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Original Article

Risk factors of drug-resistant epilepsy in children under 3-year-old

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Abstract

Background Repeated seizures may result in chronic injury to the brain, triggering the neuroplasticity process that can cause or augment existing pathological processes. High neuroplasticity during first 3 year of life may influence the clinical course and outcome of children with epilepsy.

Objective To evaluate initial risk factors and evolution risk factors during treatment to predict drug-resistant epilepsy in children under 3 years old. Initial risk factors consist of initial seizure frequency, seizure type, imaging result, history of febrile convulsion, neurodevelopmental status and initial electroencephalography (EEG) result. Evolution risk factors evaluate changes in initial risk factors and seizure control after treatment. Evolution risk factors consist of early response to therapy (seizure control during the first 6 months of treatment), evolution of seizure type and frequency, changes in EEG (background rhythm and epileptiform discharges) during treatment and neurodevelopmental evolution.

Methods This retrospective cohort study used medical record data of pediatric patients 1 month to 3 years old with drug-resistant epilepsy seeking treatment at Dr. Cipto Mangunkusumo Hospital, Anakku Clinic Pondok Pinang, and National Brain Center Hospital, Jakarta, from 2015 to 2020.

Results Thirty-three subjects met drug-resistant epilepsy criteria. Abnormal EEG was the only initial risk factor significantly associated with drug-resistant epilepsy (OR 4.48; 95%CI 1.82 to 11.03; P=0.001). Increased seizure frequency (aOR 7.0; 95%CI 1.0 to 49.7; P=0.048) and seizure persistence during the first six months of treatment (aOR 10.92; 95%CI 2.6 to 45.87; P=0.01) were significantly related with drug-resistant epilepsy.

Conclusion Abnormal initial EEG result was the only initial risk factor associated with drug-resistant epilepsy. Evolution risk factors associated with drug-resistant epilepsy were increased seizure frequency and seizure persistence in the first six months of treatment. **[Paediatr Indones. 2025;65:42-7; DOI: https://doi.org/10.14238/pi65.6.2025.42-7].**

Keywords: *risk factor; drug-resistant epilepsy; neuroplasticity*

Recurrent seizures during early brain development has been shown to alter neurogenesis, synaptogenesis, neuronal network connectivity, and temporal coding associated with cognitive impairment in animal models. The rapidly developing brain has a higher tendency to develop seizures. At the same time, the brain during early child development has high neuroplasticity.[1,2,3] Repeated seizures may result in chronic injury to the brain, thereby inducing neuroplasticity. Neuroplasticity may augment existing pathological processes.[4] Neuroplasticity during early brain growth may influence the clinical course and outcome of children with epilepsy.

Drug-resistant epilepsy is defined as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs to achieve a sustained seizure-free state.[5] Various studies have evaluated risk factors for drug-resistant epilepsy in children. A study reported abnormal EEG, symptomatic etiology, febrile seizures, and multiple

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seizure types as strong risk factors for drug-resistant epilepsy in children aged 1-18 years.[6] Few studies have evaluated changes during the treatment course in children under 3-year-old. This study aimed to evaluate the role of initial risk factors and changes (evolution) during treatment in children under 3-year-old with epilepsy to predict the occurrence of drug-resistant epilepsy.

Methods

This retrospective cohort study used medical record data from Dr. Cipto Mangunkusumo Hospital, Anakku Clinic Pondok Pinang, and National Brain Center Hospital, Jakarta, from 2015 to 2020. Inclusion criteria were children aged 1 month to 3 years diagnosed with epilepsy who sought treatment for at least 6 months and were treated with one antiepileptic drug at the beginning of observation. Exclusion criteria were poor compliance, incomplete medical records, and multiple congenital anaomalies. The required sample size determined by rule-of-thumb was 140 subjects.

