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Evaluation and management of the first unprovoked seizure in children: Single-center experience first unprovoked seizure in children

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Abstract

Aim: We aimed to evaluate clinical and laboratory features in children who presented unprovoked seizure for the first time and also to determine possible risk factors for seizure recurrence.

Materials and Methods: A total of 219 patients (113 female, 106 male) presented with first unprovoked seizure were included in the study. Demographic, clinical findings (type and duration of seizures, seizure recurrence, antiseizure drugs), neuroimaging findings and electroencephalography (EEG) results were recorded retrospectively.

Results: Median age of the patients was 30 months (IQR 12-66). A history of birth hypoxia and/or phototherapy and family history of epilepsy were present in 21% and 17.4%, respectively. Generalized seizures were the most common seizure type (42%), with a predominance at <2 years of age compared to the other age groups (p=0,007). Seizures recurred in 28% of the patients. Abnormal EEG findings were detected in 33.8% and most of them were >2 years of age (p<0,01). Brain MRI abnormalities were detected in 19% and recurrence was higher in the patients with abnormal MRI (p<0,001). No correlation was found between seizure recurrence and EEG abnormality. In focal seizures, the rate of seizure recurrence was higher than generalized seizures. Antiseizure therapy was initiated in 44% of the patients. Drug switch were required in 22 patients due to side effects. Etiology was determined in nearly half of the patients.

Conclusion: In our study, abnormal brain MRI were determined as possible risk factors for seizure recurrence. Comprehensive etiological investigation should be considered following the first episode of unprovoked seizures, especially in patients under two years.

Introduction

The first unprovoked seizure in children is a frequent cause of pediatric neurology visits. About 4-10% of children have at least one episode of seizure before the age of 16 years [1,2]. Based on the International League Against Epilepsy (ILAE) definition, epilepsy can be diagnosed even after a first episode of seizure, if there is a possibility of further similar seizures. The risk of seizure recurrence after two unprovoked seizures has been reported about 60% over the following 10 years [3]. Therefore, the experience of a single seizure event deserves a detailed evaluation. In the first step, a differentiation should be made between provoked and unprovoked seizures. The occurrence of an unprovoked seizure may be associated with an underlying neurological defect, that may predispose to recurrent seizures. In the literature, focal seizures, symptomatic etiology, history of febrile convulsion, neurodevelopmental delay, family history of epilepsy, and abnormal EEG were reported as possible risk factors for seizure recurrence [4, 5]. Herein, we aimed to review the current diagnostic approach in the evaluation and management of children presenting with a first unprovoked seizure.

Materials and Methods

Study group

There was a total of 458 patients followed with a first unprovoked seizure between January 2019 and September 2021 in the department of pediatric neurology at Ankara City Hospital. Among those, 239 patients with febrile seizures, acute symptomatic seizures (occurs acutely, within a week of central nervous system insult or at the time of systemic/neurologic event), patients without an EEG recording, and neonatal seizures were excluded. We retrospectively reviewed the clinical and laboratory features of 219 patients with a follow up at least 3 months.

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Medical data were obtained from hospital records. Demographic features follow up period, perinatal and family history, type and duration of seizures, EEG and MRI findings, antiseizure medications, seizure recurrence were recorded. Patients were divided into age groups as follows: <2 years, 2-5 years, and >5 years. According to the last definition of ILAE, the types of seizures were grouped as generalized, focal, and unknown. The etiology was defined as structural, genetic, metabolic, infectious, immune, and unknown [3]. Follow-up visits were performed every 3 to 6 months, or sooner if necessary. The study was conducted with the approval of the Institutional Ethics Committee from the Turkish Ministry of Health, Ankara City Hospital Ethics Committee 2 (E2-21-1160).

Statistical analysis

Statistical analyses were performed using the SPSS software version 23.

For statistical analysis, SPSS version 23 (SPSS Inc., Chicago, IL, USA) was used. Descriptive analyses were presented using median and minimum and maximum values. Numbers and percentages are used for categorical variables. Mann-Whitney U-test was applied for the non-normally distributed variables. The Chi-square test or Fisher's exact test, where appropriate, was used to compare these proportions in different groups. A p-value of less than 0.05 is considered to be statistically significant result.

Results

A total of 219 children (113 female, 106 male) were included. Median age of the patients at admission was 30 months (IQR 12-66, range: 1 month-18 years). Median duration of follow up was 16 months (IQR 15-19). History of hypoxia and phototherapy were present in 8.7% and 4.6% of the patients, respectively. Forty-four of the patients (20.1%) had a history of febrile seizure. A family history of epilepsy was present in 17.4% (n=38). On the first visit, 77.6% of patients had only one seizure, 10% had two seizure episodes, and the remaining had more than two seizures. The most common seizure type was generalized seizures occurred in 42% of the patients. Focal seizures occurred in 28.8%, while seizure type was not identified in 29.2. Generalized seizures were more common under 2 years (p=0.007). According to parents' reports, duration of seizures was >5 minutes in 13.7% (n=27) and 3 patients were presented with status epilepticus.

