

Risk of seizure recurrence after antiepileptic drug withdrawal in Thai children with epilepsy

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Abstract

Objectives: To determine the incidence and risk factors of seizure recurrence in children with epilepsy after withdrawal of antiepileptic drugs (AEDs) in Thai children. **Methods:** This was a prospective cohort study from April 1995 to December 2005. The study population was children with epilepsy followed up in the neurology clinic, Hatyai Hospital, southern Thailand. The eligible children were less than 15 years, seizure-free for at least 24 months. The AEDs were withdrawn slowly. The patients were then followed up to look for seizure recurrence. **Results:** Seventy one children were recruited in the study. The average age of onset of epilepsy was 8.4 years. Most patients had generalized seizures (76%), were receiving monotherapy (93%), and were treated with phenobarbital (72%). The seizure-free duration before commencing AED withdrawal was 43.2 months. None of the patients had seizure recurrence while the AEDs were being tapered. There were 10 patients (14%) with seizure recurrence. The average duration of follow-up for the patients who did not have seizure recurrence was 43.5 months. The cumulative probability of patients remaining seizure free was 90% at 12 months, 90% at 24 months, and 88% at 36 months. The risk factor of seizure recurrence was the need for 2 AEDs. **Conclusions:** The risk of recurrence after AED withdrawal in Thai children was low at 14%.

INTRODUCTION

Seizure is a common neurological disorder in children. Antiepileptic drugs (AEDs) are usually used long-term. The medication is only tapered after a seizure-free interval to minimize the risk of recurrence.^{1,2} There are many studies on the risk of seizure recurrence after withdrawal of AEDs, which varies from 10% to 50%, partly depending on the study designs.¹⁻⁵ The risk factors of seizure recurrence identified include older age of onset of epilepsy, remote symptomatic epilepsy, abnormal electroencephalography (EEG), some epilepsy syndromes such as juvenile myoclonic epilepsy, severity of epilepsies, and those with family history.⁶⁻¹² There are to date only rare reports on risk of seizure recurrence after AED withdrawal Asian countries, particularly those published in English.¹³ The objectives of this study were to determine the incidence and risk factors of seizure recurrence after AEDs discontinuation in Thai children with epilepsy.

METHODS

This was a prospective cohort study. The study population was children with epilepsy at pediatric neurology clinic of Hatyai Hospital, southern Thailand. The study was conducted over the 10 years period from April 1995 to December 2005.

The eligible subjects were children with age of onset of epilepsy less than 15 years, who were seizure-free while on AEDs for at least 24 months. The AEDs were usually tapered slowly, over at least 3 months. The exact duration over which the AEDs were withdrawn was however, varied among the patients, based on the joint decision of the attending physicians, parents, and the patients. If the patients were receiving more than one AEDs, the AEDs were withdrawn sequentially with each AED being withdrawn over at least 3 months. Phenobarbital was usually the last AED to be withdrawn. After total drug withdrawal, the study subjects were followed up regularly until seizure recurrence. For patients who could not come to hospital for follow up, the ascertainment of seizure recurrence was determined through mails. The seizures were classified as generalized, partial, and undetermined mainly on the basis of history. Electroencephalography (EEG) was not obtained in all children as it was not available during the early period of study. Demographic data, age at onset of epilepsy, and any neurological deficit were also recorded.

Statistical analysis

A survival analysis was performed with seizure recurrence as the hazard ratio and the interval of seizure recurrence (failure time) start of complete

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drug withdrawal. Log rank test was used for univariate analysis and Cox proportional-hazard model was used for multivariate analysis for risk factors of seizure recurrence. Kaplan-Meier plots of the data were constructed. All statistical tests were 2-tailed. The p-value of less than 0.05 was regarded as statistically significant.

RESULTS

A total of 71 patients were enrolled in this study, which was from April 1995 to December 2005. The characteristics of patients are shown in Table 1. As shown, the average age at onset of epilepsy was 8.4 years (100 months). The most common seizure was generalized (76%). Most patients were treated with monotherapy (93%). Phenobarbital was the most common AED used (72%). The neurological deficits included mental retardation, global delay development, delay speech, hydrocephalus, and cerebral palsy. The average duration of follow-up after AED withdrawal was 43.5 months (range 0.1 to 96 months) for patients who did not have seizure recurrence. None of the patients developed seizure recurrence while the AEDs were being tapered. There were 10 patients (14 %) who developed seizure recurrence after AED withdrawal. The incidence density was 0.003 person-months. The details of patients with seizure recurrence are shown in Table 2. There were 7 boys and 3 girls. Most of those with seizure recurrence had generalized seizures. The average interval after AED withdrawal when seizure recurrence

occurred was 13.0 ± 17.1 months (range 0.1 – 41.6 months). The Kaplan-Meier plot for seizure recurrence is shown in Figure 1. Most patients who had seizure recurrence did so within 12 months after AED withdrawal. The cumulative probability of patients remaining seizure free was 90% at 12 months, 90% at 24 months, and 88% at 36 months.

