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Original Article

Predictors for seizure relapse in children with epilepsy after antiepileptic drug withdrawal:

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Abstract

Background Epilepsy is defined as a neurologic condition caused by a pathological brain condition. Epilepsy patients who have stopped treatment and are seizure-free for two years are considered to have achieved complete remission. Relapse occurs when seizures return after anti-epileptic drug (AED) withdrawal. Several studies reported that frequent seizures, prolonged duration to control seizures, number of AEDs consumed, and abnormal electroencephalography (EEG) found during AEDs tapered, were reported as predictors of relapse.

Methods This retrospective, case-control study was carried out from 2012-2016 using multisite medical record evaluation, followed by interviews and EEG examinations. The case group included children with epilepsy who had seizure relapse, while the control group included children with complete remission of epilepsy. Bivariate and multivariate analyses were performed to identify predictors of relapse.

Results Relapse predictors in bivariate analysis were symptomatic etiology epilepsy (OR 5.000; 95%CI 2.345 to 10.660; P<0.001), time to seizure control ≥1 year (OR 3.689; 95%CI 1.493 to 9.116; P=0.003), and worsened EEG evolution at pre-withdrawal compared to EEG at the time of diagnosis (OR 2.310; 95%CI 1.132 to 4.717; P=0.021). Statistically significant relapse predictors in multivariate analysis were symptomatic etiology epilepsy (OR 4.384; 95%CI 1.985 to 9.681; P<0.001) and slow (≥1 year) time to seizure control (OR 4.355; 95%CI 1.753 to 10.817; P 0.002).

Conclusion Symptomatic etiology epilepsy and time to seizure control ≥1 year are independent predictive factors for seizure relapse in children with epilepsy. Therefore, children with these conditions require a longer period and careful, gradual dose reduction before anti-epileptic drugs withdrawal. **[Paediatr Indones. 2024;64:120-5; DOI: 10.14238/pi64.2.2024.120-5**].

Keywords: *children; epilepsy; predictor; seizure; relapse*

Epilepsy is defined as a neurologic condition characterized by recurrent, paroxysmal, irregular and excessive seizures caused by a pathological brain condition.[1,2] Annual epilepsy events were reported to be 139 per 100,000 in developing countries and 49 per 100,000 in developed countries.[3] Epilepsy is a chronic condition that affects not only patients, but also their families. Loss of self-control and independence can lead to low self-esteem, fear, depression, social stigma, and barriers to social life that are challenging, as well as other negative impacts on patients. These conditions indirectly affect the social, work, and economic conditions of the family.[4]

The dose of anti-epileptic drugs (AEDs) can be tapered over 6-12 months before being stopped for patients with epilepsy who are seizure-free for 2 years.[5] Epilepsy patients who have stopped treatment and seizure-free for 2 years are considered to have achieved complete remission. Despite being in complete remission, seizures can occur again at any

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time.[6] Relapse is a condition when seizures reoccur during the dose reduction of the AED or after it is completely discontinued.[5] The incidence of relapse is 28.6-36%, with half of relapses occurring during dose reduction, and the other half occurring after the AED is stopped.[7,8] The cumulative incidence of relapse after AED withdrawal is 54.5% within the first 6 months, 63.6% at 12 months, 81.8% at 18 months, and 95.4% at 24 months.[5]

There is no protocol or consensus on when to withdrawal AEDs safely to prevent relapse, but long-term usage of AEDs can cause many side effects. Therefore, various factors must be considered in the decision to withdrawal AEDs and it must be adjusted to the condition of each patient. Rapid withdrawal of AEDs increases the risk of relapse and may subsequently lead to difficulty in achieving complete remission.[1,9] The risk of relapse in children with epilepsy is 16-56%, with 63% of relapse patients having drug-resistant epilepsy.[10]

