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Original Article

Duration of active epilepsy as a predictor of seizure control after relapse in child epilepsy

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Abstract

Background Epilepsy is a chronic illness that may affect childhood growth and development. Some epilepsy cases are easy to control, either with monotherapy or politherapy antiepileptic-drugs, but many cases are difficult to control. Several factors influence the risk of relapse, but information is limited on factors predictive of seizure control after relapse. Our study investigate patient with epilepsy relaps and see whether the duration of active epilepsy prior to initial remission can be use as a predictor of seizure control after relaps.

Objective To assess whether duration of active epilepsy was predictive of seizure control after relapse.

Methods This retrospective cohort study was performed in Dr Sardjito Hospital, Yogyakarta, on epileptic relapse patients aged 2 to 18 years , who had achieved remission for at least a 2-year seizure-free interval, and relapsed after antiepileptic drud (AED) discontinuation. We excluded patients with progressive neurological diseases, inborn errors of metabolism, febrile seizures, and those who could not be followed up for at least 2 years, or those with incomplete medical records. Subjects were divided into those who had a duration of active epilepsy prior to initial remission within 6 months and ≥6 months. Time to seizure control after relapse was analysed by Kaplan-Meier survival analysis.

Results A total of 80 patients were included in the study. Overall median for seizure control after relapse was 3.6 (95%CI 1.1 to 6.0) months. Median for seizure control after relapse for those who had a duration of active epilepsy prior to initial remission within 6 months and ≥ 6 months were 3 (95%CI 0.1 to 5.8) months and 12 (95%CI 4.4 to 19.5) months, respectively. Log-rank test revealed no significant difference between groups (P=0.12).

Conclusion Duration of active epilepsy prior to initial remission was not a predictor for seizure control after relapse. **[Paediatr Indones. 2020;60:212-7 ; DOI: 10.14238/pi60.4.2020.212-7]**.

Keywords: *active epilepsy; predictor; seizure control; relapse*

Epilepsy is a chronic disease with the potential to disturb child development. Survival rates of infants at high risk of neurological and developmental disorders, including epilepsy, have increased in developing countries like Indonesia, because of increased availability of medical services for perinatal and infant patients.[1-3] Epilepsy is a neurologic condition characterized by complex symptoms such as irregular and excessive sudden paroxysmal nerve excitation caused by various pathological processes in the brain.[4] The incidence of epilepsy in children is higher than in adults, and usually starts at a young age. In developing countries, the incidence of epilepsy in children is around 40 cases/100,000 children per year.[2,3,5]

Approximately two-thirds of children with epilepsy reach a seizure-free state within the first or second anti-epileptic drug (AED) therapy,

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while the rest (around 35%) have intractable or difficult to control conditions.[6,7] Various factors should be considered in the withdrawal of AEDs, based on individual assessments including AED effects during the first therapy, side effects, psychosocial considerations, and if seizure relapse occurs within the withdrawal period.[4] Inappropriate AED withdrawal increases the risk of relapse in controlled epilepsy. If relapse occurs during AED withdrawal, complete remission of epilepsy is more difficult to achieve. In fact, approximately 63% of patients who relapse develop drug resistance.[8] Discontinuation of AEDs should be considered for children who have been seizure-free for at least 2 consecutive years, as 60-70% of these children do not experience relapse after stopping the AEDs. For the remainder who experience relapse, long-term remission can still be achieved by standard treatment protocols.[3]

Several factors reportedly can be used to predict relapse: symptomatic epilepsy, epilepsy syndrome, age of onset, seizure-free interval duration, and abnormal EEG imaging if AEDs are discontinued.[3] Relapse risk after AED discontinuation in children was estimated to be 16-56%.8 Other systematic reviews, including 28 case reports involving 2,758 children with most having a seizure-free interval of more than 2 years before AED withdrawal, concluded that cumulative probability for being seizure-free after AED withdrawal was around 66-96% in the first year, and 61-91% in the second year. Furthermore, relapse risk was higher in the first year (especially first six months) after stopping AEDs, and then decreased in the following months.[8,9]

To our knowledge, this is the first study on predictive factors of seizure control after relapse in Indonesia. We aimed to assess if the duration of active epilepsy before AED therapy was a predictor for the time to seizure control after relapse.

