

Prognostic factors of epilepsy in patients with neonatal seizures history

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Abstract

Background Seizures in neonates are often associated with neurological disorders in early life, including epilepsy. Several possible prognostic factors may influence the development of epilepsy in these patients.

Objective To evaluate prognostic factors that may influence the occurrence of epilepsy in the first two years of life in patients with a history of neonatal seizures.

Methods We performed a cohort retrospective study on patients with neonatal seizures in Sardjito Hospital during 2004-2009. Prognostic factors observed were gender, family history of epilepsy, neonatal hypoglycemia, assisted labor, hypoxic ischemic encephalopathy, preterm infant delivery, and epileptic state.

Results Hypoxic ischemic encephalopathy and epileptic state increased the risk of epilepsy (HR 5.8; 95%CI 1.63 to 20.43 and HR 6.3; 95%CI 2.0 to 19.70, respectively). Assisted labor, preterm delivery, neonatal hypoglycemia, family history of epilepsy, and gender did not increase the risk of epilepsy in the first two years of life.

Conclusion Hypoxic ischemic encephalopathy and epileptic state in neonates presenting with seizures are the prognostic factors to be epileptic children during the first two years of life. [Paediatr Indones. 2013;53:218-22.].

Keywords: neonatal seizures, epilepsy, prognostic factors, hypoxic ischemic encephalopathy, epileptic state

Epilepsy is a chronic disorder that is not only marked by the recurrence of seizures, but also has a variety of medical and psychosocial implications. The incidence of epilepsy is 40-70 per 100,000 in developed countries and 100-190 per 100,000 in developing countries.¹ However, previous studies reported the incidence to be 20-70 per 100,000 per year.^{2,3} The incidence of epilepsy varies by age, with the highest incidence in children at early ages then dropping during early adulthood, followed by increases during old age. There are generally fewer females with epilepsy than males.¹

Of infants with neonatal seizures, 25% present with recurrent seizures in the first 7 years, and 75% develop epilepsy.⁴ Epilepsy reportedly occurs in 15 of 27 children with neonatal seizures who survived.^{5,6} Several studies have reported associations of some factors that may influence the incidence of neonatal seizures with epilepsy in children, including hypoxic ischemic encephalopathy (HIE), low birth weight (LBW), preterm delivery, type of seizure, epileptic state, assisted labor, meningitis, abnormal

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electroencephalography (EEG) findings, and the use of epilepsy drugs.⁷⁻¹⁰

The aim of this study was to assess whether gender, family history of epilepsy, hypoglycemia, assisted labor, HIE, preterm delivery, and epileptic state were associated with the occurrence of epilepsy in the first two years of life.

Methods

We performed a retrospective inception cohort study. Subjects were neonates with seizures admitted in the Perinatology Ward of Dr. Sardjito Hospital in Yogyakarta during 2004-2009, and recruited by consecutive sampling. Subjects were followed up until 2 years of age to identify the occurrence of epilepsy within this period.

This study was approved by the Medical and Health Research Ethics Committee, Gadjah Mada University Medical School. Parents gave written informed consent for their children's participation.

Inclusion criteria were all neonates with seizures, who were treated in the hospital. We excluded neonates with suspected syndromes or metabolic abnormalities, such as congenital rubella syndrome, Down syndrome, microcephaly, or prolonged hypoglycemia.

Prognostic factors of epilepsy examined in this study were gender, HIE, preterm delivery, epileptic state, assisted labor, neonatal hypoglycemia, and family history of epilepsy.

Epilepsy was a brain disorder characterized by at least two recurrent seizures, without fever or

stimulation. Neonatal seizure occurred at an age of <28 days. Hypoxic ischemic encephalopathy was defined as neurological symptoms of neonatal encephalopathy, such as impairment of consciousness, hypotonicity, hypoactivity or hyperactivity, and seizures. Hypoxic ischemic encephalopathy was associated with a history of asphyxia at birth, as defined by decreased Apgar score or a need for resuscitation at birth. Preterm delivery was defined as infants born at <37 weeks (<259 days) gestation. Epileptic state was defined as recurrent seizures without recovery of consciousness between seizures for >30 minutes. Assisted labor was the mode of delivery that required assistance, such as vacuum or Caesarian section. Neonatal hypoglycemia was defined as a condition in infants with blood glucose <45 mg/dL (2.6 mmol/L). Family history of epilepsy was defined as a history of family members who suffered from epilepsy.

Variables were presented descriptively by calculating the frequency distribution and proportion to describe the characteristics of study subjects. Prognostic factors of epilepsy were analyzed by univariate and multivariate Cox regression hazard models. Variables with P of < 0.2 in univariate analysis were included in the multivariate analysis.

Results

During the study period, a total of 8,238 neonates were admitted to the Perinatology Ward. There were 114 neonates with seizures, of which 21 neonates died during treatment. Therefore, we recruited 93 neonates to the study, but 9.6% of these neonates were

Table 1. Baseline characteristics of study subjects

Characteristics	Epileptic group (n = 17)	Non-epileptic group (n = 67)
Gender, n		
Male	12	44
Female	5	23
Maternal age at delivery, n		
<35 years	10	42
>35 years	7	25
Onset of seizures, n		
<24 hours after birth	9	21
> 24 hours after birth	8	46
Family history of epilepsy, n		
Yes	3	4
No	14	63
With hypoxic ischemic encephalopathy, n	13	25

