Clinical Research

Risk of seizure recurrence in children with new-onset afebrile seizure

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ABSTRACT

BACKGROUND A seizure is a brief change in the normal neuronal electrical activity of the brain that causes changes in consciousness, perception, behavior, or movement. This study aimed to evaluate clinical findings, initial electroencephalography (EEG), and brain imaging findings as predictors of seizure recurrence after the first nonfebrile seizure.

METHODS This prospective follow-up study was conducted at Azadi Teaching Hospital, Kirkuk from July 2019 to January 2022 and enrolled 150 patients, ranging from 1 month to 15 years of age, who presented with their first afebrile seizure. The seizure types were classified based on the International League Against Epilepsy in 2017. A brain imaging with EEG was performed within 72 hours after admission.

RESULTS The median age of the patients was 5 years. A higher risk of seizure recurrence occurred in patients with focal seizure (relative risk [RR] = 6.604) (95% confidence interval [CI] 3.975–10.971), seizure occurrence at sleep (RR = 3.815) (95% CI 2.410–6.039), an abnormal neurological presentation such as Todd's paralysis (RR = 1.739) (95% CI 1.252–2.415), a positive family history of seizures (RR = 2.333) (95% CI 1.598–3.408), abnormal EEG (RR = 0.171) (95% CI 0.092–0.318), and abnormal brain image findings (RR = 0.681) (95% CI 0.492–0.941) within 72 hours. Seizure recurrence was not correlated with sex.

CONCLUSIONS Early and late childhood new-onset afebrile seizures with a positive family history, focal epilepsy, seizure during sleep, prolonged attack duration with frequent attacks within 24 hours, and abnormal initial EEG and brain image had a high risk of seizure recurrence.

KEYWORDS electroencephalography, neuroimaging, recurrence, seizure

A seizure refers to a short alteration in the typical electrical activity of brain cells, resulting in shifts in awareness, conduct, sense, or motion. Epilepsy represents a recognized neurological condition marked by recurrent seizure episodes, affecting approximately 65 million people worldwide.[1] Seizures are classified as febrile and afebrile. Various underlying pathological conditions, such as electrolyte imbalance, genetic triggers, brain injuries from either trauma or non-trauma, and neurodevelopmental and cardiovascular diseases, can cause abnormal neuronal activity without fever.[2] Therefore, seizure diagnosis is challenging and raises concerns about its underlying causes and the probability of recurrence.

Patients with the first unprovoked seizure should be closely reviewed to determine whether the index events constitute epilepsy or whether the patients are at a higher risk of experiencing seizure recurrence. This evaluation aims to guide diagnostic ceonsiderations, treatment initiation, and administration of anti-seizure

medications to reduce the life-threatening effects of prolonged seizures and status epilepticus,[3] as well as global cognitive impairment.[4]

The first seizure episode is a life-changing event with psychophysical consequences.[5] Patients must be appropriately assessed and managed immediately after an unprovoked seizure. Although the probability of seizure recurrence may be uncertain, clinicians should review the available evidence. When assessing patients after their first seizure, physicians must look for predisposing factors for seizure recurrence and accordingly stratify the risk of future events.

Despite extensive research on seizures and epilepsy, there remains a critical gap in the literature pertaining specifically to children with new-onset afebrile seizures. While previous studies have explored aspects of seizure diagnosis and management, there is a paucity of research dedicated to understanding the predictive factors associated with seizure recurrence following the initial nonfebrile seizure in pediatric patients. The significance of this study lies in its focus on filling this knowledge gap, as it seeks to provide valuable insights into the evaluation of children who experience their first unprovoked seizure. Therefore, this study aimed to evaluate clinical, initial electroencephalography (EEG), and brain imaging findings as predictors of seizure recurrence after the first nonfebrile seizure.

METHODS

This study was conducted from July 2019 to January 2022 and enrolled 150 patients who experienced their first afebrile seizure at the outpatient clinic and the Department of Emergency Pediatrics and Neurology of Azadi Teaching Hospital. The study population included 77 males and 73 females, ranging from 1 month to 15 years of age. Children who arrived at the hospital more than 72 hours after the seizure event, as well as patients whose caregivers and medical records did not provide sufficient information for the proper classification of seizures and mimics of seizures, were excluded from the study.

