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Original Article

Prognostic factors of refractory epilepsy in children

Ramzi,[1] Yati Soenarto,[1] Sunartini,[1] M Hakimi[2]

Abstract

Background Epilepsy is one of the most common pediatric neurological disorders. Twenty percent of patients will develop refractory epilepsy. Early identification of refractory epilepsy will be helpful to conduct adequate counseling and selecting patients who need more intensive investigation and treatment.

Objective To identify the clinical characteristics and other factors that are related to refractory epilepsy in children.

Methods We conducted a case control study in patients of two to 18 years old with epilepsy that admitted to Dr. Sardjito Hospital. There were 47 children with refractory epilepsy compared with 122 subjects who have been one year free of seizure.

Results Strong association had been noted between refractory and several clinical factors: early onset of seizure, high initial seizure frequency, neonatal asphyxia, symptomatic etiology, status epilepticus, abnormal neurodevelopmental status, and early breakthrough seizures after treatment initiation. On multivariate analysis, more than 20 seizures prior to treatment initiation (OR 3.40, 95% CI 1.03 to 11.3), and more than three seizures in the subsequent six month after treatment initiation (OR 16.02, 95% CI 4.98 to 51.5) were independent prognostic factors related to refractory epilepsy.

Conclusion Children who present high frequency seizures at onset and more than 3 breakthrough seizures subsequent to six month after treatment have risks of developing refractory epilepsy. **[Paediatr Indones 2008;48:269-73]**.

Keywords: *refractory epilepsy, high frequency seizures, breakthrough seizures, anti epileptic drug*

Epilepsy is one of the most common pediatric neurological disorders. There are four to 50 million sufferers in the world today, 85% of whom live in developing countries. At least 50% of cases begin at childhood or adolescence.[1] The overall prognosis is favorable with 70-80% of patients being seizure free, however, 20-30% of epilepsy patients develop refractory epilepsy.[2] Refractory epilepsy is defined as continued seizures in children despite adequate therapy with more than two anti epileptic drugs (AEDs).[3] There is increasing evidence that patients with refractory epilepsy can be identified early in the course of their illness, and could, potentially, be spared damaging years of avoidable seizures and the resultant downward spiraling in quality of life.[4] Clinical predictors of refractory epilepsy are needed because early identification of these patients will be helpful to do adequate counseling to patients and their family and to identify patients who need more intensive investigation and treatment. There are

From the Department of Child Health, Medical School, Gadjah Mada University, Yogyakarta, Indonesia (R, YS, S).[1]

From the Department of Obstetrics and Gynecology, Medical School, Gadjah Mada University, Yogyakarta, Indonesia (MH).[2]

Request reprint to: Ramzi, MD, Department of Child Health, Medical School, Gadjah Mada University, Dr. Sardjito Hospital, Jln.Kesehatan no.1 ,Sekip Utara, Yogyakarta 55281, Indonesia.Tel 62-274-587333 ext.232. Fax.62-274-583745.

relatively few studies regarding refractory epilepsy and its predictors of prognosis in developing country,[5-7] especially in Indonesia.

This study aimed to identify the clinical characteristics and other factors that relate to refractory epilepsy in children.

Methods

We conducted a case control study at Dr Sardjito Hospital Yogyakarta, Indonesia. Data were collected from medical record. To obtain missing information, we also interviewed patients and their families. A total of 47 cases with refractory epilepsy dan 122 controls with well-controlled epilepsy were enrolled in this study.

We included children of two to 18 years old who had been visitting Dr Sardjito Hospital regularly for at least two years from Januari 1998 to January 2007. Cases with shorter periods of follow up or inadequate follow up were excluded. We also excluded children who were treated with inappropriate drug (e.g., carbamazepine for absence epilepsy).

Refractory epilepsy was defined as continued seizures for at least one year in the last follow up, despite adequate trials of more than two AEDs, using either single or combination therapy.[3] Well-controlled epilepsy was defined as having no seizures for a minimum of one year during the follow-up periods. Definitions and principles were referring to the International League Against Epilepsy (ILAE) Commission on Classification and Terminology and the Commission on Epidemiology and Prognosis.[8-10] The co-morbid conditions present at onset include one of developmental delay at minimal (global, pure motor, or isolated speech delay), mental retardation, attention-deficit hyperactivity disorder (ADHD), or learning disabilities. The following features on neurological examination were recorded: microcephaly or macrocephaly, dysmorphic features, pyramidal tract signs (diplegia, hemiplegia, quadriplegia), and developmental delay.[11] Breakthrough seizures defined as seizures occurring after medication were prescribed but before medication was withdrawn for those patients who were seizure free for a sufficient period.[12] We analyzed breakthrough seizures at first and subsequent six months to treatment initiation.