Methods

This retrospective study was done in Dr. Sardjito Hospital, Yogyakarta, using medical record data. The study period was January 2012 to December 2017, and subjects were included by purposive sampling. All medical records were assessed by a pediatric neurologist to determine if patients met the inclusion criteria, which were children aged 2-18 years, diagnosed with epilepsy, had achieved remission for at least a 2-year seizure-free interval, and relapsed after AED discontinuation. Patients with progressive neurological diseases, inborn errors of metabolism, febrile seizures, those who could not be followed up for at least 2 years, or those with incomplete medical record data were excluded. A total of 80 subjects were divided into two groups of 40 subjects each: those with duration of active epilepsy prior to initial remission was less than 6 months , and those with duration of active epilepsy prior to initial remission was >6 months.

Data were analyzed using the *Statistical Package for the Social Science (SPSS) version 20.0* software. Chi-square analysis was used for bivariate data, followed by Mantel-Haenzel test for multivariate analysis of confounding variables. Survival analysis was done to assess time-to-event outcomes. Ethical approval of the study was obtained from the Ethics Committee of the Universitas Gadjah Mada Medical School, Indonesia.

Results

Baseline characteristics of study subjects are shown in **Table 1**. The ratio between males and females was 1:1. The median patient age at onset of epilepsy diagnosis was 6.04 (range 0.08-16) years, and 51.2% of patients were >6 years old at diagnosis. The median age at the time of relapse was 9.49 (range 2-18) years. Most subjects relapsed in the first six months after AED withdrawal (**Table 2**).

Bivariate analysis results of potentially predictive factors in seizure control post-relapse are shown in **Table 2**. Using risk ratio calculation, duration of active epilepsy prior to initial remission did not influence the seizure control after relapse (RR 1.42; 95%CI 0.55 to 3.67; P=0.47).

Analysis was continued using a Kaplan-Meier curve. From a total of 80 subjects, overall median time to seizure control after relapse was 3.6 (95%CI 1.1 to 6.0) months (**Figure 1**). The median time to seizure control after relapse in the group with < 6 month duration of active epilepsy prior to initial remission was 3 (95%CI 0.1 to 5.8) months, while that of the group with ≥ 6 month duration of active epilepsy was 12 (95%CI 4.4 to 19.5) months. Log-rank test revealed no significant differences between the two groups (P=0.12).

Table 1. Baseline characteristics of subjects

Characteristics	N=80
Gender	
Male, n (%)	40 (50)
Female, n (%)	40 (50)
Age at onset of epilepsy diagnosis, n (%)	
< 6 years	39 (48.8)
≥ 6 years	41 (51.2)
Median age at onset of epilepsy diagnosis (range), years	6.04 (0.08-16)
Median age at the time of relapse diagnosis (range), years	9.49 (2-18)
Time to relapse after AED withdrawal	
< 6 months	48 (60)
6-12 months	32 (40)
Seizure type, n (%)	
Partial	19 (23.8)
General	51 (76.2)
Seizure etiology, n (%)	
Symptomatic	41 (51.2)
Idiopathic	39 (48.8)
AED therapy, n (%)	
Polytherapy	11 (13.8)
Monotherapy	69 (86.2)
EEG evaluation, n (%)	
Epileptiform	67 (83.8)
Normal	13 (16.2)
History of status epilepticus, n (%)	
Yes	16 (20)
No	64 (80)
History of epilepsy in the family, n (%)	
Yes	13 (16.2)
No	67 (83.8)
Head CT-scan results, n (%)*	
Abnormal	21 (91.3)
Normal	2 (8.7)
Seizure frequency before AED withdrawal, n (%)	46 (57.5)
> 1x/month	34 (42.5)
< 1x/month	
Seizure control after relapse	
< 6 months	50 (62.5)
6-12 months	12 (15)
1-2 years	9 (11.2)
>2 years	9 (11.2)

