

# Risk of Seizure Recurrence Following a First Unprovoked Seizure in Childhood

S Inaloo<sup>1</sup>, E Sadeghi<sup>1</sup>, M Rafiee<sup>1</sup>, ST Heydari<sup>2\*</sup>

<sup>1</sup>Department of Pediatric Neurology, <sup>2</sup>Gastroenterohepatology Research Center, Nemazee Hospital, Shiraz University of Medical Science, Shiraz, Iran/Lorstan University of Medical Science, Khoramabad, Iran

## Abstract

**Background:** There is still a question whether first seizure leads to epilepsy. Several risk factors have been reported in this relation. This study was undertaken to determine the risk of recurrence after a first unprovoked seizure in children.

**Methods:** In a prospective study between December 2003 and December 2005, 156 children who presented with a first unprovoked seizure were enrolled and followed for at least 18 months. Potential predictors of recurrence were compared, using the Cox Proportional Hazard model in a univariable and multivariate analysis. Survival analysis was performed, using the Kaplan-Meire curves.

**Results:** Seventy two children (46.2%) experienced subsequent seizures. The cumulative risk of seizure recurrence was 28.8%, 41.7% and 46.2% at 6, 12, and 24 months following the first seizure, respectively. The median time for repeated seizure was 4 months while 62.5% of the recurrence occurred within 6 months, 88.9% within 1 year and 100% till the end of the second year. On multiple analysis, risk factors for resumption of seizure consisted of abnormal electroencephalography (EEG), seizure during sleep, abnormal brain imaging and history of perinatal problems. On univariable analysis, abnormal EEG, abnormal imaging (remote etiology of seizure), history of neonatal problems, previous febrile seizure, and family history of afebrile seizure increased the risk of recurrence.

**Conclusion:** The study revealed that the risk of seizure recurrence in our patients was relatively high. Those who had abnormal electroencephalography, past history of prenatal problems, remote etiology for seizure, abnormal brain imaging, and seizure during sleep were at greater risk for recurrence of seizure.

**Keywords:** First seizure; Children; Recurrence; Epilepsy

## Introduction

Seizure and epilepsy are not synonymous; epilepsy refers to recurrent unprovoked seizure.<sup>1</sup> Knowledge of the natural history after a single unprovoked seizure and the risk factors for recurrence are a necessary prerequisite for making rational decisions regarding long-term treatment with antiepileptic drugs (AEDs).<sup>2</sup> Most children with a single unprovoked seizure do not experience a recurrence.<sup>2-5</sup>

The recurrence rate after first unprovoked seizure

in adults and children is high (21 to 71%), depending mainly on the design and duration of the study and the inclusion criteria of the subjects. Risk factors of recurrence are also different in various studies, and the vast majority of them have been performed in developed countries.<sup>2-4</sup>

Several factors predicting the recurrence have been pointed out, e.g. the etiology of seizures, abnormal EEG, family history of epilepsy, age of the onset and the occurrence of seizure during sleep. No consensus has been reached.<sup>1,2</sup>

There are few studies about seizure recurrence and risk factors for epilepsy in Iran. The aim of this study was to evaluate the recurrent risk and risk factors of recurrence after a first unprovoked seizure in children and adolescents in Iran.

\*Correspondence: Seyed Taghi Heydari, PhD, Department of Biostatistics, Shiraz University of Medical Science, Shiraz, Iran. P.O.Box: 71345-1874, Tel: +98-09173034420, Fax: +98 711 2349330, e-mail: [heidaryt@sums.ac.ir](mailto:heidaryt@sums.ac.ir)

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## Materials and Methods

This prospective study was performed on 156 children, 1 month to 18 years of age, with a first unprovoked seizure who referred to Nemazee and Dastgheib hospitals and Pediatric Neurology Clinic, the major reference centers in the in Shiraz, southern Iran from December 2003 to December 2005. The study protocol was approved by the University Research Ethics Committee.

