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Original Article

Neonatal seizures: clinical manifestations and etiology

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ABSTRACT

Background Neonatal seizures or fits are signs of central nervous system (CNS) diseases, metabolic disorders, or other diseases disrupting the CNS. Neonatal seizures are poorly classified, under-recognized and often difficult to treat. It is important to recognize the type of neonatal seizures that might be the only sign of a CNS disorder.

Objective To recognize the type and etiology of neonatal seizures in several hospitals in Jakarta.

Methods This was an observational case series study on full-term and preterm infants who had seizures during hospitalization in Cipto Mangunkusumo, Harapan Kita, and Fatmawati Hospitals between January-June 2005. Neonatal seizures were defined as seizures occurring in the first 28 days of life of a term infant or 44 completed weeks of the infant's conception age of preterm infant.

Results There were 40 neonates who born within the study period and had seizures. Girls were outnumbered boys. Most neonates were full-term with birth weight of more than 2500 grams. Analyses were done on 38 neonates with epileptic and non-epileptic seizures, while the other two who had mixed clinical manifestation were not included. Most seizures occurred in the first 3 days of life (23/38). The most common type was focal clonic (12/14) followed by general tonic (11/24) and motor automatism or subtle (10/24). The most common etiology was hypoxic ischemic encephalopathy (HIE) (19/38) followed by metabolic disturbances, mainly hypocalcaemia (11/38).

Conclusion Common types of seizures in neonates were focal clonic, general tonic, and motor automatism (subtle). The most common etiology was HIE followed by metabolic disturbances, mainly hypocalcaemia **[Paediatr Indones 2006;46:266-270]**.

Keywords*: neonatal seizures, convulsion, clinical classification, characteristics, intracranial hemorrhage, hypoxic ischemic encephalopathy, metabolic disturbances*

Neonatal seizures are an emergency condition that might cause permanent injury on the developing nervous system.[1] Clinical neonatal seizures represent a high risk for neonatal death or neurodevelopmental sequelae including epilepsy for both full-term and preterm infants.[2-4] Neonatal seizures may be defined as paroxysmal alterations in neurological function (e.g. behavioral, motor, or autonomic function) initiated by hypersynchronous activity of neurons in the brain which occurs during neonatal period. Neonatal period is defined as the first 28 days of life in a term infant and gestational age of 44 weeks (the age of the infant from conception to 44 weeks) for premature infant. [2,3,5]

Although the prevalence of neonatal seizures is low (1.5-14 of every 1000 life births), the frequency is relatively high compared to the prevalence of childhood seizures.[3,6-8] A previous study in Jakarta (1971) reported that the prevalence of neonatal seizures in Cipto Mangunkusumo (CM) Hospital was 0.7%.[9] The diagnosis of neonatal seizures is difficult to establish due to its form that mimics normal movements. To recognize the type or form of neonatal seizures is im-

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portant because it might be the only sign of CNS disorders. Clinical manifestations, etiology, and electroencephalograms are very useful in determining the prognosis.[10] This study aimed to recognize the types and etiologies of neonatal seizures in three hospitals in Jakarta.

Methods

An observational study was conducted on neonates hospitalized in Cipto Mangunkusumo, Harapan Kita, and Fatmawati Hospitals within the period of January-June 2005. Subjects were recruited consecutively from all full-term and preterm infants who had experienced first seizures during the hospitalization in the neonatology wards, NICU, or emergency rooms of those three hospitals. Informed consent was obtained from all parents. This study was approved by the Ethics Committee of Medical School, University of Indonesia.

Before the study began, all doctors and medical staffs in the neonatology, NICU, and emergency wards were trained to recognize the types of neonatal seizures. Data collection using questionnaires consisted of the subject's identities, maternal risk factors, labor and delivery history, and types of seizures were recorded. Neurological examination was done for all neonates. Further consultation to the pediatric neurologist was conducted when necessary. Premature infants and neonates who were suspected of having intracranial hemorrhage as the cause of seizures underwent funduscopic examination or head ultrasonography, then continued by CT-scan whenever possible. Other neonates who were suspected to have CNS infection underwent lumbar puncture for cerebrospinal fluid analysis and culture. Blood glucose, sodium, magnesium, and ionized calcium were investigated as soon as possible after seizures episodes. All neonates who survived had electroencephalography examination. The management of seizures was adjusted to the local policy.

