ORIGINAL ARTICLES

Risk factors for drug-resistant epilepsy (DRE) in children and a model to predict development of DRE

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ABSTRACT

Purpose. This study was conducted to investigate possible risk factors that could increase the occurrence of drug-resistant epilepsy (DRE), in hopes that the results could be used to educate the patient and their caregivers as well as increase early detection efforts.

Methods. Case control study was conducted at neurology outpatient pediatric RSDS between May to December 2022. Risk factor of DRE such as sex, age of onset, type of seizure, initial seizure frequencies, history of cranial hemorrhage, cerebral infection, febrile seizure, status epilepticus, neonatal seizure, neonatal asphyxia, family history of epilepsy, present of neurological deficit, electroencephalogram (EE) finding, and result of neuroimaging examination were obtained through anamnesis and clinical examination. Risk factors were analyzed with bivariate analysis and multivariate analysis. A model was generated to predict probabilities of DRE in children with epilepsy.

Results. DRE was observed in 84/137 (54%) patients. Bivariate analysis showed age of onset <1 years old (OR 2.31, p = 0.016), initial seizure frequencies >5 times/day (OR 3.0, p = 0.011), neonatal seizure (OR 3, p = 0.034), presence of neurologic deficit (OR 3.1, p=0.002), and abnormality of EEG (OR 2.82, p = 0.013) are significantly associated with DRE. Logistic regression revealed that initial seizure frequencies > 5 times/day (OR=2.5; 95%CI 1.051 to 6.028; P=0.038), present of neurological deficit (OR=2.58; 95%CI 1.205 to 5.531; P=0.031), and EE abnormality (OR=2.84; 95%CI 1.170 6.914; P=0.021) were significantly correlated with DRE. Our model sensitivity was 75.3% and 55.76% to predict DRE (AUC = 0.704, p=0.000).

Conclusion. Seizure onsets of >5 times, neurological deficits, and EEG abnormality were found to be associated with drug resistant epilepsy.

Keywords: drug resistant epilepsy, risk factors, seizures

INTRODUCTION

Epilepsy is a neurological condition marked by repeated episodes without obvious reasons. The International League against Epilepsy (ILAE) defined epilepsy as a disorder of the brain that is marked by the brain's tendency to cause epilepsy, and causing neurobiological, cognitive, psychological, and social consequences. The prevalence of epilepsy in the general population is about 1-2%. Most of them occurs in children at 3.5 to 7.2 occurrence every 1000 children. Drug resistant epilepsy is found in 30% of patients with epilepsy. Resistance to drug is defined as failure of remission after the second administration of adequate and tolerated anti-epileptic drug

that is chosen as mono-therapy or combination-therapy to achieve a state of epilepsy-free. Many factors were suggested to be related to drug-resistant epilepsy (DRE), some of them includes sex, age of first episode, family history, history of febrile-seizure, neonatal seizure, neurological deficit, type of seizures, status epilepticus, presence of epileptic syndrome, abnormal findings in electroencephalogram (EE) and abnormal radiological findings [1,2].

Drug resistant epilepsy increases risk for morbidity and mortality in children with epilepsy. They increase the cost and length of treatment. This creates an urgency to assess the risk factors for drug resistance. Investigation of risk factors would also allow early diagnosis of refractory seizures that

prompt starting more intensive medication, surgery, or other interventions that could be done to manage epilepsy and prevent anti-epileptic drug toxicity [3].

Several studies have been made to identify the factors to predict failure of medication on patients with epilepsy. Although their results very and are inconsistent. The predictors for epileptic drug resistance in Indonesian populations may be different with other countries. Early identification of patients at increased risk for drug resistance is very important, specially to counsel the parents on taking care of their children and also important to choose the correct treatment. This early identification is very useful in countries with limited resources. Hence, we decided to make this research to identify early predictors of drug-resistant epilepsy [4-7].

MATERIAL AND METHODS

This is an observational analytic study with a case-control design. The sample of this study were patients with drug-resistant epilepsy that came to the Child Neurology Clinic at Dr. Soetomo General Hospital, in which several data personal and medical data were collected. Personal data includes age and sex. Medical data that were collected includes their current medical history such as seizure onset, type of seizures, and frequency of seizures. Their past medical histories were also collected such as history of intracranial hemorrhage, central nervous system infection, history of status epilepticus, febrile seizures, epilepsy in the family, neonatal seizures, neonatal asphyxia, microcephaly, delayed development, history of anti-epileptic drug and amount taken, neurological deficits as well as results of additional examinations such as EE and MRI findings. The inclusion criteria were epilepsy children age 1 month of corrected age to 18 years old which has been treated with antiepileptic drugs for at least 6 months.

