Risk factors for seizure recurrence in a pediatric observation unit

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A R T I C L E   I N F O

A B S T R A C T

Background: Most patients present with seizures to pediatric emergency department (PED) are observed for extended periods for the risk of possible acute recurrence.
Objective: The aim of this study is to determine the risk factors of acute recurrence within first 24 h.
Methods: Patients who presented to PED with seizure during past 24 h were enrolled. Demographic features, number and duration of seizures, diagnostic studies, physical examination findings, presence and time of seizure recurrence in PED were noted.
Results: 187 patients were eligible for the study. 46% had recurrence of seizures in 24 h, 90,8% of recurrence within the first 6 h. Univariate analysis showed that younger patients, epileptic patients who were on multiple antiepileptic drugs (AEDs), who had multiple seizures during the past 24 h, who had abnormal neurological examination or neuroimaging findings had increased risk of seizure recurrence. Multivariate analysis showed that number of seizures during the past 24 h and previous use of AEDs was significantly associated with increased risk of recurrence.
Conclusion: Risk factors for acute recurrence should be evaluated for each patient. Patients without risk factors and no seizures during the first 6 h should not be observed for extended periods in PED.

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1. Introduction

Seizures are common clinical conditions presented at Pediatric Emergency Departments (PED), comprising approximately 1% of all PED visits [1-3]. These patients are generally observed for extended periods in the PED [4]. In addition to necessary interventions to stop seizures, a series of diagnostic tests including electroencephalograms (EEG), lumbar punctures, neuroimaging studies, and pediatric-neurology consultation at the PED may be necessary [1-6]. There is an ongoing debate about the utility of diagnostic tests and the necessity of extensive evaluation in the PED, for although these tests provide substantial information about prognosis and the risk of recurrence, at times they may unnecessarily consume the resources of the PED [3-8].

The risks of remote recurrence in patients with either first seizure or epilepsy have been evaluated in the literature, but acute recurrence can also lead to poor prognoses, and so risk factors for acute recurrence should also be studied [9-13]. Our aim is to determine the risk factors for acute recurrence of seizures and to find the most common recurrence time of seizures in order to establish a suitable and safe observation period for patients who are admitted to the PED with seizures.

2. Materials and methods

Our study was designed as a prospective cohort study conducted in a tertiary university hospital with an average admission rate of 60,000 patients/year. Included in the study were patients from 0 to 18 years old who presented to our hospital between 1 September 2013 and 31 December 2014 and who complained of seizure within the past 24 h or had a seizure when they presented at the PED. A seizure was defined as a witnessed event with a change in the patient's level of consciousness and/or motor activity and which was considered as a seizure by the treating physician. Patients who did not complete the observation period in the PED or who did not give consent to the study were excluded from the study. Patients who had simple febrile seizures were also excluded from the study, as they were not followed in the emergency department for 24 h. Patients with paroxysmal events that were not considered as seizures by the treating physician were also excluded.

Patients were evaluated by pediatric-emergency staff who recorded the following information on a standard form: demo-

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graphic features; number and duration of seizures; previous diagnosis of epilepsy or any other disease that might cause seizures; accompanying complaints; previous treatment with antiepileptic drugs (AED); previous diagnostic studies; history of febrile seizures; family history of seizures; and physical examination findings. Diagnostic tests and treatment measures were determined independently of the study by the treating physician and consulting doctors from the pediatric neurology department. All patients were followed in the PED for at least 24 h. Diagnostic studies in the PED and the incidence and time of seizure recurrence in the PED were also documented.

Abnormal imaging findings were defined as generalized or focal and as acute or chronic lesions, including malformations in cortical development, periventricular leukomalacia, cortical atrophy, hydrocephaly, gliosis, sclerosis, and benign lesions such as hamartomas.

Statistical analysis was performed using SPSS 15.0. Descriptive statistics were presented with frequencies and percentages for discrete variables and with mean and standard deviation for continuous variables. To analyze risk factors for seizure recurrence, the study population was divided into two groups: those who experienced seizure recurrence at any time interval in the PED within 24 h and those who did not. The discrete variables of the two groups were compared using the Pearson chi-square test and Fisher's exact test. Continuous variables were compared using the Mann-Whitney _U_ test for univariate analysis. For multivariate analysis, a logistic-regression test was performed. For all tests, $p < 0.05$ was considered statistically significant.

