article is available online.

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