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# Risk of recurrence following a first unprovoked seizure in Thai children

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### *Abstract*

*Objectives:* To determine the seizure recurrence rate following a first unprovoked seizure in Thai children and the risk factors for the recurrence. *Methods:* This is a prospective cohort study on children less than 15 years of age presented to the Hatyai Hospital, Southern Thailand with a first unprovoked afebrile seizure. The patients were followed up regularly and were not given anti-epileptic drug until seizure recurrence. Factors that may affect the seizure recurrence rate were analyzed. *Results:* Ninety-one children were studied. The mean age was 6.0 years. The Kaplan-Meier estimate of cumulative risk of recurrence was 50% at 4 months, and 66% at 12 months. The incidence density was 6.9 per 100 person-months. With univariate and multivariate analyses, age, gender, seizure type, history of febrile seizure, family history of febrile seizure, family history of epilepsy, delay in developmental milestones, and abnormal electroencephalogram were not significant risk factors for seizure recurrence.
*Conclusions:* The risk of recurrence after the first unprovoked afebrile seizure in Thai children is high at 66% in 12 months. No significant risk factor for recurrence was identified.

## INTRODUCTION

First unprovoked seizure in children is a dramatic and frightening event. In order to make a rational decision whether to treat or not to treat after a first unprovoked seizure, natural history after the first seizure and the risk factors for recurrence are necessary information. Previous studies showed the rate of recurrence varies from 23% to 71%.[1-9] The wide range of the reported recurrence rate reflects differences in methods of study. It is also likely to reflect the heterogeneity of epilepsy and the variables that influence the prognosis of a particular study population. The main factors associated with a higher risk of recurrence are epileptiform abnormalities in electro-encephalogram (EEG) and remote symptomatic etiology.[3,5-8]

There has not been any previous study on the risk of seizure recurrence after a first unprovoked seizure in Asian children. The objective of this study was to determine the seizure recurrence rate following a first unprovoked seizure in Thai children and the risk factors of the recurrence.

## METHODS

### *Subjects*

This is a prospective cohort study conducted on 91 children with a first unprovoked afebrile seizure seen at Child Neurology Clinic of Hatyai Hospital. Hatyai Hospital is the regional referral center of Southern Thailand. The patients were enrolled and followed-up between April 1998 and December 2002. The age of the study subjects was less than 15 years. A seizure was considered unprovoked when there was no identifiable proximate insult. Patients with a cluster of seizures occurring within 24 hours, and status epilepticus where there was a series of seizures lasting more than 30 minutes or a series of seizures lasting less than 30 minutes between which consciousness was not regained, were included in this study. Children with past history of neonatal seizures, febrile convulsions or other provoked seizures were also included in the study.

Children with typical absence seizures, myoclonic seizures and infantile spasms were excluded because the recurrences of these syndromes were 100%. Non-epileptic events such as syncope were also excluded.

### *Data collection*

Physical examinations and a wakeful EEG were performed on all children. Further laboratory examination such as CT brain scan was performed when clinically indicated. Information on factors that may affect the seizure recurrence was collected. These were: age, gender, seizure type,

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history of febrile seizure, family history of febrile seizure, epilepsy in first degree relatives, delay of developmental milestones, underlying neurological diseases and EEG findings. The EEG was classified as normal, epileptiform abnormality (focal discharges or generalized spike or spike and wave complexes), and non-epileptiform abnormality (focal or generalized abnormal background pattern). Seizures were classified according to seizure semiology and/or EEG data as generalized and partial seizure in accordance with that from the International League Against Epilepsy (ILAE).[10]

*Follow-up*

After recruitment, the patients were followed up at neurology clinic three monthly to look for seizure recurrence, or by letter if they could not attend the clinic for follow up. A seizure recurrence was defined as any unprovoked seizure occurring more than 24 hours after the first unprovoked seizure.

The practice guideline of our Hospital was not to treat children with a first unprovoked seizure. At the time of initial visit, the parents were given information regarding the general treatment strategy and probability of seizure recurrence. None of the patients was given antiepileptic drug after the first unprovoked seizure.