Results

Forty neonates who had seizures were eligible for the study. Fifteen neonates were born in Cipto Mangunkusumo

Table 1. Characteristics of subjects (n=40)

	*Epileptic (n=14)	Non epileptic (n=24)	Mixed epileptic + non epileptic (n=2)
Sex			
Male	5	12	1
Female	9	12	1
Gestational age			
<37 weeks	3	4	1
≥37 weeks	11	20	1
Birth-weights			
<2500 grams	4	4	1
≥2500 grams	10	20	1
Etiology			
HIE	6	10	0
HIE & intracranial hemorrhage	0	3	0
Metabolic disturbances	6	5	1
Intracranial hemorrhage	1	3	1
Congenital abnormality	0	2	0
Intracranial infections	1	0	0
Idiopathic	0	1	0
First seizures			
£3 days	8	15	0
>3 days	6	9	2
EEG (n=20)			
Normal	5	7	0
Abnormal	4	3	1
Passed away	5	13	1
Survived	9	11	1

*Three patiens with epileptic type had seizures of more than one type of epileptic form.
*HIE: Hypoxic Ischemic Encephalopathy

TABLE 2. THE DISTRIBUTION OF CLINICAL MANIFESTATIONS ACCORDING TO THE TYPE OF SEIZURES AND GESTATIONAL AGE

Type of seizures	Gestational Age <37 weeks (n=7)	Gestational Age =37 weeks (n=31)
Epileptic * (n=14)		
Focal clonic	2	10
Focal tonic	1	1
Myoclonic	0	0
Spasme	0	0
Non epileptic* (n=24)		
Generalized tonic	1	10
Myoclonic	1	2
Motor automatism (subtle)	2	8
Electrical seizures without clinical seizures activity	0	0

*Clinical manifestation can occur with more than one seizures type

Hospital, 21 of them in Harapan Kita Hospital, and 4 of them in Fatmawati Hospital while the rest were referred from other hospitals.

There were 22 girls and 18 boys with the birth-weights ranged from 1000-4025 grams (mean 2880, SD 720 grams) and the range of gestational age was 28-41 weeks (mean 37, SD 2.7 weeks). More than one type of seizures could be detected in one patient. Non-epileptic seizures were found more often (24/38) both in boys (12/17) and girls (12/21) also in neonates who had gestational age of $\geq$37 weeks (20/31) or birth-weight of $\geq$2500 g (20/30). The first seizure occurring at age of $\leq$3 days were found in 23 of 38 subjects which majority showed non-epileptic type (15/23 *vs* 8/23). There were two subjects with mixed clinical manifestations (epileptic and non epileptic) who were excluded from further analysis. These two cases comprised of a girl, term baby with birth-weight of 3200 grams, who had first subtle and focal clonic seizures at the age of 5 days and 3 hours caused by intracranial hemorrhage, and survived; the other one is a boy, premature baby with birth-weight of 1900 grams, who had first *subtle* and focal clonic seizures at the age of 17 days caused by metabolic disturbances, and finally passed away. The characteristics of subjects are shown in **Table 1**. Twenty one neonates were still survived at the end period of the study and EEG was performed on 20 subjects. The result showed that 12 neonates had normal EEG and 8 had abnormal in which three of them shown as non epileptic seizures.

The distribution of clinical manifestations according to the type of seizures and gestational age is shown in **Table 2**. The most prevalent type of seizures in this series was focal clonic, a derived form of epileptic seizures (epileptic form). Generalized tonic and motor automatism (subtle) categorized as non epileptic seizures (non epileptic form) were found second after the epileptic form.

The distribution of possible etiology of neonatal seizures according to the age of onset of the first seizures and gestational age is shown in **Table 3**. There were 19 cases with HIE of 38 subjects at this study, 3 cases among them also had intracranial hemorrhage. Metabolic disturbances (11 cases) were the second most prevalent etiology after HIE, mainly it was due to hypocalcaemia. This occurred in 10 neonates. Hypoglycemia accompanied by hypocalcaemia was only found in 1 neonate. These disturbances mostly occured in full-term infants who had problems, such as HIE (16/31), metabolic disturbances (9/31), and intracranial hemorrhage (6/31); but these findings had no clinical relevance since these figures were well balanced with the proportion of cases (full-term *vs* premature: 31*vs* 7).

The distribution of outcome in relation to clinical manifestation and possible etiology of neonatal seizures is shown in **Table 4**. Nine out of 20 survived neonates had epileptic seizures while others 11 neonates were non epileptic. Metabolic disturbances were more prominent in dying neonates rather than in survived ones (7/11 *vs* 4/11). On the other side, the proportion of neonates with HIE and intracranial hemorrhage who survived was higher than dead cases (11/19 *vs* 8/19; 5/7 *vs* 2/7).