Focal seizures are an important predictor of relapse. Symptomatic epilepsy and developmental disorders are also predictors of relapse.[5,10-13] Several studies have reported that frequent seizures and prolonged duration to control seizure are predictors of relapse.[8,11,14] Prolonged and recurrent seizures have also been reported to cause brain damage and decrease seizure thresholds.[5,11,15] Abnormal electroencephalography (EEG) during anti-epileptic drug (AED) dosage tapering was also found to be a predictor of epilepsy relapse. EEG status before, during, and after therapy is related to the incidence of relapse.[9,10,12] The number of AEDs consumed was also reported as a predictor of relapse.[5] The risk of relapse was higher in patients receiving polytherapy than in the monotherapy group.[5,11] We aimed to describe the characteristics of children with epilepsy who experience seizure relapse and to determine the predictive factors for seizure relapse.

Methods

This retrospective, case-control study included patients from one tertiary referral hospital, one secondary hospital, and two pediatric neurology clinics. The study population was children aged 2-18 years who had been diagnosed with epilepsy relapse and children of similar age who had achieved complete remission. The inclusion criteria for the case group were children with epilepsy relapse (experienced seizure recurrence after an AED dose reduction or discontinuation). The control group included children with complete remission (achieved seizure-free remission for at least 2 years of therapy plus a 2-year follow-up period without AEDs). The exclusion criterion was incomplete medical record data. The minimum required sample size was calculated using the formula for a case-control study and found to be 60 subjects for each group. Subjects were included by consecutive sampling from medical record data dated 2012-2016. Interviews and EEG examinations for the case group were conducted between June and December 2016.

Factors investigated were the number of AEDs used, time to control seizures since diagnosis (categorized as slow if seizures were controlled for more than 1 year), symptomatic epilepsy or underlying neurological disorder, seizure type, and EEG wave evolution. An EEG wave evolution was the result of an EEG comparison between the time at diagnosis and prereduction of AED dose. Evolutionary EEG worsened if the wave frequency of epilepsy increased or if there was a slowing wave or similar wave compared to the previous EEG, while EEG evolution improved if epileptiform waves disappeared or decreased or there were no slowing waves compared to the previous EEG.

Data were analyzed with *SPSS 22.0* software (*IBM Corp*., Armonk, NY). Data were analyzed descriptively, followed by Chi-square test for bivariate analysis and multivariate logistic regression analysis to identify factors predictive of relapse. After determining the odds ratio (OR) with 95% confidence interval (CI), P values < 0.05 were considered to be statistically significant. The study was approved by the Medical and Health Research Ethics Committee Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia.

Results

There were 78 identified epilepsy relapse cases and 129 epilepsy with complete remission cases. A total of 15 patients with epilepsy relapse were excluded because of incomplete medical record data, thus, 63

epilepsy relapse patients were included in the case group. From 129 epilepsy with complete remission cases, 63 patients were subsequently selected for the control group.

The mean age of subjects in the case group was significantly higher than that of the control group [12.71 (SD 0.67) *vs.* 9.83 (SD 0.54) years; P= 0.001]. The onset age of epilepsy was also higher in the case group than in the control group [4.53 (SD 0.60) *vs.* 2.98 (SD 0.45) years; P=0.042]. Presenting epileptic seizure types at the time of diagnosis were simple focal in 5 (4%) subjects, focal complex in 2 (1.6%) subjects, focal to general in 9 (7.1%) subjects , absence in 8 (6.3%) subjects , general myoclonic in 3 (2.4%) subjects, general tonic in 6 (4.8%) subjects, general tonic-clonic in 79 (62.7%) subjects, general atonic in 3 (2.4%) subjects, general idiopathic seizure in 2 (1.6%) subjects , and generalized epilepsy with febrile seizure plus (GEFS+) in 6 (4.8%) subjects. There were 3 subjects with epilepsy syndrome, including 1 infantile seizure in the case group, as well as 1 infantile seizure and 1 rolandic epilepsy type in the control group.