Table 2. Univariate and multivariate analyses of prognostic factors

Variables	Epileptic group (n=17)	Non-epileptic group (n=67)	P value	Univariate		Multivariate	
				HR	95% CI	HR	95% CI
Gender, n							
Male	12	44	0.85	0.9	0.31 to 2.56	-	-
Female	5	23					
Family history of epilepsy, n							
Yes	3	4	0.52	0.6	0.14 to 2.70	-	-
No	14	63					
Hypoglycemia, n							
Yes	3	13	0.98	1.0	0.29 to 3.55	-	-
No	14	54					
Assisted labor, n							
Yes	5	27	0.30	1.8	0.58 to 5.54	-	-
No	12	40					
Hypoxic ischemic encephalopathy, n							
Yes	13	25	0.003	6.6	1.91 to 23.19	5.8	1.63 to 20.43
No	4	42					
Preterm delivery, n							
Yes	7	11	0.01	3.2	1.21 to 8.18	1.1	0.37 to 3.45
No	10	56					
Epileptic state, n							
Yes	10	9	0.001	7.5	2.84 to 19.88	6.3	2.0 to 19.70
No	7	58					

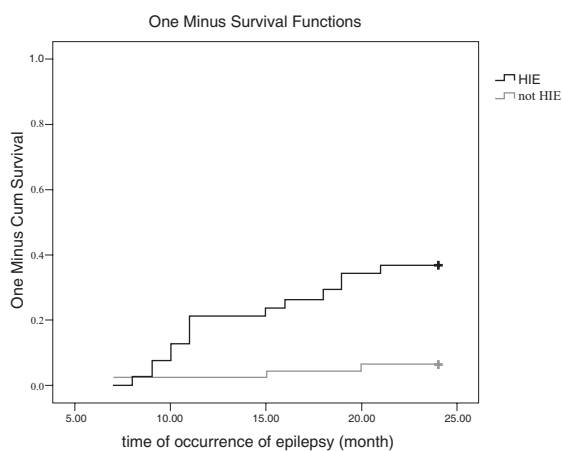


Figure 1. Kaplan-Meier curves incidence of epilepsy in hypoxic ischemic encephalopathy

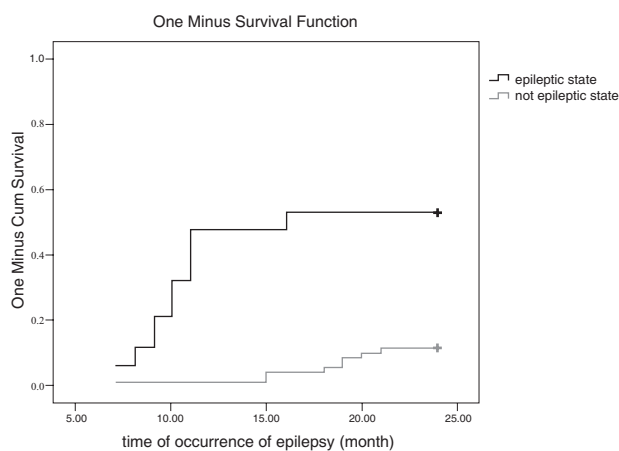


Figure 2. Kaplan-Meier curves incidence of epilepsy in epileptic state

lost to follow-up, due to death (2 infants) and loss of contact (7 infants). Finally, 84 neonates were followed up until 2 years of age. From these 84 neonates, 17 infants (20%) developed epilepsy. Epilepsy was more prevalent in boys than in girls (Table 1).

Table 2 shows that HIE, preterm delivery and epileptic state increased the risk of epilepsy in patients with a history of neonatal seizures. However, gender,

neonatal hypoglycemia, family history of epilepsy, and history of assisted delivery did not increase the risk of epilepsy. Multivariate analysis indicated that HIE and epileptic state were the only significant prognostic factors for developing epilepsy. Kaplan-Meier curves showed that at the end of the observation, the number of subjects who became epileptic increased significantly in subjects with these risk factors (Figures 1 and Figure 2).

Discussion

We found that HIE increased the likelihood of epilepsy in the first 2 years of life of neonatal seizure patients. Similar with a study reported that HIE was the leading cause of neonatal seizures and postnatal epilepsy in a sample of 101 neonates with seizures,¹¹⁻¹³ although there was other study reported the otherwise.¹⁴ This difference may be due to the low number of neonates with HIE who had seizures in their study, only 5 subjects.⁷

We found that patients with neonatal seizures who experienced an epileptic state had an increased likelihood of epilepsy. This result was similar to some cohort studies on both preterm and term infants¹⁴ with neonatal seizures reported that epileptic state was a prognostic factor for developing epilepsy.¹⁰

In our study, multivariate analysis revealed that preterm delivery did not increase the likelihood of epilepsy in neonates with seizures, consistent with other studies.^{8,12,15} However, Ronen *et al.* found that preterm infants had worse prognoses. This difference might be due to a longer follow-up time of 10 years in their study.⁹

During seizures in patients with HIE and epileptic state, there is a sharp decline in brain glucose levels accompanied by an increase in lactate production. The transport mechanisms in the brain cannot compensate for the increased demand for glucose. Oxygen demand and cerebral blood flow also increase. Lactate accumulated during the occurrence of seizures decreases arterial blood pH while blood pressure and blood flow to the brain increase. This dramatic, short-term effect is followed by changes in cell structure and synaptic connections that eventually could become a focus of epilepsy.¹⁶

The limitation of this study was the possibility of selection bias and information recall bias. Subjects' families may not accurately remember events and history information, and medical records may have been incomplete. Selection bias was also a possible limitation, due to patterns of patient referral (referral bias), which may occur in a hospital-based study.

This study may be useful for clinicians to improve care for infants with neonatal seizures and raise awareness of the possibility of future development of epilepsy, in order to evaluate for it at follow-up visits to the hospital.

In conclusion, epileptic state and HIE increase the risk of developing epilepsy in the first two years of life in patients with a history of neonatal seizures, even though assisted labor, preterm delivery, hypoglycemia, family history of epilepsy, and gender give the otherwise result.

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