The children with the following inclusion criteria were enrolled in the study: (a) a first unprovoked seizure defined as a seizure or a cluster of seizure or status all occurring in a 24 hr period with no association with an acute illness, fever, infection, trauma or toxic and metabolic encephalopathy,<sup>6-8</sup> (b) chronological age between 1 month and 18 years.

Exclusion Criteria were typical absence seizures, myoclonic seizures and infantile spasms, the children who presented with their first generalized tonic clonic seizure and were found to have a prior absence or a partial seizure, and finally the children with a provoked seizure.

A seizure was classified as a remote symptomatic if the child was known to have a static encephalopathy from birth prior to the seizure and/or had sustained a prior neurological insult such as perinatal asphyxia, stroke or significant head trauma (associated with a depressed skull fracture, loss of consciousness more than 30 minutes, and intracranial bleeding), and abnormal brain image. All other unprovoked seizures were considered idiopathic. A family history of seizure was defined as a history of an unprovoked seizure or seizures in a first or second degree relative. The type of seizure was classified according to the Revised International Classification of Epileptic Seizure.<sup>9</sup>

Recurrence was defined as any unprovoked seizure occurring later than 24 hr after the first seizure. At the time of the initial visit, informed consent was obtained from the parents and from the children when feasible. Detailed data consisting of age, sex, seizure characteristics, duration, number of seizures, history of prior provoked seizure, prior neurological insult, developmental history, birth history and family history of seizure were included. Physical and neurological examination was recorded for all the children. An electroencephalogram (EEG) was scheduled for most patients (142 patients) as soon as feasible.

All EEGs were interpreted by two researchers who were blind to the outcome. EEGs were classified to

normal or abnormal types. Specific epileptic abnormalities (focal spikes, multifocal spikes, centrotemporal spikes, generalized spikes and waves and photic convulsive response) as well as focal or generalized slowing waves were coded separately.

Biochemical studies including fasting blood sugar and calcium level were checked for all patients. Computer tomography scan and/or magnetic resonance imaging of the brain were performed when clinically indicated.

After enrollment, the patients were followed in a clinic or by telephone interview. Recurrence was defined as any unprovoked seizure occurring more than 24 hours after the first seizure.

Due to the length of follow up influences, the probability of observing recurrence, the variable length of follow up for each child was statistically analyzed. Univariate analysis for dichotomous variables was performed, using Kaplan-Meier survival analysis. Univariate analysis for all risk factors and multivariable analysis were performed, using the Cox Proportional Hazard Model. A P value <0.05 was considered significant.

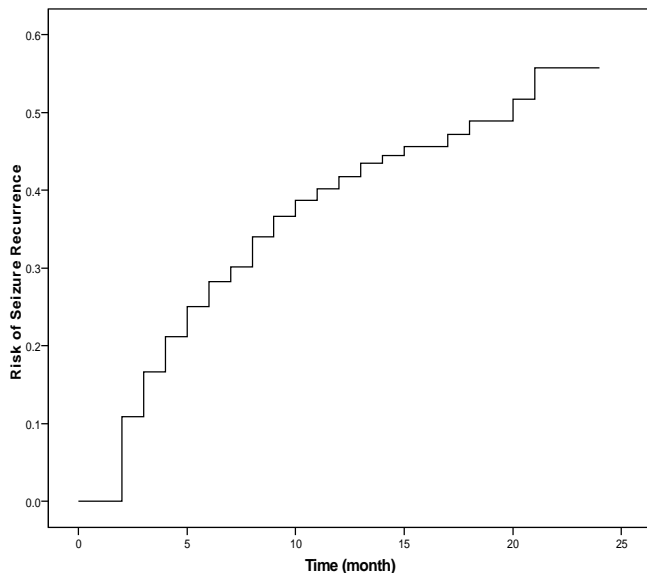
## Results

The study group consisted of 156 patients, 85 (54.5%) boys and 71 (45.5%) girls. Their age ranged from 2 months to 16 years with a mean of  $6.9 \pm 4.4$  and median of 7 years. The mean follow-up period was  $14.9 \pm 4.5$  months.