We studied initial risk factors, which were intrinsic risk factors present at the beginning of treatment, and evolution risk factors, which were changes arising after treatment was started. Initial risk factors consisted of initial seizure frequency, initial seizure type, history of febrile seizure, abnormal brain structure, the presence of neurological abnormality, developmental history, and initial EEG. Evolution risk factors consisted of early response to therapy, evolution (changes) in seizure type and frequency, evolution (changes) in neurodevelopmental status, and evolution (changes) in EEG.

A patient was considered to have drug-resistant epilepsy when they did not achieve seizure freedom after they were given two adequately dosed and well-tolerated antiepileptic drugs for an ample duration. We recorded the subjects' outcome, i.e. whether they developed drug-resistant epilepsy, and analyzed the association between each risk factor and the occurrence of drug-resistant epilepsy using the chi-square or Fisher's exact test.

Results

We obtained a total of 150 subjects; 50.7% were male and 49.3% were female. Most subjects (72.7%) had seizure onset at <1 year of age and were diagnosed with generalized epilepsy (64.7%). Thirty-three (22%) subjects were diagnosed with drug-resistant epilepsy 6-12 months after initial treatment.

Bivariate analysis of initial risk factors showed that initial seizure frequency, abnormal brain imaging, initial neurodevelopmental status, and initial EEG were significantly related with drug-resistant epilepsy (**Table 1**). We were able to analyze evolution risk factors in 109 subjects; the remaining 41 subjects only had initial EEG results and were excluded from the analysis for evolution risk factors. Early response to treatment, increased seizure frequency, change in background rhythm to abnormal, the presence of epileptiform abnormalities in the EEG, and evolution of neurodevelopmental status to abnormal were significantly related to drug-resistant epilepsy (**Table 2**).

Variables with P value <0.25 in bivariate analysis were included in multivariate analysis. Imaging result could not included in multivariate analysis because some brain imaging data were not available. Logistic regression multivariate analysis revealed that abnormal initial EEG was significantly associated with drug-resistant epilepsy, with an R-squared of 19.9 (**Table 3**). Multivariate analysis with logistic regression method showed that poor early response to therapy and increased seizure frequency during therapy were significantly associated with drug-resistant epilepsy, with an R-squared of 59.2% (**Table 4**).

Discussion

In this study, the incidence of drug-resistant epilepsy in children <3 year old was 22%. Previous studies have reported incidence levels of 30% and 35%.[7,8] Most subjects (72.8%) were diagnosed with drug-resistant epilepsy after 6 months of treatment. In this study, abnormal initial EEG was the only initial risk factor significantly associated with drug-resistant epilepsy (OR 4.48; 95%CI 1.82 to 11.03; P=0.001). This result was similar to other study.[6,8-11] In a meta-analysis, both slow waves (RR 2.65; 95%CI 1.55 to 4.52) and

Table 1. Bivariate analysis of initial risk factor (N=150)

Variables	Drug resistant epilepsy		OR (95%CI)	P value
	Yes (n=33)	No (117)		
Initial seizure frequency				
>3x/day	24 (28.2)	61 (71.8)	2.45 (1.05 to 5.71)	0.035*
<3x/day	9 (13.8)	56 (86.2)		
Early seizure type				
General	24 (19.8)	97 (80.2)	0.55 (0.22 to 1.36)	0.191*
Focal/multiple	9 (31.1)	20 (68.9)		
Febrile convulsion				
No	27 (22.9)	91 (77.1)	1.29 (0.48 to 3.45)	0.617*
Yes	6 (18.8)	26 (81.2)		
Head CT scan/MRI results (n=81)				
Abnormal	25 (42.4)	34 (57.6)	4.66 (1.24 to 17.48)	0.016*
Normal	3 (13.6)	19 (86.4)		
Initial neurological status				
Abnormal	21 (29.2)	51 (70.8)	2.27 (1.02 to 5.03)	0.042*
Normal	12 (16.2)	66 (84.6)		
Early developmental status				
Abnormal	21 (27.6)	55 (72.4)	1.97 (0.89 to 4.38)	0.092*
Normal	12 (16.2)	62 (83.8)		
Initial EEG				
Abnormal	24 (36.9)	41 (63.1)	4.94 (2.10 to 11.62)	<0.001*
Normal	9 (10.6)	76 (89.4)		