ETHICAL STATEMENT

This study was approved by Dr. Soetomo General Hospital Ethics Committee (0439/KEPK/VII/2022). The authors' institutional review board or comparable organization approved the present research for human use, which followed all relevant national rules, institutional procedures, and the precepts of the Helsinki Declaration of 1975, as revised in 2013

RESULTS

In this study there were 137 patients with epilepsy that satisfy the inclusion and exclusion criteria from which were found that 84 of them had refrac-

tory epilepsy and 53 of them are sensitive to anti-epileptic drugs. Majority of the subjects were male (55.5%) and mostly were based in Surabaya (58.4%). The percentage of epileptic seizures that occurs on subjects under 1 years old were 56.2%. Previous medical history suggests that 7 children had hemorrhage, 25 children had central nervous system infection, 38 children had status epilepticus, 49 children had history of febrile seizures, 25 children had history of neonatal seizures, and 20 children had history of epilepsy in the family (Table 1).

Table 2 shows risk factors for drug-resistant epilepsy. This study found that age of seizures onset less than 1 year was risk factor for DRE (p=0.016, OR 2.34). Initial frequency of seizures more than five times per day was also a risk factor for DRE (p=0.009, OR 3.009). Presence of neonatal seizures is also a risk factor for drug-resistant epilepsy (p = 0.034, OR 3). Abnormal head circumference is a risk factor for drug-resistant epilepsy (p = 0.01, OR 2.66). The presence of neurological deficits was a risk factor for drug-resistant epilepsy (p = 0.002, OR 3.11). Ancillary examination findings, namely EE appearance, were a risk factor for drug-resistant epilepsy (p = 0.013, OR 2.833). Abnormal findings on CT and MRI imaging based on etiology (p = 0.09) are also risk factors for drug-resistant epilepsy. Seizure type, CNS bleeding, CNS infection, history of status epilepticus, history of febrile seizures, history of neonatal asphyxia, family history of epilepsy, and abnormalities in MRI and CT imaging were not proven to be risk factors for drug-resistant epilepsy in children (p>0.05).

In multivariate analysis, variable frequency of seizure onset more than five times (p 0.038, OR 2.517 (95% CI 1.051-6.028)), presence of neurological deficits (p 0.015, OR 2.58 (95% CI 1.205-5.531)), and abnormal findings in EE (p 0.021, OR 2.844 (95% CI 1.170-6.914)) were significant risk factors for drug-resistant epilepsy in children. While the age of onset of seizures is less than 1 year, history of CNS infection, history of neonatal asphyxia, presence of head circumference abnormalities, and abnormalities in MRI and CT images are not significant as risk factors for drug-resistant epilepsy in children (Table 3).

From linear regression, it was found that if the patient has risk factors for onset of seizures >5x/day, neurological deficits, and EE abnormalities, then the probability of developing drug-resistant epilepsy is 85.2%. If the patient has risk factors for onset of seizures >5x/day and neurological deficits, then the probability of developing drug-resistant epilepsy is 67%. If the patient has risk factors for onset of seizures >5x/day and abnormal EEG, then the probability of developing drug-resistant epilepsy is 69.1%. If the patient has risk factors for neurological deficits

TABLE 1. Characteristics of Study Subjects

Variable		n (137)	%
Epilepsy type	Intractable	84	61.3
	Drug sensitive	53	38.7
Sex	Male	76	55.5
	Female	61	44.5
Domicile	Surabaya	80	58.4
	Out of Surabaya	57	41.6
Age	≤ 3 Years	51	37.2
	> 3 Years	86	62.8
Age of onset	≤ 1 Year	77	56.2
	> 1 Year	60	43.8
Seizure Type	Partial	40	29.2
	General	97	70.8
Frequency of seizures	1-2 x/Day	72	52.6
	3-5 x/Day	24	17.5
	6-10 x/Day	14	10.2
	> 10 x/Day	27	19.7
Intracranial Hemorrhage	Yes	7	5.1
	No	130	94.9
CNS infection	Yes	25	18.2
	No	112	81.8
Status Epilepticus	Yes	38	27.7
	No	99	72.3
Febrile Seizures	Yes	49	35.8
	No	88	64.2
Neonatal Asphyxia	Yes	15	10.9
	No	122	89.1
Neonatal Seizures	Yes	25	18.2
	No	112	81.8
Family History	Yes	20	14.6
	No	117	85.4
Number of drugs	1 drug	53	38.7
	2 drugs	48	35
	3 drugs	28	20.4
	4 drugs	8	5.8
Head Circumference	Microcephaly	37	27
	Normocephaly	85	62
	Macrocephaly	15	0.9
Neurological Deficit	Present	89	65
	Absent	48	35
Electroencephalogram	Normal	28	20.4
	Abnormal 1	10	7.3
	Abnormal 2	23	16.8
	Abnormal 3	76	55.5
Neuroimaging abnormality	Present	76	55.5
	Absent	61	44.5
Location of Neuroimaging abnormality	Normal	61	44.5
	Cortical	57	62
	Non Cortical	19	13.8
Etiology of Abnormality	Normal	61	44.5
	Congenital	54	39.4
	Infeksi	11	8
	Vaskuler	9	6.6
	Tumor	2	1.5