Abnormal EEG findings were detected in 33.8% (n=74) including generalized epileptiform discharges in 15% and focal epileptiform discharges in 18.8%. In the patients younger than 2 years of age, EEG abnormalities were less frequent compared to the other age groups (p=0.001). Abnormal EEG findings were more common in patients with focal seizures (p=0.009) and longer seizure duration (>5 minutes) (p=0.01). Seventeen patients with centrotemporal spikes on EEG defined as rolandic epilepsy and 13 patients was defined as occipital lobe epilepsy according to EEG findings and seizure type. Nine patients with myoclonic seizures were diagnosed with JME and 12 patients with absence seizures revealed childhood absence epilepsy.

Table 1. Baseline clinical characteristics of the patients presented with first unprovoked seizures (n=219).

Variables	
Sex	n (%)
Male	106 (49%)
Female	113 (51%)
Age groups	
< 2 years	93 (42%)
2-5 years	66 (30%)
≥5 years	60 (28%)
Duration of follow-up, median (range), months	16 (3-37)
Type of the first seizure	
Generalized	92 (42%)
Focal	63 (29%)
Unknown	64 (29%)
Duration of seizures	
<1 minute	78 (36%)
1-5 minutes	88 (40%)
≥5 minutes	27 (12%)
Unknown	26 (12%)
History of prior febrile seizures	44 (20%)
Family history of epilepsy	38 (17%)
EEG	
Normal	145 (66%)
Abnormal	74 (34%)
MRI	
Normal	136 (62%)
Abnormal	32 (15%)
Not performed	51 (23%)

Brain MRI was performed in 168 (76%) patients and 19% of them showed abnormal findings. Most common causes were perinatal insult (n=16), followed by hydrocephalus (n=5), and TORCH infection (n=4) in the patients <2 years of age. MRI revealed intracranial stroke in 4 patients and cortical dysplasia in one patient. In two patients, seizures were associated with head trauma. Baseline clinical and laboratory features of the patients are summarized in Table 1.

Epileptic encephalopathy gene panel was performed in six patients with epileptic spasms. Two patients were diagnosed as SCN2A mutation syndrome. Two patients with combined afebrile/febrile seizures and neurodevelopmental regression were diagnosed with Dravet syndrome. Metabolic etiology was determined in five patients, including organic aciduria (n=2), nonketotic hyperglycinaemia (n=2), biotin-thiamine responsive basal ganglia disease (n=1), and GLUT-1 deficiency (n=1).

Sixty-one patients had seizure recurrence during follow up and 81% of them were under 2 years of age. Seizures recurred in the first month in 19, within 3 months in 26, 6 months in 11, and 12 months in five patients. The re-

Table 2. Comparison of the clinical variables according to seizure recurrence.

	Recurrence (n=61, 28%)	No-recurrence (n=158, 72%)	p value
Age at admission, n (%)			
<2 years	28 (46%)	65 (41%)	0.455
2-5 years	20 (33%)	46 (29%)	
>5 years	13 (21%)	47 (30%)	
Seizure type, n (%)			
Focal	19 (31%)	44 (28%)	0.147
Generalized	30 (49%)	62 (40%)	
Unknown	12 (20%)	52 (32%)	
EEG findings, n (%)			
Normal	43 (70%)	102 (65%)	0.405
Abnormal	18 (30%)	56 (35%)	
MRI, n (%)			
Normal	28 (22%)	108 (79%)	<0.001*
Abnormal	25 (78%)	7 (21%)	
Seizure duration			
<1 minute	23 (28%)	64 (40%)	0.302
1-5 minutes	24 (27%)	69 (43%)	
≥5 minutes	7 (26%)	13 (8%)	
Unknown	7 (27%)	12 (7%)	

*<0.05: statistically significant.

currence rate in the first 3 months was higher in patients with focal seizures compared to generalized and unknown seizure groups. (p=0.053). The rate of seizure recurrence was slightly higher in patients with focal seizures than in generalized seizures (p=0.066). No statistical difference was found between seizure recurrence and EEG abnormality. Seizures recurred in 78% of patients with MRI abnormalities (25/32) (p<0.001). No relationship was found between seizure recurrence and history of febrile seizure and also seizure duration (Table 2).

Anti-epileptic medications were initiated in 43.8% (n=96) of cases. Antiepileptics were needed more frequently in patients with a history of neonatal hypoxia/jaundice (p=0.001). The most common used antiseizure medications were levetiracetam (51.1%), followed by valproic acid (11.9 %) and topiramate (4.6%). In 22 patients, switch off antiseizure medication required due to side effects. Most common side effects were aggressive behavioural changes/ irritability and loss of appetite.