*Chi-square

Table 2. Bivariate analysis of evolution risk factor (N=109)

Variables	Drug resistant epilepsy		OR (95%CI)	P value
	Yes (n=26)	No (n=83)		
Early response to therapy				
Persistent seizure	21 (56.8)	16 (43.2)	17.59 (5.75 to 53.77)	<0.001*
Seizure free	5 (6.9)	67 (93.1)		
Evolution of seizure type				
Change in seizure type	4 (50)	4 (50)	3.59 (0.83 to 15.53)	0.090**
Same seizure type	22 (21.8)	79 (78.2)		
Evolution of seizure frequency				
Increased frequency	8 (80)	2 (20)	18 (3.52 to 92.01)	<0.001*
Decreased frequency/seizure-free	18 (18.2)	81(81.8)		
EEG basic rhythm wave evolution				
Abnormal rhythm	18 (52.9)	16 (47.1)	9.42 (3.48 to 25.50)	<0.001**
Normal rhythm	8 (10.7)	67 (89.3)		
EEG epileptiform wave evolution				
Diminished epileptiform wave	21 (55.3)	17 (44.7)	16.31 (5.37 to 49.55)	<0.001**
Persistent epileptiform wave	5 (7)	66 (93)		
Evolution of neurological status				
Abnormal	19 (50)	19 (50)	9.14 (3.34 to 25.02)	<0.001**
Normal	7 (9.9)	64 (90.1)		
Evolution of development status				
Abnormal	22 (32.8)	45 (67.2)	4.64 (1.47 to 14.66)	0.005**
Normal	4 (9.5)	38 (90.5)		

Table 3. Multivariate analysis of initial risk factors

Variables	B	SE	aOR (95%CI)	P value
Initial seizure frequency	0.64	0.47	1.89 (0.76 to 4.71)	0.172
Initial seizure type	0.74	0.53	0.48 (0.17 to 1.30)	0.147
Initial neurologic status	0.33	0.49	1.39 (0.54 to 3.62)	0.498
Early development status	0.12	0.49	1.13 (0.43 to 2.94)	0.804
Initial EEG	1.49	0.46	4.48 (1.82 to 11.03)	0.001

R square =19.9%; B=unstandardized regression weight; SE=standard errors; aOR=adjusted odds ratio

Table 4. Multivariate analysis of evolution risk factors

Variables	B	SE	aOR (95% CI)	P value
Early response to therapy	2.39	0.73	10.92 (2.6 to 45.87)	0.001
Evolution of seizure type	-0.48	0.99	0.62 (0.09 to 4.31)	0.626
Evolution of seizure frequency	1.96	0.99	7.1 (1.01 to 49.7)	0.048
EEG basic rhythm wave evoluion	1.43	0.82	4.18 (0.83 to 20.89)	0.082
EEG epileptiform wave evolution	0.73	0.87	2.09 (0.38 to 11.39)	0.396
Evolution of neurological status	0.42	0.81	1.52 (0.31 to 7.48)	0.609
Evolution of development status	0.1	0.95	1.11 (0.17 to 7.07)	0.915