and EE abnormalities, then the probability of developing drug-resistant epilepsy is 69.6% (Table 4).

The goodness of fit (GoF) test results obtained p = 0.993 so that the model stated that there was no significant difference between the model and the observed value. The results of the ROC curve analysis show that the value of the area under the ROC curve is 0.704, as shown in Figure 1. In the analysis of the sensitivity and specificity values using the Youden index, it was found that this prognostic model of intractable epilepsy had a sensitivity value of 75.3% and a specificity of 55.76%.

DISCUSSION

Based on statistical analysis in this study, seizure type, history of CNS Hemorrhage, CNS infection, status epilepticus, febrile seizures, seizures in the family, neonatal asphyxia, neonatal epilepsy, and abnormal brain imaging were not proven to be risk factors for drug-resistant epilepsy in children (p>0.05) in both bivariate and multivariate analysis.

The largest age group of people with epilepsy was in children over 3 years of age, with 86 children (62.8%). Based on the results of bivariate analysis, age of seizures onset <1 year proved to be a significant risk factor for DRE but not in multivariate analysis. Age of seizures onset <1 year is at risk of developing drug-resistant epilepsy 2.3 times greater. These findings support the hypothesis that early-onset seizures indicate a tendency for the epileptogenesis to occur in developing brains, which can lead to intractable epilepsy [8]. In the age period up to 3 years, the child's brain has a plasticity ability that allows changes or rearrangement of brain tissue circuits, however, during this period the brain is also very vulnerable to seizures. This can be explained because there are more electrical synapses compared to a mature brain and it makes it easier for nerve cell membranes to depolarize resulting in seizures or electrical discharges. This immature brain also has excitation synapses that develop earlier and low gamma-aminobutyric acid (GABA) neurotransmitter inhibitory factors [9].

Aside from age, frequency of seizure onset >5 times/day was significantly proven to be a risk factor for drug-resistant epilepsy in children (p<0.05). These results were supported by multivariate analysis which stated that frequency of seizure onset >5 times/day was an independent risk factor for drug-resistant epilepsy with an OR of 2.517 (p<0.05). The results of this study are in accordance with previous study of 213 children with epilepsy which stated that seizures > 5 times increased the risk of drug-resistant epilepsy up to 9.9 times greater based on bivariate analysis and 8.2 times greater in multivariate analysis [10,11]. The thing that underlies the role of the frequency of onset of seizures as a risk factor for drug-resistant epilepsy is that a high fre-