*Analysis*

The results were displayed as Kaplan-Meier survival curves with the cumulative probability of seizure recurrence plotted as function of time from the first unprovoked seizure. The 95% confidence intervals (CI) for Kaplan-Meier estimates of recurrence risks were calculated using approximate Greenwood formula for the standard error. Univariate analysis for dichotomous variable was performed using Log-rank test and continuous variable using t-test or Mann-Whitney U test as appropriate. Multivariate analysis was performed using the Cox proportional-hazards model to obtain crude and adjusted rate ratio for each independent variable. Significance was declared at $p < 0.05$. All p-values were two tailed.

## RESULTS

A total of 91 children were included in the study. This consisted of 47 boys (52%) and 44 girls (48%). The average age was $6.0 \pm 4.1$ years (range 3 months to 14 years). Nine patients (10%) had two or more seizures within 24 hours. Seventy six patients (84%) had generalized seizures, none of the patients had status epilepticus. Seventeen patients (19%) had history of febrile convulsions, 12 patients (13%) had family history of febrile convulsion, 6 patients (7%) had family history of epilepsy, and 6 patients (7%) had delay of developmental milestones. As for EEG, 63 patients (84%) were normal, 9 patients (12%) had epileptiform activity and 3 patients (4%) had abnormal non-epileptiform activity. The duration of time at risk was 904.4 months. The mean duration of follow-up was 9.9 months per person (median 3.5 months, range 2 days- 55.0 months). Overall, 62 cases relapsed during the follow up period (68%). The incidence density of seizure recurrence was 6.9 per 100 person-months. The mean age of patients with seizure recurrence was $6.0 \pm 4.0$ years, whereas the mean age of patients without recurrence was $6.0 \pm 4.4$ years. The mean duration of seizure recurrence after the first seizure was 2.9 months (range 2 days to 12.2 months). The probability of seizure recurrence is shown in figure 1. The Kaplan-Meier estimate of cumulative risk of recurrence was 25% at 14 days, 50% at 4 month, 51% at 6 months, and 66% at 12 months. Most of the seizure recurrence occurred in the first four months.

*Risk factor of seizure recurrence*

Factors that may affect the seizure recurrence is analyzed in Table 1. As shown, gender, seizure type, history of febrile seizure, family history of febrile seizure and history of epilepsy in first degree relatives, abnormal interictal EEG, and delay of developmental milestones were not significant risk factor for seizure recurrence. Multivariate analysis was performed with model as appropriate in Table 2. As shown, none of the risk factors was statistically significant in influencing seizure recurrence. Even though delay of developmental milestone and epileptiform abnormality on EEG showed high hazard ratio at 1.70 and 1.51 respectively, these were also not statistically significant.

## DISCUSSION

This prospective study on 91 Thai children with first unprovoked seizure showed that 68% had recurrence of seizure, most of the recurrence occurred within 4 months. The cumulative risk of recurrence was 50% at 4 months and 66% at 12 months. After 12 months, the cumulative risk only increased slightly. The overall recurrence rate of this cohort study is higher than in most of

