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Original Article

Risk factors for poor initial response to valproic acid therapy in children with epilepsy

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Abstract

Background The initial response in the first three months of valproic acid therapy is a prognostic factor for predicting treatment success, and it is considered to be poor if seizures persist during the three months of valproic acid treatment. Several factors might influence the initial response to valproic acid therapy, including gender, age, family history of epilepsy, electroencephalogram (EEG), head circumference, type of seizure, cerebral palsy, and pre-therapy seizure frequency.

Objective To determine the risk factors for poor early response to valproic acid therapy in children with epilepsy.

Methods This retrospective cohort study was conducted in children newly diagnosed with epilepsy. Data were collected from medical records of patients who had been treated at the Pediatric Polyclinic of Dr. Zainoel Abidin Hospital for one year.

Results Of 90 subjects, most were male (58; 64.4%) and aged three years or older (79; 87.8%). Forty-five (50%) patients had a family history of epilepsy. More than a quarter of the subjects (35; 38.9%) showed initial poor responses to valproic acid therapy. Bivariate analysis revealed risk factors for poor initial response to valproic acid therapy were age ≥3 years, family history of epilepsy, normal EEG, normal head circumference, generalized seizure type, cerebral palsy, and pre-therapy seizure frequency. However, multivariate analysis revealed that risk factors for poor initial response to valproic acid therapy in children with epilepsy that retained significance were family history of epilepsy (RR 6.58; 95%CI 1.67 to 25.95; P=0.001), abnormal EEG (RR 5.27; 95%CI 1.16 to 23.87; P=0.000), focal seizures (RR 7.10; 95%CI 1.15 to 43.80; P=0.000), and cerebral palsy (RR 62.62; 95%CI 3.93 to 996.45; P=0.001).

Conclusion The risk factors for poor initial response to valproic acid therapy in children with epilepsy are family history of epilepsy, abnormal EEG, focal seizures, and cerebral palsy. **[Paediatr Indones. 2025;65:286-91; DOI: https://doi.org/10.14238/pi65.4.2025.286-91**].

Keywords: *epilepsy; risk factors; initial response to valproic acid therapy*

Epilepsy is a disease in children with a high incidence in developing countries.[1] Treatment with antiepileptic drugs (AEDs) can effectively control seizures by 60-70%.[2] The initial response to valproic acid therapy is considered poor if seizures persist during the first three months of treatment. Several risk factors, including gender, age ≥3 years, family history of epilepsy, normal EEG, normal head circumference, cerebral palsy, generalized seizure type, and frequency of seizures before therapy, might influence the initial response to valproic acid therapy.[3]

A case-control study in 2009 showed that 51 children with epilepsy (35.3%) had poor initial response to valproic acid.[4] A prospective cohort study at Cipto Mangunkusumo Hospital between January and August 2017 showed a similar result: 92 pediatric subjects with epilepsy (22.8%) who received valproic acid therapy had poor initial responses in the first three months.[3] In a 2020 prospective cohort study in Yogyakarta, 39 children (35.9%) with epilepsy had poor initial response to valproic acid.[5] This study

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aimed to determine the risk factors for poor early response to valproic acid therapy in children with epilepsy.

Methods

This retrospective cohort study used consecutive sampling to include subjects who sought treatment at the Pediatric Polyclinic of Dr. Zainoel Abidin Hospital between 1 January and 31 December 2022. The inclusion criteria were pediatric patients between one and eighteen years, newly diagnosed with epilepsy, and had received valproic acid therapy for at least three months. We collected subjects' medical record data including gender, age, family history of epilepsy, frequency of seizures before therapy, cerebral palsy, head circumference, type of seizure, and EEG results. The exclusion criteria were incomplete medical records, non-compliance patient, or discontinuation of AEDs. Poor response was defined if seizures persist during the three months of valproic acid treatment. This study was approved by the Ethics Committee of Syiah Kuala Medical School or Dr. Zainoel Abidin Hospital, Banda Aceh. The collected data was entered into *SPSS® 18* software. The data were analyzed using bivariate analysis with Chi-square and Fisher's tests, as well as multivariate analysis using logistic regression. Results with P values <0.05 were considered to be statistically significant.

Results

In 2022, a total of 131 pediatric patients were diagnosed with epilepsy. Fifty-eight patients (64.4%) were male, 79 patients (87.8%) aged three years or older, and 45 patients (50%) had a family history of epilepsy, as shown in **Table 1**.

The EEGs in 46 patients' (51.1%) were normal, while 77 patients (85.6%) had normocephaly. Based on the seizure type, 46 children (51.1%) experienced generalized seizures. Fifty-two children (57.8%) had 10 times or more seizures before therapy, while 80 children (88.9%) had no cerebral palsy. In addition, 35 patients (38.9%) showed poor initial response to valproic acid therapy. These data are presented in **Table 1**.