Chi-square analysis revealed that the significant predictive factors of epilepsy relapse in children were slow time to seizure control (OR 3.69; 95%CI 1.49 to 9.12; P=0.003), symptomatic epilepsy (OR 5.00; 95%CI 2.34 to 10.66; P<0.001), and deteriorating EEG evolution (OR 2.31; 95%CI 1.13 to 4.72; P=0.021) (**Table 1**).

The three significant predictive factors from bivariate analysis were analyzed by multivariate logistic regression using the backward stepwise regression method. Symptomatic epilepsy (OR 4.384; 95%CI 1.985 to 9.681; P <0.001) and slow time to seizure control (OR 4.355; 95%CI 1.753 to 10.817; P 0.002) were independent predictive factors for relapse in pediatric epilepsy (**Table 2**).

Discussion

The mean age and age at onset of seizures in the

Table 1. Characteristics of subjects and bivariate analysis (N=126)

Characteristics	Relapse (n=63)	Complete remission (n=63)	OR	95% CI	P value
Seizure type[a], n (%)					
Focal	10 (15.9)	6 (9.5)	1.792	0.609 to 5.273	0.285
General	53 (84.1)	57 (90.5)			
Etiology[b], n (%)					
Symptomatic	45 (71.4)	21 (33.3)	5.000	2.345 to 10.660	<0.001*
Idiopathic	18 (28.8)	42 (66.7)			
Time to seizure control[c], n (%					
Slow (≥1 year)	22 (34.9)	8 (12.7)	3.689	1.493 to 9.116	0.003*
Fast (<1 year)	41 (65.1)	55 (87.3)			
EEG evolution[d], n (%)					
Worsened	38 (60.3)	25 (34.9)	2.310	1.132 to 4.717	0.021*
Improved	25 (39.7)	38 (65.1)			
EEG pre-withdrawal, n (%					
Epileptiform	49 (77.8)	48 (76.2)	1.094	0.477 to 2.508	0.832
Normal	14 (22.2)	15 (23.8)			
Number of AED, n (%)					
Polytherapy (≥2)	8 (12.7)	4 (6.3)	2.145	0.612 to 7.527	0.225
Monotherapy	55 (87.3)	59 (93.7)			

[a]Focal type: simple focal seizure, focal complex seizure, focal to general seizure. General type: absence seizure, general myoclonic seizure, general tonic-clonic seizure, general atonic seizure, general idiopathic seizure, GEFS+.
[b]Symptomatic etiology epilepsy: epilepsy that follows an injury to the brain known to be capable of causing epilepsy. Idiopathic epilepsy: epilepsy with no findings of neuroanatomical or neuropathological abnormalities
[c]Time to seizure control: the time interval from the first AED intake until the seizure become controlled.
[d]EEG evolution worsened: if the wave frequency of epilepsy increased or if there were slowing waves or similar waves compared to the previous EEG; EEG evolution improved: if epileptiform waves disappeared or decreased or there were no slowing waves compared to the previous EEG.

Table 2. Multivariate logistic regression analysis

Variables	B	SE	OR	95% CI	P value
Symptomatic etiology	1.478	0.404	4.384	1.985 to 9.681	<0.001
Slow time to seizure control	1.471	0.464	4.355	1.753 to 10.817	0.002
Worsened EEG evolution	1.193	0.318	1.757	0.786 to 3.923	0.169

case group were higher than in the control group. Past studies have suggested that the age at onset of epilepsy is a significant factor, as an epilepsy onset age of 4-12 years was associated with decreased incidence of relapse.[7,11] Young children generally have better resistance to seizure events because of their brain plasticity.[16]

The proportion of general-type seizures in our study was greater than that of focal-type seizures. Differences in the proportions of seizure types in various studies may have been influenced by differences in populations and inclusion criteria between studies.[8] Focal seizures were more common in the relapse group, though the difference was not significant. This result was in contrast with other studies in which general-type seizures were more common in the relapse group.[8,17] Seizure type as a predictive factor for epilepsy relapse remains controversial. Previous studies report that the seizure type is a significant predictive factor.[18,19-21]