3. Results

A total of 202 patients were evaluated during the study period. Fifteen of the patients were excluded for not completing the 24-hour observation period. One hundred and eighty-seven patients

Table 1
General characteristics of the patients.

Characteristics	n (%)
Mean age (y)[a]	5.8 ± 5.2
Gender (Male)	100 (53.5)
Seizure	
First seizure	72 (38.5)
Epilepsy	115 (61.5)
Number of patients who use AEDs	100 (53.5)
The number of AEDs	
1	34 (31.2)[b]
2–4	58 (53.2)[b]
≥5	17 (15.6)[b]
Duration of seizure	
<5 min	140 (75.7)
5–10 min	22 (11.8)
>10 min	23 (12.4)
Number of seizures in previous 24 h	
1	93 (49.7)
2–4	53 (28.3)
≥5	41 (21.9)
Accompanying symptoms	
Fever	38 (20.3)
Trauma	6 (3.2)
Abnormal neurological examination	54 (28.9)
History of febrile seizure	25 (13.4)
Underlying disease	64 (34.2)
Family history of epilepsy	82 (17.5)
Previous abnormal EEG results	82 (71.3)[b]
Previous abnormal cranial imaging results	79 (42.7)[b]
The number of EEG in the PED	116 (62.4)
Abnormal EEG findings in PED	74 (62.2)[b]

[a] Mean ± Standard deviation.
[b] Valid percent; AED: Antiepileptic drug; EEG: electroencephalography; PED: Pediatric emergency department.

were eligible for the study, and detailed characteristics of the patients are presented in Table 1. Most seizures lasted for <5 min (75%), only 12% of the patients had seizures of longer than 10 min or were still having a seizure when they arrived at the PED, while 22% had experienced more than five seizures during the past 24 h. Forty-two percent of the patients had abnormal neuroimaging findings, with cortical volume loss and atrophy being the most common neuroimaging features (22%). Sixty-two percent of patients had an EEG obtained in the PED, and 62% of those were abnormal (showing epileptiform discharge and/or abnormal background activity). Twenty-two percent of patients had neuroimaging (CT and/or MRI) at the PED, and 41% of them had abnormal findings, with two (5%) showing acute abnormalities that required immediate intervention.

Eighty-six patients (46%) had recurrent seizures in the PED, with 42% of patients having their recurrence within the first 6 h and 4% having recurrence after 6 h (Fig. 1). AED adjustment was made in 65% of patients, and 9% of patients were admitted to the hospital for further management of seizures or treatment of the underlying disease.

When the seizure-recurrence and non–seizure-recurrence groups were compared by univariate analysis, several clinic characteristics were found to be statistically significant between the two groups. Younger patients had more risk of recurrence. Recurrence risk also increased in children with epilepsy when first seizure took place at a younger age.

Patients who had undergone their last EEG within the previous six months had significantly more risk for recurrent seizures, but the result of the EEG did not seem to increase the risk. Adjustment in AED treatment and admission to the hospital were also related to an increased risk of recurrence ($p < 0.05$) Neither accompanying symptoms such as fever, trauma, and headache nor physical-examination findings related to infections increased the risk of recurrence, nor did a history of febrile seizures or a family history of epilepsy or underlying diseases increase the risk of seizure recurrence. Variables related to increased risk of recurrence were listed in Table 2.

When recurrence and non-recurrence groups were compared by multivariate analysis, the number of seizures in the previous 24 h and the use of AED treatment were significantly associated with an increased risk of recurrence of seizures in the PED (Table 3).

When patients with epilepsy and patients with first seizure were analyzed separately, the recurrence risk in patients with epilepsy increased with the number of seizures before arriving at the PED and with having had an EEG in the past six months ($p < 0.05$). Younger epileptic patients showed more risk of recurrence ($p < 0.05$). In patients with first seizures, the seizure risk also increased with the number of seizures before coming to the PED, but other factors did not seem to increase the risk of recurrence ($p < 0.05$).

When seizure-recurrence time periods were compared, seizure recurrences between null and 6 h were significantly more common than recurrences at other time intervals (6–24 h) ($p < 0.05$).