*CT scan was only performed in 23 subjects

Discussion

The relapse rate in the last year of our observation was 23 (6.2%), as shown in a study about the predictive factors of relapse in children with epilepsy after AED withdrawal in Dr. Sardjito Hospital, Yogyakarta, showed the prevalence of relapse was 3.6%.10 Reported rates varied from 22.4% to 40% in other studies.[6,10,11] This discrepancy may be due to the heterogeneity of the population, as well as different criteria for relapse, follow-up periods, and statistical methods. The relapse criteria in our study were patients who had achieved remission (seizure-free) for at least 2 consecutive years and experienced seizures at the AED withdrawal phase or after AED discontinuation. Our relatively lower relapse rate may have been due to our exclusion of patients with progressive neurological deficits or inborn errors of metabolism, which have poor prognoses and have higher relapse rates. In addition, the low incidence of relapse in our study may have also been due to the predominance of the general seizure type, the use of monotherapy, and few subjects with a history of status epilepticus. Similarly, a previous study showed that relapse could be predicted by abnormal EEGs (especially epileptiform), onset of epilepsy (higher risk if <2 years, or >10 years of age), history of status epilepticus, intellectual disability, and seizure frequencies before and during AED treatment.[5]

Few investigators have addressed the question of what happens to children when medication is withdrawn after prolonged seizure control, but no study has specifically investigated the after relapse condition. Some authors found that females had a higher rate of relapse. A study showed that females predominated the relapse group (52.4% females vs. 47.6% males), but the difference was not statistically significant.10 In our study with 40 female subjects, 70% (28/40) attained seizure control at < 6 months after relapse.

Overall median age at epilepsy diagnosis in our study was 6.04 (range 0.08-16) years. From total subjects that had first relapse episode, 41 (51.2%) subjects had the onset of epilepsy at ≥ 6 year old compared to those diagnosed onset of epilepsy at < 6 years of age. In contrast, a previous study showed that children diagnosed with epilepsy at >6 years of age had a 29.4% greater risk of relapse compared to those diagnosed with epilepsy at <6 years of age.[9] This discrepancy may support other study that showed age was not a predictor for seizure relapse in epilepsy.

In our study, 62.5% of subjects needed less than 6 months to seizure control after relapse, the relapse

Table 2. Bivariate analysis of potential factors predictive of seizure control after relapse

Variables	Seizure control after relapse				
	≥ 6 months (n=25)	<6 months (n=55)	RR	95%CI	P value
Duration of active epilepsy, n					
≥ 6 months	14	26	1.42	0.54 to 367	0.46
< 6 months	11	29			
Seizure type, n					
Partial	6	13	1.02	0.33 to 3.09	0.97
General	19	42			
Seizure etiology, n					
Symptomatic	15	26	1.67	0.64 to 4.36	0.29
Idiopathic	10	29			
AED therapy, n					
Polytherapy	6	5	3.15	0 .86 to 11.5	0.09
Monotherapy	19	50			
EEG evaluation, n					
Epileptiform	22	45	1.63	0.41 to 6.52	0.74
Normal	3	10			

