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Risk factors influencing the outcomes in infants with epilepsy

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Abstract

Background Epilepsy in young children should always be considered as a symptom of an underlying brain disease. Parents and caregivers often asked whether the seizures can be controlled and whether the epilepsy will affect the child development.

Objective To find out risk factors influencing the outcomes in infants with epilepsy.

Methods This was a retrospective study on infants aged 1 month until 12 months with recurrent epileptic seizures. We looked for the risk factors as sex, types of medication, age at onset of seizure, epilepsy syndrome, etiology of epilepsy, history of neonatal seizure, first EEG features, and type of seizure for the last 6 month-period. The outcomes evaluated were controlled seizure and developmental status.

Results Hundred forty infants with epilepsy were reviewed, consisted of 84 (60%) infants with symptomatic epilepsy, and 56 (40%) infants categorized as idiopathic. Forty-six (33%) infants had controlled seizure, while 94 (67%) infants had uncontrolled seizure. Abnormal developmental status was found in 75 infants (54%). Abnormal developmental status was more found in infants with polytherapy, age at onset of 1-4 months, symptomatic epilepsy, positive remote symptomatic, history of neonatal seizure, abnormality of first EEG, and uncontrolled seizure. Uncontrolled seizure of epilepsy was more found in infants with polytherapy, early age at onset (1-4 month old), symptomatic epilepsy, positive remote symptomatic, history of neonatal seizure, and abnormality of first EEG.

Conclusion Our data indicate that classifying syndrome of epilepsy through diagnostic screening and age of onset are important to determine the outcomes. **[Paediatr Indones 2007;47:202-206]**.

Keywords: *recurrent epileptic seizure, symptomatic epilepsy, risk factors*

Epilepsy in young children should always be considered as a symptom of an underlying brain disease, and therefore needs diagnostic screening, including neurogenetic, neurometabolic, and neuroradiologic testing. Seizures are common in infancy and reflect a variety of underlying causes. The most frequent seizure in that age group is febrile seizure, which is usually benign and has no risk on the further child's development.[1-3] On the other hand, infantile spasm in infancy indicates an age-specific catastrophic epilepsy syndrome, with major negative implications for the development of the child.[4,5] The two most important questions regarding seizures usually asked by parents and caregivers are whether the seizures can be controlled and whether the epilepsy will affect the child development. We performed a retrospective study to find out risk factors for outcomes in infants with epilepsy.

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Methods

We collected medical records of all children aged between 1 month - 12 months with recurrent epileptic seizures, admitted to our hospital for diagnosis and treatment during January 2000 - October 2005. Infants with febrile seizures or infantile spasm were excluded. The diagnosis was based on history, clinical manifestations, physical examination, standard electroencephalogram, and head CT-scan. All patients received monotherapy with valproic acid or phenobarbital as the first line treatment; in the case that the seizures could not be controlled, the drug was changed or added. We traced back the possible risk factors for outcomes, i.e., type of therapy (monotherapy or polytherapy), age at onset (1-4 months, 5-8 months, or 9-12 months), type of epilepsy (localized or generalized, symptomatic or idiopathic), remote symptomatic, history of neonatal seizures, and abnormality of first EEG features. Remote symptomatic was defined when the child had either preexisting neurological abnormalities, a history of brain insult, or disorders associated with an increased risk of epilepsy that were presumed to be etiologically related to the infant's epilepsy.[6] The outcomes, i.e., controlled epilepsy and developmental status were determined. Controlled epilepsy was defined as the child had no seizure during the last 6 month-period, while uncontrolled epilepsy was if there were still epileptic seizures. Developmental status was assessed by specific history taking and clinical examination. We used Bailey Infants Neurodevelopmental Scale (BINS) for screening combined with neurological examination such as physiological reflexes, pathological reflexes, tone, and neurodevelopmental examination. Developmental status was considered abnormal when developmental milestones were not achieved at an expected age, or when language and communication developments were delayed. All infants in this study visited regularly every 1-3 months to our hospital, so the infant development and respond to therapy were well-recorded.

The study subjects were also categorized into the idiopathic or symptomatic group. Infants in symptomatic group had a definite cause for the epileptic seizures or had developmental delay without a definite cause or etiology, which was called cryptogenic. In the idiopathic group, infants had no cause for the epilepsy other than a possible hereditary predisposition.[7] Data were analyzed with chi-square test, relative risk (RR) and 95% confidence intervals (CI) were supplied.