Univariate analysis was performed for risk factors of seizure recurrence as shown in Table 3. The risk factor for seizure recurrence is patients who required 2 AEDs. Figure 2 shows the cumulative probability of seizure recurrence comparing between patients with monotherapy and those requiring 2 AEDs. Multivariate analysis was also performed for risk factors of seizure recurrence as shown in Table 4. As shown, patients who required 2 AEDs had significant risk of recurrence with hazard ratio of 5.35 as compared to those with monotherapy.

DISCUSSION

The risk of seizure recurrence after AED withdrawal in this study was 14 % that is better than most series previously reported.^{1-5,14} There are a number of characteristics in our cohort, which may explain the lower rate of seizure recurrence. Our patients consist of Thai children, with average age of onset of epilepsy of 8.4 years. Children have been shown to have better prognosis after AED withdrawal.^{3,15} The proportion with neurological deficits in our cohort is relatively low at 14%. For example, the proportion with

Table 1: Characteristic of the patients with AED withdrawal (n=71)

Characteristic	No of patients (%)
1. Male	42 (59)
2. Age at onset of epilepsy in months	100 ± 48 (range 3-180)
3. Types of seizures	
a. generalized	54 (76)
b. partial	14 (20)
c. undetermined	3 (4)
4. Antiepileptic drug (AED)	
a. Phenobarbital	51 (72)
b. Phenytoin	4 (6)
c. Sodium valproate	14 (20)
d. Carbamazepine	2 (3)
5. Patients taking more than 2 AEDs	5 (7)
6. Patients with neurological deficit	10 (14)
7. Seizure-free duration before commencing AED withdrawal in months	43.2 ± 19.1 (range 24.3-121.7)

Table 2: Characteristic of patients with seizure recurrence (n = 10 cases)

Sex	Types of seizure	AED	EEG	Seizure-free duration (months)*	Recurrence (months)**	Other disease
1. Male	Gen	PB,VPA		32.9	1.9	
2. Male	Gen	PB	NA	41.6	41.6	history of FC
3. Male	Gen	PHT,VPA	NA	36.5	27.1	
4. Male	Partial	PB	Abn	41.6	12.3	
5. Male	Gen	PB	NA	39.4	0.7	
6. Female	Gen	PB	NA	121.7	0.1	systemic carnitine deficiency
7. Female	Gen	PB	NA	29.4	0.5	
8. Male	Partial	VPA,PHT	NA	35.5	4.4	
9. Female	Partial	PB	NA	40.7	1.9	
10. Male	Gen	PB	NA	23.3	1.6	

* Seizure-free duration before commencing AED withdrawal

** Interval after AED withdrawal when seizure recurrence occurred

AED = antiepileptic drug, Gen = generalized seizures, PB = phenobarbital, PHT = phenytoin, VPA = valproic acid, FC = febrile convulsions, EEG = electroencephalography, NA = not available
Abn = abnormal

Table 3: Univariate analysis by Log rank test for risk factors of seizure recurrence

Variable	Total No.	No. with recurrence	Incidence rate	p-value
1) Male	42	7	0.004	0.54
Female	29	3	0.003	
2) Generalized seizure	54	7	0.003	0.55
Partial seizure	14	3	0.006	
Undetermined	3	0	0	
3) No neurological deficit	61	9	0.004	0.63
Neurological deficit	10	1	0.002	
4) AED medication				0.001
monotherapy	66	7	0.002	
2 AEDs	5	3	0.025	

Table 4: Multivariate analysis by Cox proportional-hazard model for the risk factor of seizure recurrence

Variable	Hazard ratio	95% CI	p-value
1. Neurological deficits	1.04	0.06-15.76	0.97
2. Age at onset of epilepsy	1.00	0.99-1.02	0.37
3. Seizure-free interval during medication	1.00	0.96-1.05	0.83
4. Patients with 2 AEDs	5.35	1.20-23.81	0.03
5. Male	0.78	0.19-3.22	0.74
6. Partial seizures	0.87	0.25-2.97	0.83