Data were analyzed for each factor separately with bivariate analysis. Standard tests of significance, such as chi square or Mann-Whitney test and t-test, were used whenever applicable. Multivariate analysis was performed by multiple logistic regression by entering methods to examine the association between refractory epilepsy and potential prognostic factors. Odds ratios (OR) and 95% confidence interval (CI) were also calculated.

Results

The clinical profiles of the patients are presented in **Table 1**. There were no differences of sex and type of seizure between the two groups. The age of seizure onset in refractory group was younger than that in well-controlled group; 93.2% of patients in refractory group had more frequent initial seizure frequency. Poor compliance was detected slightly in refractory epilepsy group.

Analysis of factors related to refractory epilepsy are demonstrated in **Table 2**. Early onset of seizure (0-5 years of age) had a positive association with refractory epilepsy. Nevertheless, cases and control groups were not statistically different for age of onset prior to one year. Early frequent seizures prior to therapy were also statistically associated with the development of refractory epilepsy (OR 9.53, 95% CI 4.23 to 21.4). History of neonatal asphyxia and history

Table 1. General characteristics of patients

Characteristic	Cases (n= 47)	Controls (n= 122)
Duration of *follow-up*		
Mean (SD) [a]	6.1 ± 3.7	3.4 ± 1,5
Median (years)	5.67	3.0
Median number of AED	3	1
Initial seizure type		
Partial (%)	21.3	18.0
Age of seizure onset [a]	4.2 ± 3.5	5.8 ± 4.3
0-1 year (%)	29.8	20.5
1-5 years (%)	36.2	27.9
5-10 years (%)	21.3	36.1
>10 years (%)	12.8	15.6
Initial seizure frequency		
>20 seizures (%)	53.2	10.7
Poor compliance (%)[b]	21.3	9.8

[a] P<0.05 (*Mann-Whitney test*), years (mean SD)
[b] P = 0.048

Table 2. Factors related refractory epilepsy

Prognostic Factors	Cases (n = 47)		Controls (n = 122)		OR (95% CI)	P value
	No	%	No	%		
Male	25	53.2	71	58.2	0.82 (0.42 to 1.61)	0.56
Age of seizure onset						
0-5 years	31	66	59	48.4	2.07 (1.03 to 4.17)	0.04
Initial seizure frequency						
> 20 seizures	25	53.2	13	10.7	9.53 (4.23 to 21.4)	<0.01
Family history of epilepsy	9	19.1	23	18.9	1.02 (0.43 to 2.40)	0.96
History of febrile seizures	16	34	40	32.8	1.06 (0.52 to 2.16)	0.88
Neonatal asphyxia	9	19.1	9	7.4	2.95 (1.10 to 8.04)	0.03
History of status epilepticus	12	25.5	12	9.8	3.14 (1.30 to 7.62)	<0.01
Partial seizure type	10	21.3	22	18	1.23 (0.53 to 2.84)	0.63
Symptomatic cryptogenic	19	40.4	7	5.7	11.2 (4.29 to 29.1)	<0.01
epilepsy	15	31.9	5	14.4	10.9 (3.71 to 32.5)	<0.01
Neurological deficits	26	55.3	20	16.4	6.31 (2.98 to 13.3)	<0.01
Comorbid conditions						
≥ 3 breakthrough seizures in the first 6 months after treatment	41	87.2	38	31.1	15.1 (5.91 to 38.6)	<0.01
≥3 breakthrough seizures in the subsequent 6 months after treatment	42	89.4	23	18.9	36.2 (12.9 to 101)	<0.01

Table 3. Multivariate analysis of prognosis factors related to refractory epilepsy

Prognostic factors	B	SE	Exp (B)	95% CI	P value
> 20 seizure at onset	1.22	0.61	3.40	1.03; 11.3	0.045
≥ 3 breakthrough seizures in the subsequent 6 months after treatment	2.77	0.60	16.02	4.98; 51.5	< 0.01

of status epilepticus were more common in cases than control group. Similarly, the risk was significantly higher in children with symptomatic epilepsy or neurological deficits or in children with comorbid conditions. However, the following variables were not found to be significantly different in the groups of: male gender, history of febrile seizure, family history of epilepsy and partial type of seizure.