Results

A total of 140 consecutive infants (74 girls and 66 boys) were included in this study. The observation period ranged from 6 months to 55 months, with the median of 16 months. Eighty-four infants (60%) were classified in the symptomatic group and 56 (40%) in the idiopathic group. Developmental abnormalities were found in 75 infants (53%), 72 infants in symptomatic group and 3 infants in idiopathic group. Sixty-five infants had normal development (47%), most of them (53 infants) were in idiopathic group and 12 infants in symptomatic group. Uncontrolled seizures were found in 46 infants (32%), 44 infants in symptomatic group, 2 infants in idiopathic group. Seizures were controlled in 94 infants (68%), 40 infants in symptomatic group, and 54 infants in idiopathic group. Compared to those in idiopathic group, infants in symptomatic group had significantly higher proportion of having polytherapy, earlier age of onset, positive remote symptomatic, abnormal development, positive history of neonatal seizures, abnormal EEG features, and uncontrolled seizures. See **Table 1.**

During the observation, the number of infants who had treatment switch was recorded. A treatment switch indicated that another medication was prescribed, as add-on or as an alternative monotherapy. The reason for a treatment switch was related to possible failure of initial treatment. In a way, it reflected how difficult to control the epilepsy.

Developmental abnormalities were more commonly found in of infants with polytherapy, early age at onset (1-4 months), symptomatic epilepsy, positive remote symptomatic, history of neonatal seizures, abnormality of the first EEG feature, and uncontrolled seizures **(Table 2)**. The occurrence of abnormal development was not significantly different between infants with onset of seizure at 5-8 months old compared to them with onset of 9-12 months old.

Uncontrolled seizure was more commonly seen in infants with polytherapy, early age of onset (1-4 months), symptomatic epilepsy, positive remote

Table 1. Characteristics of the study subjects

Characteristics	Symptomatic group (n=84)	Idiopathic group (n=56)	P
Age at onset			
1- 4 months	38 (27%)	7 (5%)	
5- 8 months	32 (23%)	35 (25%)	
9-12 months	14 (10%)	14 (10%)	<0.001
Sex			
Girl	41 (29%)	33 (24%)	
Boy	43 (31%)	23 (16%)	>0.05
History of neonatal seizure			
Positive	13 (9%)	2 (1%)	
Negative	71 (51%)	54 (39%)	<0.05
Seizures for the last 6 month-period			
Uncontrolled	44 (31%)	2 (1%)	
Controlled	40 (29%)	54 (39%)	<0.001
Epilepsy syndrome			
Localized	13 (9%)	7 (5%)	
Generalized	71 (51%)	49 (35%)	>0.05
Remote symptomatic			
Positive	58 (41%)	1 (1%)	
Negative	26 (19%)	55 (39%)	<0.001
First EEG feature			
Abnormal	62 (44%)	9 (6%)	
Normal	22 (16%)	47 (34%)	<0.001
Type of therapy			
Polytherapy	33 (24%)	1 (1%)	
Monotherapy	51 (36%)	55 (39%)	<0.001
Developmental status			
Abnormal	72 (51%)	3 (2%)	
Normal	12 (9%)	53 (38%)	<0.001

Table 2. Distribution of risk factors for developmental outcomes

Factors	Developmental status Abnormal (n=75)	Normal (n=65)	RR	95% CI	P
Sex					
Girls	37	37			
Boys	38	28	0.87	0.64 -1.18	>0.05
Type of therapy					
Polytherapy	32	2	2.32	1.81-2.9	<0.001
Monotherapy	43	63			
Age at seizure onset					
1-4 months	34	11	1.51	1.00-2.26	<0.05
5-8 months	27	40	0.80	0.5-1.29	>0.05
9-12 months	14	14			
Epilepsy syndrome					
Symptomatic	72	12	16	5.30 – 48.27	<0.001
Idiopathic	3	53			
Localized	9	11			
Generalized	66	54	0.81	0.49-1.36	>0.05
Remote symptomatic					
Yes	56	3	4	2.71-6.02	<0.001
No	19	62			
History of neonatal seizures					
Yes	12	3	1.58	1.16-2.15	<0.05
No	63	62			
First EEG					
Abnormal	55	16	2.67	1.81-3.94	<0.001
Normal	20	49			
Seizure for the last 6 month-period					
Uncontrolled	41	5	2.46	1.85-3.28	<0.001
Controlled	34	60			