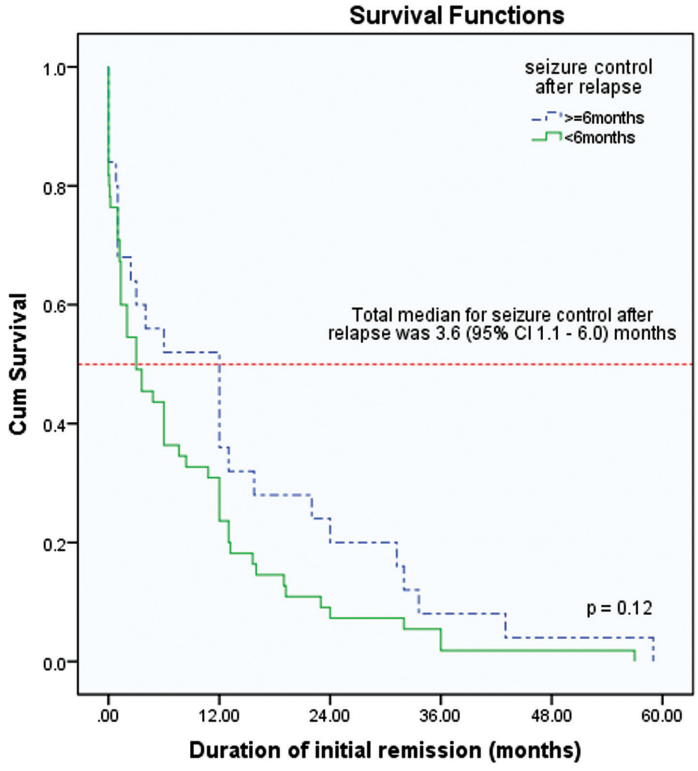

Figure 1. Kaplan-Meier curve of time to seizure control based on duration of active epilepsy groups

controlled in the first year was 15%, and after the second year at 11.2%. Similarly, a study noted that 65.3% of patients needed <6 months to control their seizure after relapse, and 34.7% patients need ≥ 6 months to control their seizure after relapse.[10] But in our study, the duration of active epilepsy prior to initial remission was not significantly related to seizure control after relapse.

Bivariate analysis showed no significant differences between groups with seizure control time <6 months and ≥6 months, with regards to seizure type, seizure etiology, type of AED treatment, or EEG evaluation at AED withdrawal. The duration of active epilepsy was not significantly different between the two groups of seizure control duration after relapse (RR 1.42; 95%CI 0.55 to 3.67; P=0.47). In our study, monotherapy had RR of 3.15 (95%CI 0.86 to 11.5; P=0.09) compared to polytherapy. Despite the predominance of subjects using monotherapy (86.2% *vs.* 13.8%, respectively), therapy type may be a potential predictor for seizure control duration after relapse. Further investigation that compares closer to equal numbers of monotherapy vs. polytherapy is needed. In addition, general seizure type was dominant in our study (76.2%) and is more likely to have a positive response to AED treatment. This result may explain why the majority of our subjects had seizure control after relapse of < 6 months (68.8%).

Survival analysis showed that for the 80 patients in this study, the total median for seizure control after relapse was 3.6 (95%CI 1.1 to 6.0) months. In the <6 month duration of active epilepsy group, the median for seizure control was 3.0 (95%CI 0.1 to 5.8) months, while that of the group with ≥6 month duration of active epilepsy was 12.0 (95%CI 4.4 to 19.5) months. Log-rank test revealed no statistically significant relationship between duration of active epilepsy prior to initial remission and seizure control duration after relapse (P=0.12). Although there was no direct correlation between duration of active epilepsy and seizure control time in relapse patients, the shorter duration of active epilepsy tended to indicate the sooner the relapse would be controlled.

The main limitation of our study was the retrospective retrieval of information from medical records, which may have led to information bias. To our knowledge, there were no studies that investigated the clinical conditions after relapse in epilepsy patients and factors that can be used as positive or negative predictors. In conclusion, the duration of active epilepsy prior to initial remission cannot be used as a predictor for seizure control duration after relapse. As such, we recommend a future study with a prospective design, more homogeneous subjects, longer follow-up time, and analysis of other potential predictive factors of relapse after AED withdrawal in epileptic children.

Conflict of Interest

None declared.

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