R square = 59.2%; B=unstandardized regression weight; SE=standard errors; aOR=adjusted odds ratio

epileptiform discharges (RR 2.92; 95%CI 1.80 to 4.75) were risk factors for drug-resistant epilepsy.[6] Another study found focal slowing to be significantly associated with drug-resistant epilepsy,[8] whereas another study reported that general deceleration was associated with drug-resistant epilepsy.[9] Age of onset <12 months, early developmental delay, imaging abnormalities, and focal slowing of the initial EEG have also been reported to be associated with drug-resistant epilepsy.[8] In children aged <2 years with epilepsy, developmental delay, multifocal epileptiform discharges, and a history of status epilepticus were significantly associated with drug-resistant epilepsy.[9] A previous study at Cipto Mangunkusumo Hospital found that age of <5 years, female sex, age of onset <1 year, initial seizure frequency >10 times/day, presence of epileptiform discharges, and abnormal MRI were significantly associated with the occurrence of drug-resistant epilepsy.[10] Similar to two previous studies, early developmental delay was not associated with drug-resistant epilepsy in this study.[9,10]

Studies have reported that abnormal brain imaging was significantly associated with the occurrence of drug-resistant epilepsy in children,6,8,10,11 similar to our study (OR 4.66; 95%CI 1.24 to 17.48; P=0.016). Unfortunately, this variable could not be included in multivariate analysis because only 54% of subjects had undergone imaging studies. Another retrospective study conducted at Dr. Cipto Mangunkusumo Hospital obtained imaging data in 35% of subjects.[12] A prospective study in the same institution obtained imaging data from 80% of subjects.[7] *The International League Against Epilepsy* (ILAE) recommends that brain imaging be performed in all children with newly diagnosed focal epilepsy, non-idiopathic generalized epilepsy syndromes, and all children with age of seizure onset below 2 years.[13] However, in Indonesia, brain imaging has not been widely carried out due to access, cost, and technical problems, such as general anesthesia protocol during imaging examination.

Multivariate analysis of evolution risk factors showed that poor early response to therapy and increased seizure frequency were associated with drug-resistant epilepsy. Poor early response to therapy was also significantly associated with drug-resistant epilepsy in other studies.[12] Another study reported change in seizure type and abnormal EEG background rhythm to be significantly associated with drug-resistant epilepsy, while early response to therapy was not a significant risk factor.[7] A meta-analysis found poor early response to therapy as a significant risk factor for drug-resistant epilepsy, but the studies

included in this meta-analysis had high heterogeneity.[6] Similar to this study, a study reported that seizure freedom within the first 6 months of treatment was a strong predictor of seizure control 3 years later.[13] Another study in Indonesia found that abnormal initial EEG and a high initial seizure frequency were risk factors for a poor initial response to therapy.[14]

Increased seizure frequency during treatment was significantly associated with drug-resistant epilepsy. Other studies found a high seizure frequency at the start of therapy to be associated with drug-resistant epilepsy.[6,10,15] Although clinical data remain inconclusive, in vitro studies have reported that one seizure in the immature brain can evoke subsequent seizures, a phenomenon referred to as the kindling phenomenon.[16-18] This may explain the finding of increased seizure frequency as a risk factor of drug-resistant epilepsy in this study.

This study had several limitations. The retrospective design was prone to information bias. In addition, some subjects only had one EEG, and some subjects were missing brain imaging data.

In conclusion, abnormal initial EEG result, seizure persistence during first 6 months of treatment, and increased seizure frequency during treatment were associated with drug-resistant epilepsy. Clinicians should refer their patients with risk factors of drug-resistant epilepsy to a tertiary healthcare center.

Conflict of interest

None declared.

