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Risk factor for hepatotoxicity in epileptic children with long-term AEDs treatment: A comprehensive analysis

Christina Silalahi[1], Sunny Mariana Samosir[1,2], Rendi Aji Prihaningtyas[1,2], Prastiya Indra Gunawan[1,2], Bagus Setyoboedi[1,2]

[1]Department of Child Health, Faculty of Medicine Universitas Airlangga, Surabaya, East Java, Indonesia
[2]Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, East Java, Indonesia

ABSTRACT

Background and objectives. The use of antiepileptic drugs (AEDs) is often required for extended periods in pediatric patients. However, there is a risk of hepatotoxicity associated with AED use. This study aimed to identify the risk factors that contribute to liver injury in pediatric patients with epilepsy who are treated with AEDs.

Materials and methods. This case-control study was conducted at the Pediatric Neurology outpatient clinic of Dr. Soetomo General Hospital in Surabaya, Indonesia, from May to July 2023. Demographic characteristics, epilepsy types, and medications were recorded for 66 children aged 1–18 years who had received AEDs, either as monotherapy or polytherapy, along with liver function tests. Epileptic children with hepatotoxicity were designated as the case group, while those without hepatotoxicity comprised the control group. Collected data were presented descriptively and analyzed using logistic regression, with statistical significance set at $p < 0.05$ for the two-tailed test.

Results. Hepatotoxicity occurred in 31 out of 66 (46.9%) patients. Bivariate analysis revealed that treatment duration ($p = 0.014$) and phenytoin use ($p = 0.002$) significantly affected the occurrence of hepatotoxicity in epileptic children. Logistic regression analysis showed that AED treatment durations of >5 years but less than 10 years (OR = 14.00; 95% CI 1.385–141.48; $p = 0.025$), phenytoin use (OR = 9.654; 95% CI 2.785–33.465; $p < 0.001$), and phenobarbital use (OR = 6.573; 95% CI 1.579–27.360; $p = 0.01$) were significantly correlated with hepatotoxicity. Meanwhile, age, nutritional status, epilepsy type and syndrome, and the incidence of intractable epilepsy were not significant risk factors for the occurrence of hepatotoxicity in children.

Conclusions. The duration of AED treatment and the type of AED used are significant risk factors for hepatotoxicity in pediatric epilepsy. Regular monitoring of hepatic enzyme levels is strongly recommended during prolonged AED therapy to mitigate the risk of liver injury.

Keywords: hepatotoxicity, antiepileptic drugs, epilepsy, children

Abbreviations (in alphabetical order):

AED – antiepileptic drug
ALP – alkaline phosphatase
ALT – alanine transaminase
GGT – gamma-glutamyl transferase

INTRODUCTION

The number of epilepsy cases in children is expected to rise continuously due to increasing life expectancy worldwide. Globally, it is estimated that approximately 10.5 million children under 15 years of age suffer from active epilepsy, representing about 25% of the world's epilepsy population [1]. In Indonesia, the number of epilepsy cases ranges from 700,000 to 1,400,000, with an increase of 70,000 new cases every year. It is estimated that around 40-50% of these cases occur in children [2].

Hepatotoxicity is a common side effect among conventional antiepileptic drugs (AEDs), with reactions ranging from mild, transient changes in hepatic