In our study, most subjects used monotherapy. Subjects who used polytherapy (≥2 AEDs) were more common in the relapse group than in the remission group. Polytherapy was not a significant predictor of relapse, similar to previous studies.[5,22] Polytherapy could be ruled out when other significant predictive factors were not found.[8,11]

Symptomatic etiology epilepsy was more common than idiopathic epilepsy. In the relapse group, symptomatic etiology was the most common, while in the remission group, idiopathic etiology was more common. The definition of symptomatic etiology epilepsy in our study was based not only on computerized tomography scans or head magnetic resonance imagery findings, but also on neurologic abnormalities, post-meningitis epilepsy, genetic etiology epilepsy, and epilepsy in patients who were confirmed to have neuroanatomic and neuropathological abnormalities in the brain. The risk of relapse was 1.5-2 times higher in the group with symptomatic etiology epilepsy compared to previous studies.[23,24] While 10 of 21 studies reported symptomatic etiology as a significant predictor of epilepsy relapse after multivariate analysis, 3 studies reported symptomatic etiology as an independent predictive factor.[11]

The most common time to seizure control in our study was <1 year of treatment, but was ≥1 year in the relapse group, similar to previous studies.[12,17] Slow time to seizure control (≥1 year) was a predictor of relapse in previous studies.[11,25] Prolonged and repeated seizures can cause brain damage through kindling models and the formation of epileptogenic foci which can cause activation of a pharmaco-resistant mechanism. Glutamate, as the main neurotransmitter, plays an important role in the kindling model and will cause excessive influx of calcium ions at the NMDA receptor, which are neurotoxic for brain tissue. This process permanently increases neuro-sensitivity to stimuli and reduces the seizure threshold.[26-28] The active duration of epilepsy since the onset of seizure and the frequency were signs of severe epilepsy and increased the risk of relapse after reduction of AED.[11,25]

As many as 50% of subjects still showed the presence of epileptiform waves on the EEG when AED withdrawal started. Both the relapse and remission groups showed mostly abnormal EEG when the drug dose was reduced (77.8% *vs.* 76.2%, respectively). The number of improved EEG evolutions was more common in the remission group than the relapse group (65.1% *vs.* 39.7%, respectively). The use of evolution of EEG as a predictive factor for relapse is still controversial.[22] It is influenced by the sensitivity of EEG in the epilepsy population. Normal EEG during therapy may give a false negative result because of the AED and does not reflect actual remission, but represents a tendency of decreasing seizures.[29,30] However, a false positive EEG can occur in normal populations.[31] Abnormalities in EEGs during AED withdrawal were reported as a predictive factor of relapse in previous studies and had significant results

in multivariate analyses in previous studies. The appearance of spikes, slowing, abnormal, or worsening EEG images were predictors of relapse.[11]

Patients with symptomatic epilepsy and/or slow time to seizure control, as well as worsened EEG evolution at AED withdrawal, should receive special attention in AED dose reduction as part of the management of pediatric epilepsy. For example, delaying AED withdrawal or slowing the dose decrease could be indicated if the incidence of epilepsy relapse increased when the AED dose is decreased rapidly in the first year.

A limitation of our study was its case-control design with a small sample size from one tertiary referral hospital, one secondary hospital, and two pediactric neurology clinics. Therefore, the results are not representative of the entire population. In addition, the lack of available standard drugs and supporting examination facilities in our country rendered us unable to describe the actual response to therapy.

Further study is needed to improve the validity of this study, such as using a prospective design, as well as including all types of epilepsy and predictive factors, in order to develop a more accurate predictive factor score of epilepsy relapse. Such a predictor score may facilitate better management of children with epilepsy. In addition, further study should be done to create a post-relapse AED protocol, including how long AEDs should be given, how long the evaluation should take, when to withdraw the AEDs, and how fast the reduction of the AEDs should be.

Conflict of interest

None declared.

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