4. Discussion

Ours is the first prospective study to evaluate risk factors and time intervals for acute recurrence of seizures in the pediatric observation unit. We found that patients with epilepsy, especially patients on multiple AEDs and patients who had experienced multiple seizures before arriving at the PED, had a significantly increased risk of recurrence in the PED. Also, patients who were young or were diagnosed with epilepsy at a younger age, patients with abnormal neurological examination results or neuroimaging findings, and patients who had an abnormal EEG at the PED were
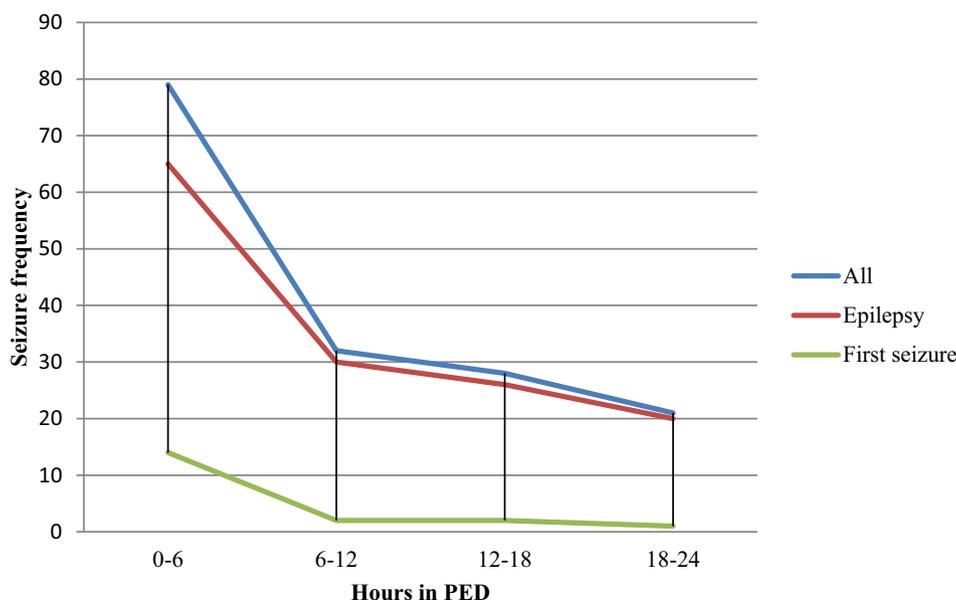
Fig. 1. Decreasing frequency of seizures after first 6 h in PED observation room in all groups.

Table 2
Variables increasing recurrence risk (univariate analysis).

	Recurrence	No recurrence	p
Diagnosis of epilepsy	60,9%	39,1%	0,000
>5 seizures before PED	90,2%	9,8%	0,000
Using of AEDs	63,0%	37%	0,000
>4 AED use	82,4%	17,6%	0,049
EEG in previous 6 months	66,2%	33,8%	0,000
Abnormal cranial imaging results	62%	38%	0,000
Abnormal neurological findings	63%	37%	0,03
Abnormal EEG in PED	57,2%	47,3%	0,02

AED: Antiepileptic drug; EEG: electroencephalography; PED: Pediatric emergency department.

Table 3
Variables increasing recurrence risk (multivariate analysis).

	B coefficient	Standard error	p	OR	CI 95%	
Number of seizures	,550	,408	,000	1,7	,780	3855
Using of AEDs	1194	,391	,036	3,3	1533	7100

AED: Antiepileptic drug.

at greater risk of recurrence within 24 h. Therefore, these patients should be observed more closely.

Among the main risk factors for recurrence in our study were a diagnosis of epilepsy and the presence and intensity of the AED treatment necessary to control seizures. Verotti et al. found that patients who used polytherapy for seizure control were more likely to relapse after drug withdrawal and that seizure-free patients had taken fewer medications before withdrawal [14]. We found a similar relationship between the number of drugs and the probability of recurrence in the short term. The number of AEDs is increased as epileptic activity becomes more difficult to control, and difficult-to-control epileptic activity can also cause recurrences in the short term. The number of AEDs can therefore be useful as an indirect indicator of increased epileptic activity.