Corresponding author:
Bagus Setyoboedi
E-mail: bagus.setyoboedi@fk.unair.ac.id

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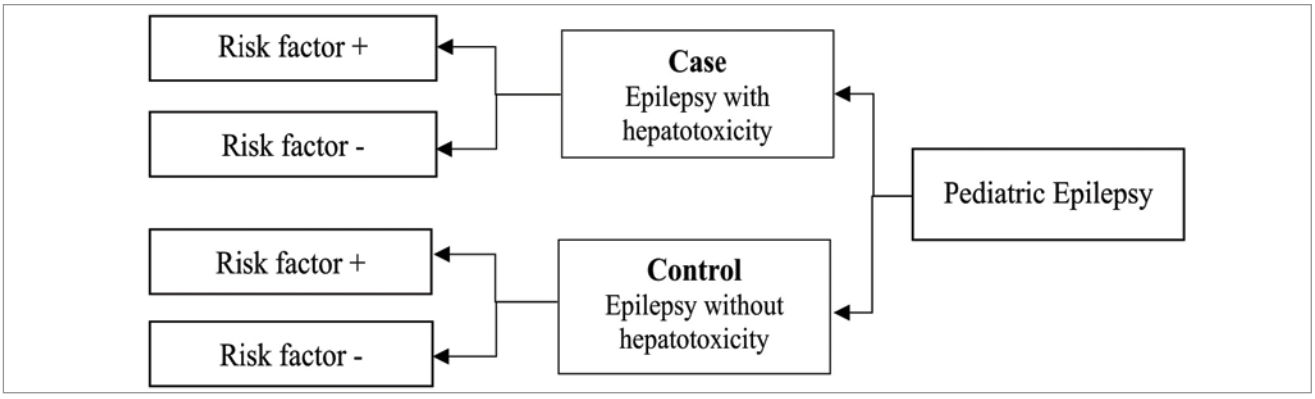

FIGURE 1. Result of collected research data

enzymes to severe liver failure [3]. The prevalence of hepatotoxicity associated with AED use was found to be around 2-4% in Europe. Although paracetamol intoxication is the most common cause of hepatotoxicity leading to liver transplantation, antiepileptic drugs are the third most common cause of liver toxicity in 15% of cases [4].

There are few studies regarding the risk factors that affect the occurrence of hepatotoxicity in children with epilepsy in Indonesia, including at our hospital. Identifying risk factors for liver disorders is necessary during long-term treatment to prevent acute liver toxicity and improve outcomes in children with epilepsy. In this study, we aimed to determine the risk factors for hepatotoxicity in pediatric patients with epilepsy at Dr. Soetomo General Academic Hospital in Surabaya, the largest tertiary hospital in eastern Indonesia. By utilizing data from Indonesia, researchers can establish benchmarks for early identification of hepatotoxicity and contribute to the development of future intervention strategies.

MATERIALS AND METHODS

Study design

This research was a case-control study designed to determine the risk factors for hepatotoxicity in children with epilepsy. The study identified 66 pediatric epilepsy patients with hepatotoxicity (cases) and without hepatotoxicity (controls) (Figure 1). The data were collected retrospectively on risk factors in the two groups. Data were obtained from patient files and electronic medical records maintained at the Pediatric Neurology Outpatient Clinic, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, from May to July 2023.

Population and sample

The study population included all children with epilepsy receiving treatment at the Pediatric Neurology Outpatient Clinic, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. Eligibility criteria included pediatric patients (1-18 years of age) who had received AED treatment (either monotherapy or polytherapy) for a minimum of six months at the Pediatric Neurology Outpatient Clinic, Dr. Soetomo General Academic Hospital, with written consent from the parents or guardians of the patient after they were informed about the study. Patients with a history of liver disorders before receiving AED treatment or who had experienced seizures defined as status epilepticus within the last three months were excluded from the study. Consecutive sampling was used to select study participants who met the inclusion and exclusion criteria.

Research variables

Risk factor data for hepatotoxicity were collected from patients, including age, gender, nutritional status, epilepsy type and syndrome, incidence of intractable epilepsy, AED type, duration of AED treatment, and information on other relevant disorders. Epilepsy types, epilepsy syndromes, and intractable epilepsy were diagnosed by a pediatric neurologist through clinical findings, neurological examinations, and electroencephalogram (EEG) analysis. Liver enzymes were used as markers of hepatocellular injury (alanine aminotransferase [ALT]) or obstruction in bile flow (cholestasis) (alkaline phosphatase [ALP] and gamma-glutamyl transferase [GGT]).