Seizures were classified according to the International League Against Epilepsy 2017 classification, distinguishing between generalized, partial, and unidentified seizure types. According to this classification, a second seizure attack more than 24 hours after the first afebrile seizure was considered a recurrence. All patients were questioned about their family history, number and duration of attacks, associations with vomiting, sphincter loss, Todd's paralysis, and seizure recurrence during follow-up. Follow-up assessments were conducted 1, 3, 6, and 12 months after the first seizure. Blood samples were drawn from all patients at admission for routine laboratory studies. Complete blood counts, blood sugar, serum potassium, sodium, magnesium, and calcium levels were assessed to exclude possible metabolic disturbances that might precipitate or contribute to future seizures, but was not presented in this paper. Brain imaging was performed on 95 patients (63.3%). EEG was performed on 117 (78.0%) patients within 72 hours of hospital admission using a 16-electrode machine (Nihon Kohden, Japan) for 30 min at a speed of 30 mm/s and an amplitude of 70 mV.

The study was conducted following the 2013 World Medical Association Declaration of Helsinki guidelines and was approved by the Research Ethics Committee of the University of Kirkuk College of Medicine, Iraq (decision no. 22, date: 18.1.2023). Informed oral consent was obtained from all participants prior to the study.

Statistical analyses were performed using the SPSS software version 26 (IBM Corp., USA). Continuous data are presented as mean (standard deviation), and categorical variables are summarized as numbers (n) and percentages (%). Groups were compared using chi-square tests (categorical variables) and independent sample *t*-tests (normally distributed continuous variables) for the number of seizures within 24 hours, duration of seizure episodes, and seizure recurrence. Relative risk (RR) was calculated to assess the risk of seizure recurrence for all independent variables. A *p*-value of <0.05 was considered statistically significant.

RESULTS

The median age of the patients was 5 years, with the majority (65.3%) being <6 years old. While 51.3% of patients were male, the remaining were female, and 68.0% experienced seizures lasting ≤5 min.

Generalized tonic-clonic seizures were the most common type, accounting for 61.0% of cases, and most seizures (54.0%) occurred while patients were awake. Approximately 44.0% of patients had a family history of seizures, while 50.0% experienced vomiting and loss of sphincter control during seizure attacks. Additionally,

Table 1. Demographic characteristics and the risk of seizure recurrence

Characteristics	Total cases (N = 150)	Recurrence		RR (95% CI)	*p*
		Yes, n (%) (N = 68)	No, n (%) (N = 82)		
Age (years)					**0.01**‡
1–5	98	43 (63)	55 (67)	1.00	
6–10	33	11 (16)	22 (27)	0.842 (0.625–1.134)	0.53§
11–15	19	14 (21)	5 (6)	2.133 (0.985–4.618)	**0.04**§
Sex					0.76¶
Female	73	34 (50)	39 (48)	1.00	
Male	77	34 (50)	43 (52)	0.948 (0.667–1.347)	
Duration of attack (min)					**0.0001****
≤5	102	23 (34)	79 (96)	1.00	
>5	48	45 (66)	3 (4)	12.392 (4.122–37.252)	
Vomiting					0.74¶
Yes	75	35 (51)	40 (49)	1.061 (0.746–1.508)	
No	75	33 (49)	42 (51)	1.00	
Sphincter loss					0.74¶
Yes	75	33 (49)	42 (51)	0.943 (0.663–1.340)	
No	75	35 (51)	40 (49)	1.00	
Todd's paralysis					**0.004**¶
Yes	29	20 (29)	9 (11)	1.739 (1.252–2.415)	
No	121	48 (71)	73 (89)	1.00	
Seizure type					**0.0001**¶
Generalized	91	13 (19)	78 (95)	1.00	
Focal	53	50 (74)	3 (4)	6.604 (3.975–10.971)	
Unidentified	6	5 (7)	1 (1)	1.143 (0.858–30.839)	
Family history of seizures					**0.0001**¶
Yes	66	44 (65)	22 (27)	2.333 (1.598–3.408)	
No	84	24 (35)	60 (73)	1.00	
Seizure occurrence					**0.001**¶
Awake	81	16 (24)	65 (79)	1.00	
Sleep	69	52 (76)	17 (21)	3.815 (2.410–6.039)	
EEG finding*					**0.0001**¶
Normal	57	12 (18)	45 (55)	1.00	
Abnormal	60	49 (72)	11 (13)	0.171 (0.092–0.318)	
Brain image type performed†					**0.0001**¶
CT	61	34 (50)	27 (33)	1.00	
CT/MRI	34	26 (38)	8 (10)	0.258 (0.154–0.432)	
Brain imaging results†					**0.0001**¶
Normal	47	24 (35)	23 (28)	1.00	
Abnormal	48	36 (53)	12 (15)	0.681 (0.492–0.941)	