Figure 1. Probability of seizure recurrence following a first unprovoked seizure

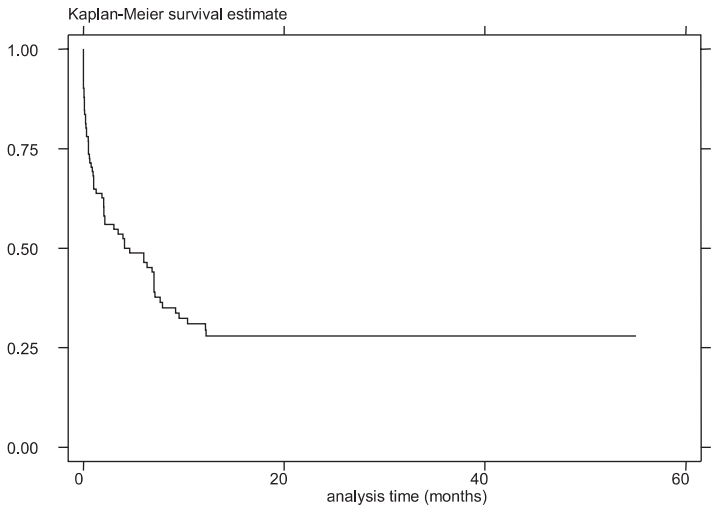


**Table 1. Univariate analysis of risk factor of seizure recurrence**

| **Risk factors** | **Univariate analysis by Log-rank test Incidence density (100 person-months)** | **p-value** |
|---|---|---|
| Male<br>Female | 7.7<br>6.1 | 0.31 |
| Generalized seizure<br>Partial seizure | 7.1<br>5.9 | 0.44 |
| History of febrile seizure<br>No<br>Yes | <br>6.3<br>10.3 | <br>0.71 |
| Family history of febrile seizure<br>No<br>Yes | <br>6.3<br>12.8 | <br>0.21 |
| Family history of epilepsy<br>No<br>Yes | <br>7.8<br>2.0 | <br>0.29 |
| Electroencephalogram<br>Normal<br>Epileptiform abnormality<br>Non-epileptiform abnormality | <br>6.3<br>17.2<br>4.8 | <br>0.49 |
| Delay of developmental milestones<br>No<br>Yes | <br>6.8<br>7.5 | <br>0.80 |

the other recent studies.[1-6,8,9] Young age is a risk factor for seizure recurrence.[11] In the National General Practice Study of Epilepsy from United Kingdom, young age was a risk factor for recurrence after a first seizure. The rate of recurrence at one year for patients 15 years and younger was 70%, as compared to 63% for those 16-39 years, and 55% for 40-59 years.[7] On the other hand, a prospective study enrolling patients at their first seizure as in the present study has a lower recurrence rate than the retrospective study including patients who had previous seizures.[11]

**Table 2. Multivariate analysis of risk factor of seizure recurrence**

| | Hazard ratio | Standard error | p-value | 95% confidence interval |
|---|---|---|---|---|
| Age (years) | 0.97 | 0.04 | 0.37 | 0.90-1.04 |
| Male | 0.83 | 0.24 | 0.52 | 0.47-1.46 |
| Partial seizure | 0.98 | 0.42 | 0.97 | 0.42-2.28 |
| History of febrile seizure | 1.20 | 0.43 | 0.61 | 0.60-2.41 |
| Family history of febrile seizure | 1.25 | 0.53 | 0.60 | 0.55-2.85 |
| Family history of epilepsy | 0.47 | 0.34 | 0.30 | 0.11-1.95 |
| Delay of developmental milestones | 1.70 | 1.07 | 0.40 | 0.49-5.86 |
| Electroencephalogram | | | | |
| epileptiform abnormality | 1.51 | 0.62 | 0.31 | 0.68-3.38 |
| non-epileptiform abnormality | 1.10 | 0.86 | 0.91 | 0.24-5.09 |

Regarding risk factors of seizure recurrence, we have not found gender, seizure type, history of febrile seizure, family history of febrile seizure, history of epilepsy in first degree relatives, abnormal EEG, and delay of developmental milestones to be significant. Other than epileptiform abnormality in EEG and remote symptomatic etiology mentioned earlier[3,5-8], previous studies have identified family history of epilepsy[5,6], partial seizure[2,3,7], abnormal neurological examination and mental retardation[3,8] as risk factors for seizure recurrence. Our failure to identify any significant risk factor could be due to the small sample size.

Although we did not identify epileptiform abnormality to be significant in predicting seizure recurrence, the American Academy of Neurology, the Child Neurology Society and the American Epilepsy Society have recommended that EEG should be a standard investigation in all children with first afebrile seizure. This was not just to determine recurrence, but also help differentiate a seizure from other events, to diagnose epilepsy syndrome, to provide information on long-term prognosis, and as a guide to further neuroimaging studies.[12] The yield of EEG is higher if sleep as well as wakeful EEG is performed.

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