Our results also show that the number of seizures before arriving at the PED is an important risk factor for subsequent seizures in the PED. Repetition of seizures is also related to the level of activity in epileptic regions, and that is considered to be an important

factor in long-term prognosis after drug withdrawal in epilepsy patients [14]. Sogawa et al. conducted a study of acute recurrence risk in an emergency department, which also showed that multiple seizures increased the likelihood of recurrence in the PED [15]. There are contradicting results in literature, however; a study by Shinnar et al. found that neither the number nor the duration of seizures affected recurrence risk [14-19].

Age at time of admission and age at first seizure were found to be important prognostic factors for acute seizure recurrence in our study; as the patient's age and age at first seizure decreased, the risk of acute seizure recurrence increased. Several studies produced diverse findings, however. Altunbasak et al. and Shinnar et al. found that age younger than 2 years was a good prognostic factor for long-term recurrence in patients with epilepsy [19,20], and Bouma et al. and Verotti et al. found that recurrence risk significantly rises with increasing age at seizure onset [14,21]. However, Emerson et al. found that children are more prone to recurrence if their seizures started before the age of 2 years [17]. Some other authors did not find any correlation between age at onset and long-term risk of recurrence in epilepsy patients [14-18,20-24].

Abnormal neurological examination findings and neuroimaging findings were additional important risk factors for acute recurrence in our study. In previous studies, remote-symptomatic seizures were found to be more prone to recurrence in long-term follow-up, especially in patients with epilepsy after drug withdrawal [4,18,25]. Abnormal neurological findings and underlying diseases were also consistently associated with long-term recurrence risk in patients with first seizures [13,19,26]. Arthur et al. also found that MRI abnormalities predict risk of recurrence [27]. Our study showed that patients with symptomatic seizures have a higher risk of recurrence even in the short term when compared with patients who had seizures without an identifiable cause.

An abnormal EEG in the PED was found to be significantly associated with increased risk for seizure recurrence in our study, which is consistent with other studies in the literature, especially in studies considering patients with first unprovoked seizures [13,16,18,19,28-32]. Kanemura et al. showed that not only EEG abnormalities themselves but also the region and characteristics of the EEG abnormalities are important in predicting the recurrence risk of seizures [33]. However, all of these studies studied long-term recurrence rather than acute recurrence, our study

showed for the first time that EEG abnormalities can be an important risk factor for acute recurrence as well as for long-term recurrence.

A family history of epilepsy has been found to be a risk factor for long-term recurrence in many previous studies [4,18,19,25,34], but this factor was not found to increase immediate risk of recurrence in our study.

5. Limitations

There are several limitations to this study. First, it was conducted in a tertiary university hospital that serves as a referral hospital for neurological patients in the country, and therefore complicated neurological patients may be overrepresented in our population, causing patient-selection bias. Second, we did not specify seizure type and epilepsy classification as risk factors, which could have provided further information. Several other studies have found that the type of seizure, especially focal seizures, can be an important predictor of recurrence both for first seizures and epilepsy patients and that multiple types of seizures in the same patient can increase the likelihood of recurrence in the long term [4,16,19,25,30,31,34]. Therefore, seizure type should also be evaluated in future studies on immediate recurrence. Third, fifteen patients left without completing the 24-hour observation period. If all of these patients left early because they were normal and seizure free after first seizure, this may also have caused selection bias, as we may have excluded healthier subjects.

6. Conclusion

Our study is the first prospective study to evaluate risk factors and time intervals of acute recurrence of seizures in the pediatric observation unit. We found that patients with epilepsy (especially those on multiple AEDs), patients who were young or diagnosed with epilepsy at a younger age, patients who had multiple seizures before arriving at the PED, patients with abnormal neurological examination and neuroimaging findings, and patients whose EEGs were taken at the PED and were found to be abnormal were at greater risk for recurrence within 24 h. Therefore, these patients should be observed more closely. The time interval of the greatest risk for seizure recurrence in the PED is the first 6 h of the observation period at the PED.

We conclude that early discharge maybe considered for patients without risk factors and for patients who remain uneventful during the six-hour observation period. Future studies with larger study groups could gather more information about further risk factors, particularly for patients with first-time seizures.

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