TABLE 2. Bivariate analysis of drug-resistant epilepsy risk factors

Variable	Intractable Epilepsy n = 84 (%)	Drug Sensitive n = 53 (%)	p	OR	95% CI Min	95% CI Max
Sex			0.397	1.348	0.675	2.692
Male	49 (58.3)	27 (50.9)				
Female	35 (41.7)	26 (49.1)				
Domicile			0.278	0.676	0.334	1.372
Surabaya	46 (54.8)	34 (64.2)				
Out of Surabaya	38 (45.2)	19 (35.8)				
Age of onset			0.016*	2.348	1.162	4.742
≤ 1 Year	54 (64.3)	23 (43.3)				
> 1 Year	30 (35.7)	30 (56.6)				
Seizure type			0.855	1.073	0.503	2.293
Partial	25 (29.8)	15 (28.3)				
General	59 (70.2)	38 (71.7)				
Seizure frequency			0.009*	3.009	1.297	6.979
>5 x/ Day	32 (38.1)	9 (17)				
≤5 x/ Day	52 (61.9)	44 (83)				
History of Hemorrhage			0.816	0.833	0.179	3.880
Yes	4 (4.8)	3 (5.7)				
No	80 (95.2)	50 (94.3)				
CNS Infection			0.095	2.290	0.849	6.172
Yes	19 (22.6)	6 (11.3)				
No	65 (77.4)	47 (88.7)				
Status Epilepticus			0.290	1.532	0.693	3.383
Yes	26 (31)	12 (22.6)				
No	58 (69)	41 (77.4)				
Febrile Seizure			0.726	1.137	0.563	2.338
Yes	31 (36.9)	18 (34)				
No	53 (63.1)	35 (66)				
Neonate Asphyxia			0.652	1.297	0.418	4.029
Yes	10 (11.9)	5 (9.4)				
No	74 (88.1)	48 (90.6)				
Neonatal Seizure			0.034*	3.000	1.051	8.564
Yes	20 (23.8)	5 (9.4)				
No	64 (76.2)	48 (90.6)				
Family History			0.388	1.567	0.562	4.368
Yes	14 (16.7)	6 (11.3)				
No	70 (83.3)	47 (88.7)				
Neurological Deficit			0.002*	3.115	1.500	6.469
Yes	63 (75)	26 (49.1)				
No	21 (25)	27 (50.9)				
EEG			0.013*	2.833	1.223	6.565
Abnormal	72 (85.7)	36 (67.9)				
Normal	12 (14.3)	17 (32.1)				
EEG			0.013*			
Normal	11 (13.1)	17 (32.1)				
Abnormal 1	4 (4.8)	6 (11.3)				
Abnormal 2	17 (20.2)	6 (11.3)				
Abnormal 3	52 (61.9)	24 (45.3)				
CT/MRI Abnormalities	2		0.120	1.731	0.864	3.467
Yes	51 (60.7)	5 (47.2)				
No	33 (39.3)	28 (52.8)				
Abnormality location CT/MRI			0.230			
Normal	32 (38.1)	28 (52.8)				
Cortical	38 (45.2)	19 (35.8)				
Non Cortical	14 16.7)	6 (11.3)				
Etiology on CT/MRI			0.091			
Normal	32 (38.1)	28 (52.8)				
Congenital	33 (39.3)	22 (41.5)				
Infection	10 (11.9)	1 (1.9)				
Vascular	7 (8.3)	2 (3.8)				
Tumor	2 (2.4)	0 (0)				

TABLE 3. Multivariate analysis of risk factors for drug-resistant epilepsy in children

Variable	P value	OR	95% CI	
			Min	Max
Age Onset <1 year	0.230	1.662	0.725	3.811
Seizure Type	0.822	1.108	0.451	2.721
Initial Seizures Frequency >5x/day	0.038*	2.517	1.051	6.028
CNS Haemorrhage	0.245	0.373	0.071	1.964
CNS infection	0.601	1.354	0.435	4.213
Status Epilepticus	0.961	1.024	0.396	2.646
Febrile Seizures	0.536	1.303	0.564	3.009
Neonate Asphyxia	0.989	0.991	0.264	3.711
Neonatal Seizures	0.398	1.686	0.502	5.667
Family History	0.389	1.635	0.534	5.003
Neurological Deficit	0.015*	2.581	1.205	5.531
Abnormal EEG	0.021*	2.844	1.170	6.914
Abnormal CT/MRI	0.829	0.911	0.390	2.126

TABLE 4. Linear regression of risk factors for drug-resistant epilepsy in children

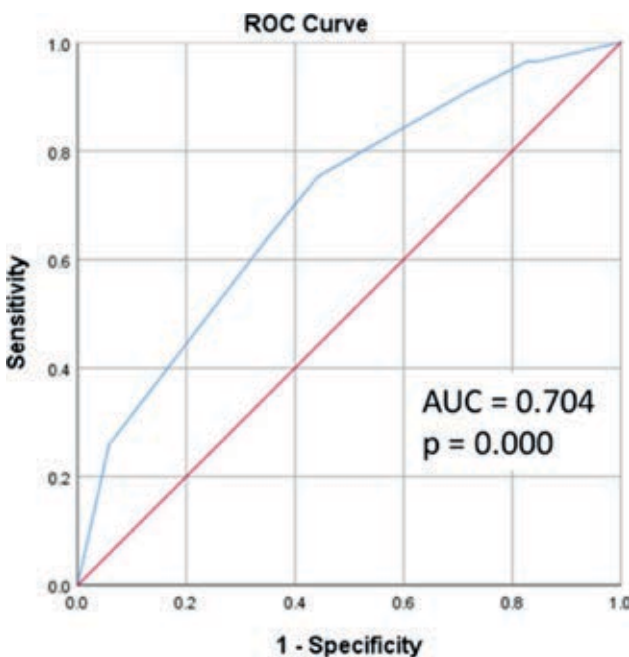| Risk Factors	Probability
Frequency >5 times + Neurological Deficit + Abnormal EE	85.24%
Frequency >5 times + Neurological Deficit	67.01%
Frequency >5 times + Abnormal EE	69.12%
Neurological Deficit + Abnormal EE	69.65%
Frequency >5 times	44.05%
Neurological deficit	44.67%
Abnormal EE	47.07%