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References

1. Hauser W. Epidemiology of epilepsy in children. In: Pellock JM, Nordli DR, Sankar R, Wheless JW, editors. Pellock's pediatric epilepsy: diagnosis and therapy. New York: Demos Medical Publishing; 2017. p. 177-205.
2. Knickmeyer R, Gouttard S, Kang C, Evans D, Wilber K, Smith JK, *et al.* A structural MRI study of human brain development from birth to 2 years. J Neurosci. 2008;28:12176-82. DOI: https://doi.org/10.1523/JNEUROSCI.3479-08.2008
3. Holmes G. Effect of seizure on the developing brain and cognition. Semin Pediatr Neurol. 2016;23:120-6. DOI: https://doi.org/10.1016/j.spen.2016.05.001
4. Jarero-Basulto JJ, Gasca-Martinez Y, Rivera-Cervantes MC, Ureña-Guerrero ME, Feria-Velasco AI, Beas-Zarate C. Interactions between epilepsy and plasticity. Pharmaceuticals. 2018;11:1-18. DOI: https://doi.org/10.3390/ph11010017
5. Kwan P, Arzimanoglou A, Berg A, Brodie MJ, Hauser W, Mathern G, *et al.* Definition of drug-resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Theurapetic Strategies. Epilepsia. 2010;51:1069-77. DOI: https://doi.org/10.1111/j.1528-1167.2009.02397.x
6. Wang X, Wang H, Zhu L, Da X, Liu L. Risk factors for drug-resistant epilepsy: a systematic review and meta-analysis. Medicine (Baltimore). 2019;98:e16402. DOI: https://doi.org/10.1097/MD.0000000000016402
7. Mangunatmadja I. Prediction of clinical outcome in patients with focal epilepsy under 3 years of age: the role of clinical evolution and electroencephalography and magnetic resonance imaging. [dissertation]. Jakarta: Universitas Indonesia; 2012.
8. Wirrel E, Kisiel L, Mandrekar J, Nickels K. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. Epilepsia. 2012;53:1563-9. DOI: https://doi.org/10.11111/j.1528-1167.2012.03562.x
9. Yildiz E, Gunes D, Bektas G, Uzunhan T, Tatli B, Calliskan M, *et al.* Predictive factors of drug-resistant epilepsy in children presenting under 2 years of age: experience of a tertiary center in Turkey. Acta Neurol Belg. 2018;118:71-5. DOI: https://doi.org/10.1007/s13760-017-0850-3
10. Widodo D. Faktor risiko terjadinya epilepsi yang sukar disembuhkan pada anak berumur di bawah 5 tahun. [dissertation]. Jakarta: Universitas Indonesia; 2012.
11. Handryastuti S, Mangunatmadja I. Risk factors influencing the outcomes in infants with epilepsy. Paediatr Indones. 2007;47:202-6. DOI: https://doi.org/10.14238/pi47.5.2007.202-6
12. Mangunatmadja I, Mulyani D, Pardede S, Tridjaja B, Wulandari H. Risk factors for intractable epilepsy in children with generalized epilepsy. J Indon Med Assoc. 2019;69:59-65. DOI: https://doi.org/10.47830/jinma-vol.69.2-2019-72
13. Xia L, Ou S, Pan S. Initial response to antiepileptic drugs in patients with newly diagnosed epilepsy as a predictor of

long-term outcome. Front Neurol. 2017;8:658. DOI: https://doi.org/10.3389/fneur.2017.00658

14. Sinaga N. Respons awal obat antiepilepsi monoterapi pada pasien epilepsi baru. [thesis]. Jakarta: Universitas Indonesia; 2017.
15. Sillanpaa M, Schmidt D. Early seizure frequency and aetiology predict long-term medical outcome in childhood onset epilepsy. Brain. 2009;132:989-98. DOI: https://doi.org/10.1093/brain/awn357
16. Auvin S. Pathophysiology of seizures in the developing brain. In: Pellock JM, Nordli DR, Sankar R, Wheless JW, editors. Pellock's pediatric epilepsy: diagnosis and therapy. New York: Demos Medical Publishing; 2017. p. 3-19.
17. Avanzini G, Depaulis A, Tassinari A, de Curtis M. Do seizures and epilepstic activity worsen epilepsy and deteriorate cognitive function? Epilepsia. 2013;54:14-21. DOI: https://doi.org/10.11111/epi.12418
18. Yehezkel B. Epilepsies and neuronal plasticity: for better or for worse? Dialogues Clin Neurosci. 2008;10:17-27. DOI: https://doi.org/10.31887/DCNS.2008.10.1/ybenari