Recurrence occurred in 72 patients (46.2%), and the overall Kaplan-Meier estimate of recurrence was 28.8% at the 6 month interval, 41.7% at 1 year and 46.2% at 2 year interval (Figure 1). The time of recurrence was between 2 days to 22 months with a mean of  $5.6 \pm 4.7$  months and a median of 4 months. There was no significant difference in the mean follow-up time between the patients who had recurrence (14.4 months) and those who did not (14.8 months).

In the study population, significant predictors of recurrence included abnormal EEGs, past history of perinatal problem, abnormal brain imaging, etiology for seizure and first seizure in sleep. A history of febrile seizure, neonatal complication, abnormal EEG, abnormal neuro-imaging, family history of epilepsy, perinatal problem were associated with an increased recurrence risk by multivariate analysis in the Cox proportional hazard model. Sex, number of seizures in 24 hr, type of seizure and treatment did not affect

the risk factors of recurrence. Individual risk factors are detailed in Table 1.



**Fig 1:** Probability of seizure recurrence after a first unprovoked seizure: Kaplan-Meier curve.

The patients were divided into four subgroups according to age. Twenty-eight (17.9%) children were 2

months to 1 year-old, 23 (14.7%) were between 1-3 years, 62 (39.7%) were between 3-10 years, and 43 (27.6%) were older than 10 years. Recurrence was 35.7%, 56.5%, 51.6% and 39.5% for these age groups, respectively ( $P=0.29$ ). The most common age of the patients with recurrence was between 1-3 years.

Eighty-five (54.5%) patients were boys and 71 (45.5%) girls of whom, thirty three boys (38.8%) and 39 (54.9%) girls had recurrence ( $P<0.05$ ).

One-hundred and twenty eight (82.0%) children had generalized seizure, 22 (14.0%) had partial seizure with secondary generalization and 6 (4.0%) patients had partial seizures. Recurrence occurred in 61 (47.7%) patients with a generalized seizure, 9 (40.9%) children with partial seizure and secondary generalization, and 2 (33.3%) patients with partial seizure ( $P >0.05$ ).

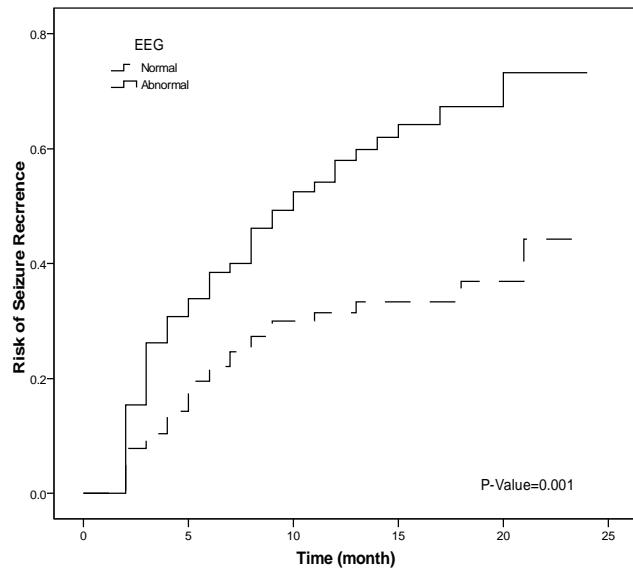
The patients were divided into two groups according to remote etiology for seizure of whom 23 had etiology of seizure and 111 cases were idiopathic. Recurrent risk for remote symptomatic group was 82.6% and for the idiopathic group was 40.2% ( $P<0.001$ ). The etiology of seizure is a significant risk factor for its recurrence (Figure 2).