Symptomatic-cryptogenic etiology of epilepsy was present in 19 patients (40.4%) at refractory group and only in 5.7 % of the children in the control group. The possible causes among the children with refractory epilepsy were intracranial infection (6 children), neonatal asphyxia (5), infantile spasms (2), Lennox-Gastaut syndrome (2), Dandy-Walker syndrome (2), tuberous sclerosis (1), and toxoplasmosis (1).

Multivariate analysis was performed to assess the association between refractory epilepsy and potential independent prognostic factors (**Table 3**). In the overall group, frequent seizures prior to treatment initiation [OR: 3.40 (95% CI 1.03; 11.3)], and more than three seizures in the subsequent six month after treatment initiation [OR: 16.02 (95% CI 4.98; 51.5)], were independent prognostic factors of refractory epilepsy.

Discussion

Identification of children at high risk of refractory epilepsy is important to design more appropriate and aggressive therapeutic options. Prognostic study will be useful not only in this decision-making process but also to prevent toxicity from an overdose of antiepileptic drugs and unnecessary polytherapy in medically intractable patients. Newer AEDs, ketogenic diet, surgical intervention may have a role in the treatment of children with refractory

epilepsy.[13,14] Criteria of refractory epilepsy used in our study were based on our consideration that these criteria are neither too inclusive nor too restrictive in our limited setting.[15]

In this study, initial seizure frequency was identified to be a significant prognostic factor and retained significance in multivariate analysis. It was similar to studies that addressed the prognostic significance of seizure frequency.[16-17] Other studies reported that initial seizure frequency is a significant prognostic factor of seizure remission[12,18] and relapse.[19]

Response to AED therapy has been thought to be a good predictor for refractory epilepsy and remission.[16,20-,22] If seizures are not controlled in the first year after diagnosis, only about 60% of patients can be expected to achieve remission.[21,22] In this study, there were association between three or more breakthrough seizure in the subsequent six months after treatment initiation and refractory epilepsy. Similar finding was addressed by other studies.

Both independent prognostic factors were tempting to attribute the association between a high number of seizures and intractability to the experimental phenomenon of kindling.[23] Thus, it is important to control earlier and to treat the seizure adequately to prevent greater damage of the brain, resulting to chronic or refractory condition.

Age at seizure onset was not found to be a prognostic factor of refractory epilepsy in our study. This finding is in contrast with the finding of other studies.[5,7,24] It could be explained by the lower prevalence of infantile spasms in our study.

Symptomatic-cryptogenic etiology was not found to be associated with refractory epilepsy in our study. There are limitation in this study that not every patients had performed CT scan or MRI caused by finantial limitations; therefore etiology of epilepsy has been explored from history and clinical findings. Regarding underlying causes, neonatal asphyxia and intracranial infection were the major causes of refractory epilepsy in this study. This finding was similar to the finding in India and supposed to be different from the result in developed country.[5]

History of status epilepticus wasn't identified to be a significant prognostic factor in our study and others.[5,17,24] It was contrary to Sillanpaa and Berg *et al*[25,26] studies. Kwong *et al* suggested that status epilepticus should be considered as a marker rather than a cause of poor control. Outcome and morbidity after status epilepticus were almost entirely related to the underlying etiology.[17,27]

Abnormal neurological status and the presence of comorbid condition were found to be significantly positive in univariate analysis but not in multivariate analysis. It may support the notion that there were association between refractoriness and severe brain damage in children.

In this study, poor compliance was found to be more common in children with refractory epilepsy. Failure to achieve seizure controlled and complexity of treatment maybe attributed to poor compliance of taking medication.

Our data show that high frequency seizures at onset and more than three breakthrough seizures in the subsequent six month after treatment are prognostic factors of developing refractory epilepsy. As this study is a case-control study, any minor limitations of the routinely collected data will apply to both cases and controls and are therefore unlikely to cause significant bias. Due to these limitations, prospective studies are required to take these factors under consideration to predict earlier refractory epilepsy to confirm their validity.

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