Bivariate analysis results in **Table 2** show that subjects under 3-year-old at diagnosis epilepsy had a 2.48 times higher risk of poor initial response to valproic acid therapy (P=0.003). Patients with a family history of epilepsy had a 2.88 times higher risk of poor initial response to valproic acid therapy (P=0.001). Gender had no significant relationship with the initial response to valproic acid therapy.

Table 3 shows that an abnormal EEG had a 6.27 times higher risk of poor initial response to valproic acid therapy (P=0.0001). Microcephaly or macrocephaly had a 2.05 times risk of a poorer initial response to valproic acid therapy (P=0.034). The focal seizure type had a 3.02 times higher risk of poor initial response to valproic acid therapy in children with epilepsy (P=0.0001). Cerebral palsy had a 2.76 times increased risk of poor initial response to valproic acid therapy (P=0.001). Patients with seizures 10 times or more before therapy had a 7.79 times increased risk of poor initial response to valproic acid therapy (P=0.0001).

Table 1. Characteristics of subjects

Characteristics	(N=90)
Gender, n (%)	
Male	58 (64.4)
Female	32 (35.6)
Age, n (%)	
< 3 years	11 (12.2)
≥ 3 years	79 (87.8)
Family history of epilepsy, n (%)	
Yes	45 (50.0)
No	45 (50.0)
EEG findings, n (%)	
Abnormal	44 (48.9)
Normal	46 (51.1)
Head circumference, n (%)	
Microcephaly/macrocephaly	13 (14.4)
Normocephaly	77 (85.6)
Type of seizure, n (%)	
Focal	44 (48.9)
General	46 (51.1)
Cerebral palsy, n (%)	
Yes	10 (11.1)
No	80 (88.9)
Seizure frequency before therapy, n (%)	
≥10 times	52 (57.8)
<10 times	38 (42.2)
Response to therapy, n (%)	
Poor	35 (38.9)
Good	55 (61.1)

Multivariate analysis with logistic regression was used to determine risk factors for poor initial response to valproic acid therapy. The seven variables analyzed were age at diagnosis, family history of epilepsy, EEG, head circumference, seizure type, cerebral palsy, and seizure frequency before therapy. Risk factors that associated with poor initial response to valproic acid therapy included cerebral palsy, focal seizure type, family history of epilepsy, and abnormal EEG, as described in **Table 4**.

Discussion

In our study, 38.9% patients had poor initial response to valproic acid therapy. Sinaga *et al.*[3] demonstrated a 22.8% poor initial response in the first three months of valproic acid monotherapy. In idiopathic epilepsy, 70% of patients were reported to have had a rapid response to valproic acid monotherapy, 76% were seizure-free within three months, and the remainder experienced

Table 2. Bivariate analysis of general characteristics and initial response to valproic acid therapy

General characteristics	Initial response to valproic acid therapy		RR (95%CI)	P value
	Poor (n=35)	Good (n=55)		
Gender, n (%)			1.20 (0.68 to 2.12)	0.670
Male	24	34 (61.8)		
Female	11	21 (38.2)		
Age, n (%)			2.48 (1.63 to 3.78)	0.003*
<3 years	9	2 (3.6)		
≥3 years*	26	53 (96.4)		
Family history of epilepsy, n (%)			2.88 (1.53 to 5.45)	0.001
Yes	26	19 (34.5)		
No	9	36 (65.5)		

*Fisher's test

Table 3. Bivariate analysis of clinical characteristics and initial response to valproic acid therapy

Clinical characteristics	Initial response to valproic acid therapy		RR 95%CI	P value
	Poor (n=35)	Good (n=55)		
EEG findings, n(%)			6.27 (2.67 to 14.7)	0.0001
Abnormal	30 (68.2)	14 (31.8)		
Normal	5 (14.3)	41 (75)		
Head circumference, n(%)			2.05 (1.27 to 3.30)	0.034
Microcephaly/macrocephaly	9 (69.2)	4 (30.8)		
Normocephaly	26 (33.8)	51 (66.2)		
Type of seizure, n(%)			3.02 (1.60 to 5.70)	0.0001
Focal	26 (59.1)	18 (40.9)		
General	9 (19.6)	37 (80.4)		
Cerebral palsy, n(%)			2.76 (1.89 to 4.03)	0.001*
Yes	9 (90)	1 (10)		
No	26 (32.5)	54 (67.5)		
Seizure frequency before epilepsy, n(%)			7.79 (2.57 to 23.58)	0.0001
10 times	32 (61.5)	20 (38.5)		
<10 times	3 (7.9)	35 (92.1		

*Fisher's test

Table 5. Logistic regression analysis of risk factors for poor initial response to valproic acid therapy