Seizure occurred in 98 waking and 58 sleeping children. Recurrence occurred in 35 (35.7%) patients

**Table 1:** Multiple analysis of the potential predictors of recurrence, using Cox proportional hazard model.

Predictor		Rate ratio	95% CI		P-value
			Lower	Upper	
Age of first seizure	Under one year	1			
	1-3 years	0.855	0.389	3.122	0.855
	3-10 years	0.404	0.552	4.362	0.404
	>10 years	0.844	0.370	3.378	0.844
Gender	Male	1.575	0.904	2.746	0.109
Type of seizure	Partial	1			
	Generalize	0.824	0.310	2.193	0.698
	Partial with secondary generalize	0.933	0.199	4.371	0.930
Time of seizure	Sleep	2.261	1.302	3.928	0.004
Number of seizure in 24h	More than one	1.759	0.950	3.258	0.072
EEG finding	Abnormal	1.929	1.045	3.561	0.036
Brian imaging	Abnormal	2.808	1.084	7.273	0.033
Febrile seizures	Positive	0.441	0.189	1.030	0.058
Perinatal problems	Positive	4.959	1.203	20.441	0.027
Family history of aferbile seizure	Positive	1.987	0.993	3.976	0.052
Treatment	Received	0.965	0.461	2.018	0.924
Abnormal neurolgic exam	Positive	0.693	0.198	2.420	0.566
Past history of provoked seizure	Positive	0.693	0.198	2.420	0.566

who had the initial event while awake and in 37 (63.8%) children who had the first seizure while asleep. The difference was significant ( $P=0.004$ ). As for multivariate Cox proportional hazard model, the recurrence of seizure in sleeping children was 2.1 times that in waking patients.



**Fig 2:** Survival plot analysis (Kaplan-Meier curve) of the EEG finding versus recurrence.

Among the 156 children in the study, 34 (21.8%) had more than one seizure within 24 hours, and 122 (78.2%) patients had only one episode of seizure within 24 hours. Recurrence occurred in 54 (44.3%) patients with one seizure and in 18 (52.9%) children with two or more seizures ( $P>0.05$ ).

EEG was done in 142 patients of whom (49.4%) had normal EEG, 65 abnormal EEG, 43 (27.6%) had epileptic EEG, and 22 (14.1%) had abnormal but non-epileptic EEG]. Recurrence occurred in 35.1% of the patients who had normal EEGs, in 88.4% of patients with epileptic EEGs, and in 18.2% of those with abnormal but non-epileptic EEG. This was statistically significant ( $P=0.025$ ). As for the multivariate Cox proportional hazard model, recurrence of seizure in patients with abnormal EEG was 1.9 times that in patients with normal EEG (with 95% CI).

Brain CT and/or MRI were done for 125 patients (80.2%). Abnormal findings were detected in 14 (9%) patients. The most common abnormal findings were hypoxic ischemic change and brain atrophy. Recurrence occurred in 45 (40.5%) patients with normal brain imaging and in 13 (92.2%) with abnormal brain

imaging. Abnormal brain imaging was a statistically significant risk factor for recurrence ( $P<0.001$ ).

Twenty-eight (17.9%) patients had a previous history of febrile seizure. Recurrence occurred in 54 (42.1%) children without any previous history of febrile seizure and 18 (64.3%) with such a history ( $P=0.043$ ).

Fourteen patients had a history of perinatal problem (asphyxia, infection, respiratory distress, bilirubin encephalopathy). Recurrence occurred in 59 (41.5%) patients without any history of perinatal problem leading to a neonatal admission and 13 (92.8%) patients with a positive history ( $P=0.001$ ).

A family history of seizures was observed in 45 (28.8%) patients. Among those with recurrence, 27 (60%) children had a positive family history and 45 (40.5%) lacked any family history of afebrile seizure. Family history of afebrile seizure was a significant risk factor for recurrence ( $P=0.021$ ).