FIGURE 1. ROC curve prognosis model for drug-resistant epilepsy in children

quency of seizures at the beginning will result in more and more nerve cells being damaged so that the greater the possibility of intractable epilepsy de-

velopment. Recurrent seizures have been shown to result in loss of neurons and growth of mossy nerve fibers in the hippocampus, which can strengthen the formation of repetitive excitation circuits [12].

History of neonatal seizures was also proven to be a risk factor for drug-resistant epilepsy in children (p<0.05) in bivariate analysis. Multivariate analysis showed a history of neonatal seizures was not an independent risk factor for drug-resistant epilepsy (p>0.05). The results of this study are similar to a study by Yilmaz in 200 children with intractable epilepsy and 208 children with drug-sensitive epilepsy which stated that a history of neonatal seizures was significantly significant as a risk factor for drug-resistant epilepsy in bivariate analysis but not in multivariate analysis [8].

In addition, neurological deficits were significantly proven to be a risk factor for drug-resistant epilepsy in children (p<0.05) both on bivariate and multivariate analysis. Our study stated that neurological deficits were an independent risk factor for drug-resistant epilepsy with an OR of 2.581 (p<0.05). The results of this study are in accordance with previous study on 213 children with epilepsy which stated that neurological deficits increased the risk of drug-resistant epilepsy up to 8.6 times greater based on bivariate analysis [11].

This study also found that EEG abnormality is an independent risk factor for drug-resistant epilepsy with an OR of 2.833 (p<0.05). The results of this study are in accordance with previous studies in the study by Yildiz stating that abnormal EEG images are an independent risk factor for drug-resistant epilepsy with an OR value of 2.844 (p <0.05) [13]. Similar results were obtained in a study by Boonluksiri in 2015, which stated that an abnormal EEG picture was a predictor of drug-resistant epilepsy with an OR value of 2.9 (p <0.05) [14].

Lastly, we also developed a predictor model for drug-resistant epilepsy that involved risk factors including frequency of seizure onset >5 times/day, presence of neurological deficits, and EE finding abnormalities. The two risk factors in this study were risk factors that were obtained through anamnesis and physical examination, so this model is expected to be a fast predictor in predicting drug-resistant epilepsy. Our predictor model has an area under the curve (AUC) value of 0.737 with a sensitivity of 77.6% and a specificity of 59.6% in predicting drug-resistant epilepsy.

Our study has several limitations and weaknesses. Our study used a strict definition of drug-responsive epilepsy, involving being seizure-free for 12 months. Some authors defined medical intractability as failure of three or more antiepileptic drugs. Our study used a definition involving two or more antiepileptic drugs, as a very small number of pa-

tients can become seizure-free with three antiepileptic drugs. One of the limitations of this study involves the research method we used. The study was conducted in a tertiary care hospital, where intractable epilepsy cases are often referred for evaluation as the hospital is the main center performing epilepsy surgery in eastern Indonesia. A limitation of the study is that the study population may not be truly representative of the actual population, but most intractable epilepsy patients in Indonesia will eventually be referred to this center due to resource differences. One of the weaknesses in case-control studies is that ascertaining the history of various risk factors will differ in cases and controls due to memory bias.

CONCLUSION

This study concludes that seizure onset of less than one year of age, types of seizures, frequency of seizures, history of bleeding, status epilepticus, febrile seizures, neonatal asphyxia, neonatal seizures, and epilepsy in the family is not related to the occurrence of drug-resistant epilepsy. On the other hand, frequency of seizure onset >5 times/day, neurological deficits and abnormal EE findings are found to be related to drug-resistant epilepsy. Our model predictor for drug-resistant epilepsy has an AUC of 0.737 with 77.6% sensitivity and 59.6% specificity in predicting drug-resistant epilepsy.

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