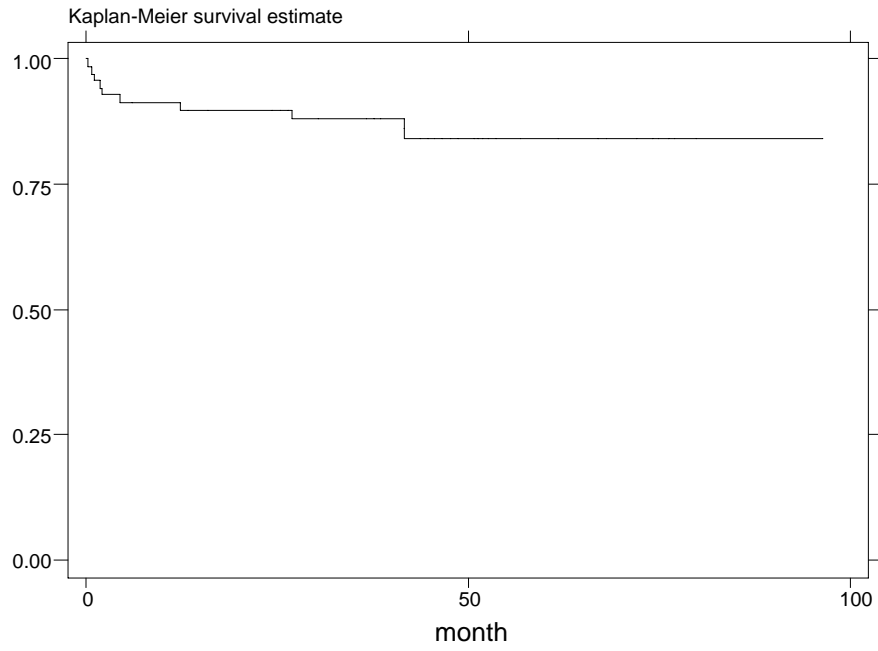


Figure 1: The cumulative probability of patients remaining seizure free after AED withdrawal

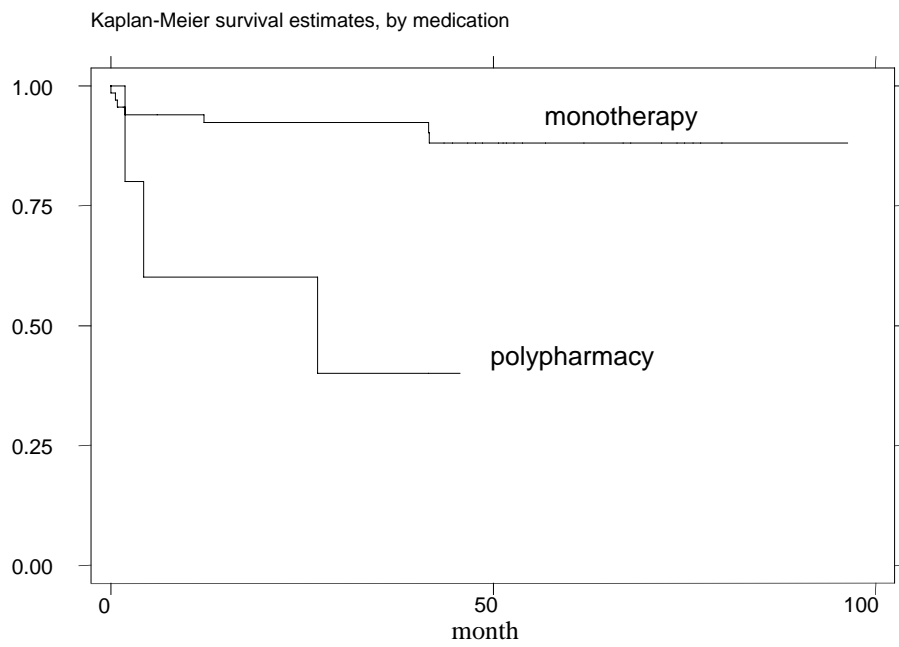


Figure 2: A comparison between patients on monotherapy and polypharmacy for the cumulative probability of remaining seizure free after AED withdrawal

neurological deficit in the MRC trial was 22-24%.⁷ Remote symptomatic epilepsy, presence of neurological deficits particularly mental retardation, have been shown to be associated with poorer prognosis.⁶⁻¹² The average seizure-free duration before commencing AED withdrawal in our patients is 43.2 months, which is relatively long. Longer period of seizure-freedom before AED withdrawal is associated with lower seizure recurrence.^{5,15} On the other hand, barbiturate has been reported to have a greater tendency to relapse as compare to other AEDs.¹⁶ It is thus gratifying to note that in our cohort where 72% of the patients were taking barbiturate, the recurrence rate after AED withdrawal was low.

In this study, we found that patients with polypharmacy had the risk of seizure recurrence five times more than monotherapy. Not surprisingly, patients who needed polypharmacy reflect their disease being more severe than those requiring monotherapy. We could not find types of seizure, neurological deficit, age at onset of epilepsy, sex, and seizure-free interval during medication as risk factors of recurrence which are different from previous studies.^{6-10,14} EEG abnormalities which have been shown to be a risk factor of recurrence¹⁴ could not be analyzed in this study because EEG recording was not available in our hospital in the early period of study. The determination of types of seizure is handicapped in some patients, being entirely clinical without the benefit of EEG.

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