Fifty (32.1%) children were either not treated at all or were treated for less than 2 weeks with antiepileptic drugs after the initial seizure. In this observational study, there was no difference in the recurrence rate between treated and untreated children (46.2% and 46%, respectively,  $P=0.55$ ).

Variables with statistically significant had an association with recurrence risks in the model. A past history of perinatal problem, abnormal EEG, abnormal brain imaging, etiology for seizure and onset of the initial seizure during sleep were significant predictors of recurrence (Table 1).

## Discussion

In this prospective study of children identified a time of their first unprovoked seizure, the risk of recurrence after 2 years of follow up is 46.2%. The risk rate is similar to that of the retrospective study of Berg, and the prospective studies of Comfiled and Winekler in which the recurrent risk was 47, 51.8, and 51.4%, respectively,<sup>1,6,9</sup> but recurrence risk in our study was more than those found in the studies of Shinnar (37%) and Scotani (34%).<sup>3,5,7</sup> This difference in the risk of recurrence might be due to the method of selecting patients.

In this study, cumulative risk of recurrence was 28.8%, 41.7%, 46.2% over 6, 12, 24 months, respectively. This is similar to the results of Stroink's study (40, 46, 54%) whose mean time of recurrence was 5.6 months. These findings are similar to those of Shinnar's<sup>5</sup> and different from those of Scotoni's (mean

time was 12 months).<sup>7</sup> In our study, the most recurrences occurred in the first year after the first unprovoked seizure (88.8%).

In our study, the most important risk factors for seizure recurrence were the etiology for seizure, abnormal EEG, abnormal brain imaging and first seizure in sleep. In the most previous studies, abnormal EEG and etiology of seizure were the most important risk factors for recurrence.<sup>3,5,11,12</sup> The association of the onset of seizure in sleep with the recurrence risk previously reported was confirmed in this study.<sup>5,7,13</sup>

In the univariable analysis in our study, the significant increased in risk of recurrence if there was prior history of febrile seizure, family history of afebrile seizure, and perinatal problem, similar to Shinnar, Hauser, Kollar and Rozsavoly's studies.<sup>3,4,12,14</sup> Reports about the influence of perinatal events on subsequent epilepsy yield conflicting results.<sup>15,16</sup> The study of Winckler revealed that seizure recurrence was significantly associated with perinatal problems.<sup>1</sup>

The ratio of normal to abnormal electroencephalography in our study was 1.1: 1 which is similar to what is reported in other studies.<sup>1,17</sup> Several authors observed the importance of EEG epileptic form pattern in the risk of seizure recurrence.<sup>1,5,17,18</sup> Our study showed an increased risk for recurrence when the first EEG was abnormal and mainly epileptic. The risk of seizure recurrence was 88.4% when the first electroencephalopathy was epileptic. Abnormal brain imaging also increased the risk of seizure recurrence, showing etiology for seizure, and remote etiology for seizure significantly increased the risk.

The majority of children in our study were treated with antiepileptic drugs but there was no significant difference between treated and untreated groups for recurrence. A number of studies have reported that treatment with antiepileptic drugs does not influence the risk of recurrence.<sup>19</sup> However, some other studies have shown that treatment of the first seizure reduces the recurrence risk by approximately 50% but does not affect the probability of attaining remission.<sup>20,21</sup>

We found that the risk of recurrent seizure after the first unprovoked seizure in our country as a developing country was 46.2% in a 24 month follow up. Most recurrences occurred in the first year and most important risk factors for recurrence were abnormal EEG, etiology for seizure, perinatal problem, and seizure in sleep.

Our study revealed an increased risk of recurrence in our children with a first unprovoked seizure. Risk factors were more or less similar to those found in other studies and included an abnormal EEG, remote etiology, seizure in sleep, positive family history and abnormal imaging. Recurrence occurred mostly during the first year following the first unprovoked seizure.

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**Conflict of interest:** None declared.

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