Table 3. The distribution of underlying disease of neonatal seizures according to the age of onset of the first seizures and gestational age (n=38)

Etiology	Days		Gestational Age	
	≤3 days (n=23)	>3 days (n=15)	Preterm (n=7)	Full-term (n=31)
HIE	16	0	3	13
HIE & intracranial haemorrhage	3	0	0	3
Metabolic disturbances	1	10	2	9
Intracranial hemorrhage	3	1	1	3
Congenital abnormality	0	2	0	2
Intracranial infections	0	1	0	1
Idiopathic	0	1	1	0

Table 4. Outcome based on clinical manifestations and etiology of neonatal seizures

	Outcome	
	Passed away (n=18)	Survived (n=20)
Clinical manifestation		
Epileptic	5	9
Non epileptic	13	11
Etiology		
HIE	7	9
HIE & intracranial haemorrhage	1	2
Metabolic disturbances	7	4
Intracranial hemorrhage	1	3
Others	2	2

Discussion

There were 40 neonates who were born and had seizures within the study period. The ratio between girls and boys was 1.22:1. Most neonates were full-term with birth weight of more than 2500 grams. The result was comparable with the study reported by Hendarto *et al*[9] in which, girls were outnumbered boys, and the range of birth-weights was 2500–3500 grams. This study showed that the incidence of neonatal seizures in CM Hospital was 0.9%, in Harapan Kita Hospital was 0.3% (5/1559), and in Fatmawati Hospital was 0.3% (2/588). These results were not significantly different with Hendarto *et al*[9] reporting that the incidence of neonatal seizures in CM Hospital was 0.7%.

There were 14 neonates with epileptic form. Three of them had 2 types of seizures which were focal clonic and focal tonic. This phenomena was also found in Brunquell[11] and Ronen[12] reporting multiple types of seizures in each neonates. Continuous EEG were infeasible to be performed. The EEG examinations were only performed in clinically stable neonates. Thus, this examination aimed to justify the prognosis rather than diagnosis. Twelve out of 20 EEG results were normal, though it were not significantly different.

This study found that focal clonic, generalized tonic, and motor aumatism (subtle type) were more frequent. The subtle type manifested as progresive movement such as rowing, swimming, cycling, and oral-bucal-lingual movement, such as sucking and chewing. Those types might be due to the immature function of neonate's cortex. Wong[13] reported that neonatal fit were more commonly focal or motor automatism (*subtle*). Meanwhile, Hendarto *et al*[9] did retrospectively.

Hendarto *et al*[9] found perinatal complications such as labour difficulties and intracranial bleeding in more than a-half of study subjects. This was followed by unknown of origin as the second most common etiology. A 7-year retrospective study (1992-1998)[11] reported that HIE was the most frequent causes of neonatal seizures found in that study (50%). Grade 2 and 3 of HIE were the most common finding as reported by Paradisis.[14] Most of HIE events occurred in full term infants. Volpe stated that risk of seizure is similar between full-term and pre-term neonates.[15]

In our study, metabolic disturbances were found in 11 neonates (28.95%), mainly resulted in hypocalcemia. Rennie[16] and Pressler[17] stated that hypocalcemia-hypomagnecemia as the etiology of 4-22% of cases. Intracranial hemorrhage was diagnosed as the etiology of neonatal seizures in 7 cases (18.42%). Brunquell[11] noted that the incidence of intracranial hemorrhage was 11%. Intracranial infections and congenital abnormalities were found in 1 case (2.5%) and 2 cases (5%), respectively. Brunquell[11] found these two kinds of etiologies as 2% and 6%, respectively. One case of seizures was found to be

idiopathic (2.5%) as reported by Pressler 2%.[17]

Most of seizures occurred primary within the first 72 hours of age. Legido *et al*[10] reported that 13 out of 40 cases were passed away. Among 38 subjects, 18 neonates died and 20 survived. The same mortality rate was also found by Hendarto *et al*[9] (43.48%). Meanwhile, the higher mortality rate was most probably due to infection problems rather than the seizures itself.

Based on the clinical manifestations, the survival rate was almost similar between the epileptic and non-epileptic group. Nevertheless, the mortality rate was higher in the non epileptic group. One literature stated that type of seizures was related to the prognosis. Generalized tonic and subtle type (non-epileptic form) have poor prognosis because it is mostly caused by HIE, bilateral intracranial hemorrhage/infarct, and diffuse CNS infection. Focal type (epileptic form) relates to hypocalcemia or other metabolic disturbance, localized intracranial infarct/bleeding, and it has a better prognosis.[18]

This study found that mortality more commonly occurred in metabolic disturbance. This evidence might be due to that the metabolic disorder appearing as one of manifestation of more serious disease. The HIE cases survived due to adequate treatment.

We concluded that the most frequent seizures types found in neonates are focal clonic, generalized tonic, and motor automatism (subtle), mainly progressive movement. Whereas, the most frequent etiology found in neonatal seizures are HIE and hypocalcemia respectively.

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