CI=confidence interval; CT=computed tomography; EEG=electroencephalography; MRI=magnetic resonance imaging; RR=relative risk
*Missing data: 33 cases (26 no recurrence, 7 recurrence); †missing data: 55 cases (47 no recurrence, 8 recurrence); ‡one-way analysis of variance; §post-hoc Tukey with 1–5 years group as reference; ¶chi-square test, significant if $p<0.05$; **independent *t*-test

Table 2. Association between the risk of seizure recurrence and the results of EEG and brain imaging

Variables	Total cases (N = 150)	Recurrence		$p^{\ddagger}$
		Yes, n (%) (N = 68)	No, n (%) (N = 82)	
EEG findings*				**0.0001**
Normal	57	12 (18)	45 (55)	
Abnormal	60	49 (72)	11 (13)	
Focal spikes	16	13 (19)	3 (4)	
Focal spikes and slow wave	15	12 (18)	3 (4)	
Temporal sharp-wave discharges	6	5 (7)	1 (1)	
Generalized spikes and slow waves	6	4 (6)	2 (2)	
Frontal sharp wave discharges	6	6 (9)	0 (0)	
Centro-temporal spikes	5	5 (7)	0 (0)	
Focal slowing	5	3 (4)	2 (2)	
Occipital spikes	1	1 (1)	0 (0)	
Brain imaging results†				**0.0001**
Normal	47	24 (35)	23 (28)	
Abnormal	48	36 (53)	12 (15)	
White matter hyperintensities	15	8 (12)	7 (9)	
Volumetric reduction of the brain hemisphere	5	4 (6)	1 (1)	
Ventricular asymmetry	4	1 (1)	3 (4)	
Subdural/epidural collection	3	3 (4)	0 (0)	
Mesial temporal sclerosis	3	3 (4)	0 (0)	
Venous sinus thrombosis	3	3 (4)	0 (0)	
Focal cortical dysplasia	2	2 (3)	0 (0)	
Feature of tuberous sclerosis	2	2 (3)	0 (0)	
Vascular malformation	2	1 (1)	1 (1)	
Feature of Herpes simplex encephalitis	2	2 (3)	0 (0)	
Absent corpus callosum with severe cerebral atrophy	2	2 (3)	0 (0)	
Right temporal arachnoid cyst	1	1 (1)	0 (0)	
Acute disseminated encephalomyelitis	1	1 (1)	0 (0)	
Subcortical heterotopia	1	1 (1)	0 (0)	
Lissencephaly	1	1 (1)	0 (0)	
Rasmussen encephalitis	1	1 (1)	0 (0)	

EEG=electroencephalography
*Not performed: 33 cases (26 no recurrence, 7 recurrence) ; †not performed: 55 cases (47 no recurrence, 8 recurrence); ‡chi-square test, significant if $p<0.05$

19.3% of patients had Todd's paralysis after the attack. While 32.0% of the cases showed abnormal brain imaging, 31.3% had normal findings. Abnormal EEG findings were observed in 40% of patients.

The seizure recurrence rate was 45.3%. Factors significantly associated with seizure recurrence included seizure duration >5 min, Todd's paralysis, occurrence of focal seizures, family history of seizures, and seizures during sleep ($p<0.05$). However, based on the RR analysis, seizures occurring during sleep (RR = 3.815), Todd's paralysis (RR = 1.739), and a family history of seizures (RR = 2.333) were identified as factors associated with a significant rate ratio (Table 1).

Seizure recurrence was significant among individuals who initially showed abnormal EEG results, with focal spike waves being the most common finding (19%), followed by focal spikes and slow waves (18%). Furthermore, significant associations were

observed between seizure recurrence and specific abnormalities detected by brain imaging. White matter hyperintensities were the most frequently identified abnormality (12%), followed by volumetric reduction of the brain hemisphere (6%) (Table 2).