Discussion

Considering the literature on the evaluation and management of the first unprovoked seizure in childhood, the natural history and possible risk factors for recurrence are still unclear. A detailed medical history and careful neurologic examination may facilitate an accurate diagnosis. Patients with known neurological disorders, such as a history of head trauma, stroke, cerebral palsy or intellectual disability, are at much higher risk for recurrence following an unprovoked seizure. Prior febrile seizure history, developmental milestones, and family history of epilepsy help to determine the cause and estimate prognosis [5,6]. In this study, most of our patients presented with first unprovoked seizure were under two years' age. History of birth hypoxia and/or phototherapy was present in nearly one fifth of patients. The distinction between focal and generalized seizures has implications for possible underlying etiologies and risk of recurrence. In our cohort, majority of seizures were generalized (42%) and type of seizures was unknown in one third of the patients. Similarly, Machado et al. reported a high frequency of undetermined seizures in their cohort including 74 children with first unprovoked seizure [6]. This might be associated with difficulty in defining type of seizure in younger patients. Since absence and myoclonic seizures are often unnoticed by parents, careful questioning of previous episodes regarding awareness and staring during which the child is truly unresponsive or muscle jerks might indicate that this is not the first event [7]. Nine of our patients with myoclonic seizures had JME diagnosis and 12 patients were diagnosed as childhood absence epilepsy. Little is known about whether the first afebrile seizure was status epilepticus. The overall recurrence risk of seizure recurrence and outcome are reported to be similar, if the first seizure was a brief seizure or status epilepticus. In our study, duration of seizure was >5 minutes in 27 and status epilepticus was detected in three patients whenever 74% have no recurrent seizures during follow up.

Experts often recommend to obtain an EEG on the evaluation of all first unprovoked seizures. Electroencephalography helps to determinate seizure type, epilepsy syndrome, and risk for recurrence [8]. Abnormal EEG findings was detected in one third of our patients with first unprovoked seizure, similar to the literature [9]. According to the literature, abnormalities on neuroimaging can be detected in up to one third of children presenting with a first seizure. Neuroimaging modalities should be considered in any child with apparent cognitive/motor deficit with unknown etiology or unexplained abnormal neurological findings [10,11]. In our study, 76% of patients (n=158) has conducted to MRI and 19% of the patients had abnormalities, including hydrocephalus, stroke, trauma, and cortical dysplasia as probable epileptogenic lesions.

The possibility of having a second seizure has been investigated in several observational studies with long-term follow-up. Etiology appears to be the most important factor for the prediction of recurrence risk. In a prospective study, the cumulative risk of seizure recurrence was reported as 29%, 37%, 42%, and 44% at 1, 2, 5, and 8 years, respectively [12]. The rate of recurrence was reported to be higher in children with symptomatic epilepsy compared to idiopathic epilepsy [13]. In another study, the risk of recurrence at the second year of follow-up was 96% for symptomatic seizures, compared with 46% for idiopathic seizures. Seizure occurrence during sleep and EEG abnormalities increased the recurrence risk [14]. In a meta-analysis including 815 neurologically and developmentally

normal children, the risk of recurrence in first unprovoked seizure was 45% within 3 years of follow-up [15]. Our study revealed that 28% of the patients had recurrent seizures and 81% of them were under two-year of age. Seizure recurrence occurred within the first three months in most of our patients (75%).

In order to provide an optimal management in children with a first unprovoked seizure, an individualized assessment should be made considering the disadvantages of antiepileptic therapy and the risk of seizure recurrence. Initiation of an AED after the first seizure may be indicated, when the detected etiology has a high risk of seizure recurrence or represents the onset of a known epileptic syndrome [16]. Anti-seizure therapy after the first afebrile seizure does not affect the long-term outcome, but reduces the risk of recurrence [17,18]. In contrast, a normal EEG, absence of other risk factors, or an afebrile seizure that does not fit into a particular epilepsy syndrome may not need treatment with an AED. Approximately 24% of patients with new-onset epilepsy reported to have side effects with frequently used AEDs [19]. In the current report, anti-epileptic medications were initiated in 44% of the cases. The management should be individualized, taking into account factors such as medical history, social background, and its access to a medical facility. Benefits of antiepileptics should be weighed against the side effects of AEDs. In 10% of our patients, switch off antiseizure medication required due to side effects in the follow up.

The limitations of our study include the retrospective collection of data, single-center experience, accurate determination of seizure type and duration was based on the information reported by parents. Despite the limitations mentioned above, our data constitutes one of the largest pediatric first unprovoked seizure series from a single-center. Prospective and multi-center studies including multidisciplinary evaluations are necessary in order to define the risk factors for seizure recurrence and to establish an evaluation and management algorithm in those patients.

Conclusion

By careful and comprehensive assessment of the event, the risks for recurrence and the treatment decision should be determined. Age at the first seizure and symptomatic etiology may help to determine the risk of recurrence. Etiology should be brightened in patients especially under two years old. The decision to initiate antiepileptic therapy following a first unprovoked seizure should be based on weighing the risk of having further seizures against the risk of AED therapy.

Ethics approval

Ethical approval for this study was obtained from the Ankara City Hospital Ethics Committee (E2-21-1160).

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