Table 3. Distribution of risk factors for controlled seizures

Factors	Controlled seizures Uncontrolled (46)	Controlled (94)	RR	95% CI	P
Sex					
Girl	26	48	1.16	0.72;1.87	>0.05
Boy	20	46			
Therapy					
Polytherapy	27	7	4.43	2.85;6.89	<0.001
Monotherapy	19	87			
Age at seizure onset					
1-4 months	24	21	2.98	1.29;6.91	<0.05
5-8 months	17	50	1.42	0.58;3.47	>0.05
9-12 months	5	23			
Epilepsy syndrome					
Symptomatic	44	40	14.67	3.70;58.07	<0.001
Idiopathic	2	54			
Localized	3	17	0.42	0.14;1.22	>0.05
Generalized	43	77			
Remote symptomatic					
Yes	32	27	3.14	1.84;5.33	<0.001
No	14	67			
Neonatal seizures					
Yes	9	6	2.03	1.23;3.32	<0.05
No	37	88			
First EEG					
Abnormal	35	36	3.09	1.71;5.58	<0.001
Normal	11	58			

symptomatic, history of neonatal seizures, and abnormality of the first EEG feature.

Discussion

Although the number of subjects in this study was rather small and the observation period was short to draw any definite conclusions, this study provides some important clinical guidelines for the pediatric epilepsy clinic. Clinical parameters that are readily available during the clinical monitoring of these young children with epilepsy were used. Infants less than 12 months of age with epileptic seizures, which neither febrile seizures nor infantile spasms, are real diagnostic challenges for neuropediatricians.

In this study, a definite cause of the epilepsy was found in 42% (59/140) infants. This proportion maybe higher if we performed other neurodiagnostic screening, including a magnetic resonance imaging study, genetic studies, and a metabolic evaluation. We did not perform such examinations because of the cost. Seventy five percent of the patients (106/140)

received monotherapy, most of them (63/106) had normal developmental and 87 patients in this group got control seizure. It was stated in the literature that more seizures and more anti epileptic drugs (AED) that we used can disturb the brain development.[6,8] So it is understood that less AED and less seizure will not influence developmental outcome.

Developmental abnormalities were more commonly found in infants with symptomatic epilepsy, earlier age of onset (1-4 months), history of neonatal seizures, positive remote symptomatic, abnormality of the first EEG, having polytherapy, and uncontrolled seizures. The first five factors reflected the underlying brain diseases. Brain in children in the early age is vulnerable against seizures. The developing brain is more affected rather than the mature brain. These factors influenced the developmental outcomes.

In children with symptomatic epilepsy (84/140), most had abnormal EEG feature (62/84), abnormal developmental status (72/84) and had uncontrolled seizures (44/84). Underlying brain diseases described by positive remote symptomatic and abnormality of first EEG might be the cause or focus for epileptic seizures. We must consider a more aggressive treatment if we find symptomatic epilepsy especially in infant to reduce the seizures.

The developmental abnormalities are also influenced by recurrent or uncontrolled seizures. The epileptic process itself, perhaps in combination with the number of seizures, can be held responsible for the developmental delay.[8]

Uncontrolled seizure means that seizure could not be terminated by monotherapy, so add-on therapy or switching drugs must be done to control the seizure. Uncontrolled seizures were more commonly found in infants having polytherapy, early age of onset (1-4 months), symptomatic epilepsy, positive remote symptomatic, history of neonatal seizures and abnormality of the first EEG group. The underlying brain disease maybe was the cause of uncontrolled seizures which did not respond to the therapy.

Our results were different from larger studies reported in the literature. In a study by Cavazzutti *et al*[9], 482 children were monitored for more than 5 years. In their subgroup of children without febrile seizures, status epilepticus, or infantile spasms, only 24% developed normally. This suggests a possible long-term negative developmental effect of seizures in the first year of life. Similar findings have been reported in the older studies of Chevrie and Aicardi.[10] In their large cohort of 313 children, poor prognosis was found even in non-febrile group of infants with seizures. Both studies further illustrated that age of onset of >6 months old, generalized seizures, and normal EEG, were associated with better, but still poor outcomes. Battaglia *et al*[11] demonstrated in their study of 150 children that partial epilepsies were associated with poor outcomes. They also drew attention to the fact that persistence of seizures was a negative factor for developmental outcome, as was also observed in this study.

In conclusion, our data together with the existing data in the literature indicate that classifying epilepsy through diagnostic screening in an infant presenting with epileptic seizures is necessary. The finding of an underlying cause is a determinant factor for outcomes, especially for developmental level and responds to therapy. Most of infants with epilepsy have seizure free with monotherapy, but seizure control is more difficult to achieve in symptomatic cases.

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