Furthermore, we examined the association between seizure recurrence and the (a) number of seizures within 24 hours and (b) duration of seizure episodes. While 2.19 (1.26) individuals experienced recurrent seizures within 24 hours, 1.33 (0.86) individuals had no recurrent seizures (p = 0.001). The duration of seizure episodes was 8.37 (4.63) min in individuals with recurrent seizures, in contrast to 3.62 (1.78) min in those without recurrence (p = 0.001). Overall, the number of seizures within 24 hours and the duration of seizure episodes were significantly associated with seizure recurrence.

DISCUSSION

The present study found that the highest percentage of first afebrile seizures (65.3%) occurred in patients under 5 years of age and gradually decreased with age. Consistent with the findings of Maia et al,[6] we found a 12.7% incidence of first afebrile seizures in patients aged 11–15 years. Furthermore, the recurrence of seizures was significantly higher in patients over 11 years than in those under 5 (RR = 1.316), which is in line with the findings of Woo et al.[7] Consistent with previous studies,[8,9] we also found that sex was not associated with recurrence following the first nonfebrile seizure. Studies investigating the risk factors associated with unprovoked seizure recurrence in children have reported recurrence rates of 27–50%,[10–12] consistent with our present findings (45.3%). We found that the recurrence of seizures after the first afebrile seizure was associated with a family history of epilepsy (RR = 2.333), seizures occurring during sleep (RR = 3.815), and seizure duration >5 min, consistent with previous studies.[13–15] Generalized seizures were more common (61.0%) than other types as the first afebrile seizure, congruent with the 63% (generalized seizures) reported by Poudyal et al.[16] In this study, Todd's paralysis was a significant predictor of seizure recurrence compared with sphincter loss and/or vomiting during the attack, although not significant. These findings are consistent with those of Woo et al,[17] who have reported abnormal neuroimaging findings for most cases of Todd's paralysis that predicted seizure recurrence.

EEG is crucial for examining patients with new-onset afebrile seizures. While previous studies have reported abnormal EEG findings in 18–63% of children with new-onset nonfebrile seizures,[18–20] the present study observed abnormal findings in 81.6% of patients with seizure recurrence. This inconsistency is attributed to the inclusion of patients who underwent EEG in the first 72 hours of admission in this study *versus* the first 24 hours of admission in the previous studies. In agreement with several previous studies highlighting the association between EEG with epileptiform activity and seizure recurrence,[21,22] this study found an increased risk of seizure recurrence when the first EEG showed abnormal epileptiform activity. Therefore, an early EEG after the first nonfebrile seizure is highly recommended to predict the recurrence of seizures.

Neuroimaging is essential in patients with new episodes of convulsions to identify tissue abnormalities or structural injuries that could be associated with seizures. Abnormal neuroimaging findings are seen in 7–67% of patients with seizures.[23–26] In the present study, 32.0% of patients had abnormal neurological imaging results. A significant correlation was seen between seizure recurrence and abnormal initial neuroimaging findings, consistent with the findings of Dedeoglu and Ardicli.[27]

This study had some limitations. First, it had a relatively small sample size, which might limit the generalizability of the findings to a larger population. Second, the study was conducted at a single center, increasing the possibility of bias and limitations. Third, the follow-up duration was limited to 1 year. While this allowed the assessment of seizure recurrence patterns within that timeframe, a large-scale, multicenter studies with longer follow-up durations would provide a more comprehensive understanding of long-term outcomes and factors that influence seizure recurrence. Additionally, exploring the potential impact of interventions and treatments on reducing seizure recurrence rates could further enhance our ability to improve the quality of life for these patients.

In conclusion, children with early- and late-onset afebrile seizures with a family history of seizures, focal epilepsy, seizures during sleep, recurrent seizures of prolonged duration within 24 hours of the first one, and abnormal initial EEG and brain imaging were at a higher risk of seizure recurrence. Seizure recurrence showed no correlation with sex. This study's implications extend to clinical practice by highlighting

the importance of early evaluation and risk assessment in children with afebrile seizures. Identifying key factors associated with seizure recurrence enables healthcare professionals to tailor their diagnostic and treatment approaches, ultimately enhancing patient care and safety. By recognizing the significance of family history, seizure characteristics, EEG findings, and neuroimaging results, clinicians can make informed decisions that may prevent life-threatening complications and minimize cognitive impairment in affected children.

Conflict of Interest
The authors affirm no conflict of interest in this study.

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