Characteristics	RR (95%CI)	P value
Cerebral palsy	62.62 (3.93 to 996.45)	0.003
Focal seizure	7.10 (1.15 to 43.80)	0.035
Family history of epilepsy	6.58 (1.67 to 25.95)	0.007
Abnormal EEG image	5.27 (1.16 to 23.87)	0.031

a relapse.[6] In contrast, a study found that almost 50% of epileptic children continued to have seizures with first-line antiepileptics after one year of treatment.[7]

Bivariate analysis revealed that subjects under 3 years old had a 2.48 times higher risk of poor initial response to valproic acid therapy. Children less than three years old are susceptible to epilepsy because their central nervous system has not developed optimally.[19] This result differed from a case-control study of 165 subjects in Egypt and demonstrated that those under two years old had a 0.96 times poorer response to valproic acid.[20]

Bivariate analysis also revealed that microcephaly or macrocephaly had a 2.05 times higher risk of poor initial response to valproic acid therapy than normocephaly. Similarly, a previous study showed that microcephaly had a 2.77 times higher risk of responding poorly to initial valproic acid therapy.4 In microcephaly, the number of gyri is reduced and separated by flat sulci, thus, microcephaly patients are susceptible to developing epilepsy.[4]

Frequency of seizure ≥10 times before therapy had 7.79 times higher risk of poor initial response to valproic acid therapy. Similarly, a study also reported a relationship between the low number of seizures before treatment and a positive response to antiepileptics.[14] Epilepsy patients who are seizure-free in the first three months were more likely to be in remission after two years.[3] However, Xia et al. reported that epilepsy patients who had less than ten seizures before treatment were 2.7 times more likely to have a poor response to valproic acid therapy. Exposure to uncontrolled seizures can cause brain damage and expand the focus of epileptogenesis.[1] Similarly, a study revealed that less than ten seizures had 9.2 times risk of poor response to valproic acid therapy.[3] Moreover, another study revealed that patients with frequency of seizure <10 times before therapy were 4.7 times more likely to have a poor response to valproic acid therapy.[16]

Multivariate analysis showed that cerebral palsy was associated with a 62.6 times higher risk for poor initial response to valproic acid therapy (P=0.003). This result agreed with a case-control study from 2015 to 2020 in 106 subjects; in which cerebral palsy increased the risk of poor initial response to valproic acid by 43 times. Genetic and perinatal factors increased the risk of epilepsy in children with cerebral palsy. Among perinatal factors, brain abnormalities, chromosomal defects, intrauterine infections, and neonatal hypoxic-ischemic encephalopathy (HIE) were the most apparent causes that can lead to seizures.[15] A previous study demonstrated that epileptic patients with cerebral palsy had a 2.5 times increased risk of drug resistance to valproic acid.[17] Moreover, two studies showed that patients with cerebral palsy had a higher risk of suffering from epilepsy.[18,19]

Multivariate analysis also showed that focal seizure type had 7.10 times greater risk of poor response to valproic acid therapy (P=0.035). A previous study reported similarly that patients with focal seizures had a 3.43 times poor response to valproic acid therapy.[15] Focal seizure is one of the most important predictive factors for worse outcomes of epilepsy in children. A strong association between intractable epilepsy and focal seizures was correlated with focal structural brain lesions.[14] A 2018 prospective cohort study in Kuala Lumpur involving 122 subjects showed that focal seizures had a 19.9 times poorer response to valproic acid.[20] In contrast, another study discovered that generalized seizures had a 4.8 times poorer risk compared to focal seizures.[3]

Family history of epilepsy had 6.58 times increased risk of poor initial response to valproic acid therapy (P=0.007). Our finding was in agreement with a study which showed that having a family history of epilepsy contributed to a 13.5 times higher risk of having a poor response to valproic acid therapy.[4] In 2004, a case-control study in Iran on 142 subjects revealed a similar result that children from families with epilepsy had a 3.33 times poorer risk for valproic acid therapy.[24] Hereditary factors have a significant effect on epilepsy. Epilepsy that occurs during childhood is a risk factor for siblings to develop epilepsy, including children who are born. This condition is caused by mutations in SLC2A1, which encodes the glucose transporter GLUT1.[10,25]

Abnormal EEG results in this study had a 5.27 times risk of poorer initial response to valproic acid therapy. Three other studies also reported greater risks of poor initial response to valproic acid with 6.7, 3.5, 1.25, and 6.3 times the risks.[3,5,9,17]

The limitation of this study was the retrospective study that used medical records. Some data in the medical records necessary for this research are

incomplete.

In conclusion, the most significant risk factors for poor initial response to valproic acid therapy in children with epilepsy are cerebral palsy, focal seizures, family history of epilepsy, and abnormal EEG findings.

Conflict of interest

None to declare.

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