According to the Council for International Organizations of Medical Sciences (CIOMS, 2020), hepatotoxicity was classified as follows: an increase in ALT levels to ≥3 times the upper limit of normal (ULN) and total bilirubin levels to ≥2 times the ULN; an increase in ALT levels to ≥5 times the ULN; and an increase in ALP levels to ≥2 times the ULN, particularly when associated with elevations in GGT. The reference ranges for the liver enzymes were as follows: ALT, 5-45 U/L; GGT, 7-12 U/L; and ALP, 100-320 U/L. Data were entered into a data collection sheet for statistical analysis.

Data instrument and analysis

The collected data were analyzed using SPSS version 24 statistical software. Descriptive statistics were reported as frequency distributions and percentages

for each characteristic variable. To analyze qualitative data, the Chi-square test and Fisher's exact test were employed. Multivariate analysis techniques were used to assess factors strongly associated with hepatotoxicity. A logistic regression model with the backward method was applied to identify potential risk factors for liver disorders. Variables with a p-value <0.25 in bivariate analysis were included in the logistic regression analysis. A p-value <0.05 was considered significant, indicating that the independent variable is an independent predictive factor for the dependent variable. The Odds Ratio (OR) expresses the magnitude of the influence (strength of relationship) of the independent variable on the dependent variable.

Research ethics

The ethical approval for the research was granted by the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital Surabaya, No. 0652/KEPK/IV/2023. The confidentiality of research subjects was maintained by not mentioning their names but referring to them by initials. The data collected were used solely for research purposes.

RESULTS

A total of 70 pediatric patients diagnosed with epilepsy and treated with AEDs for at least six months were included in the study. Four patients were excluded because they refused to undergo blood tests, leaving 66 patients who met the inclusion criteria. Of these, 31 patients experienced hepatotoxicity, and 35 patients did not. The study population consisted of more male subjects (57.6%) than female subjects. Most children had normal nutritional status (40.9%), and the mean age of children diagnosed with epilepsy was 4 years and 5 months (Table 1). Seizures most commonly began in children under 1 year of age (47%).

The most common type of seizure was generalized tonic-clonic seizures (59.1%), with a seizure frequency of 1-5 times per 6 months (37.9%). Temporal lobe epilepsy was the most common type associated with hepatotoxicity (62.5%). Epilepsy related to post-infection (53.3%) predominated in the non-hepatotoxicity group, followed by frontotemporal lobe epilepsy (75%). Over half of the study subjects were on more than two types of AEDs (77.3%), and most had good medication compliance (78.8%).

Treatment duration (P=0.014) was found to be a significant risk factor for hepatotoxicity in children (Table 2). For AED types, separate analysis was conducted for each drug, as the majority of subjects used more than two types of AEDs. The bivariate analysis showed that phenytoin was a significant risk factor for hepatotoxicity in epileptic children (P=0.002) (Table 3).

A logistic regression analysis was performed on AED types and treatment duration (P<0.25). The analysis showed that treatment duration of >5 years-10 years (P=0.025, OR 14.00 [95% CI 1.385-141.48]) was a significant risk factor for hepatotoxicity in epileptic children (Table 4). This indicates that the risk of hepatotoxicity increases 14-fold in patients treated for >5 years-10 years compared to those receiving treatment for under a year. The backward method was also used to analyze AED types and their effect on hepatotoxicity. Phenytoin (p<0.001, OR 9.654 [95% CI 2.785−33.465]) and phenobarbital (P=0.010, OR 6.573 [95% CI 1.579−27.360]) were significant risk factors for hepatotoxicity in epileptic children (Table 5).

Liver function tests were conducted for epileptic children with and without hepatotoxicity. The data were analyzed using the Kolmogorov-Smirnov or Shapiro-Wilk test, resulting in a P value of less than 0.05, indicating the data did not follow a normal distribution. Only the median GGT level showed a significant difference (P<0.001) between patients with hepatotoxicity (89 [31.5-1567.2]) and those without hepatotoxicity (20.1 [4.0-46.0]) (Table 6).

TABLE 1. Demographic of patients

Parameter	n (66)	%
Mean age (month)	4 years, 5 months	
Sex		
Male	38	57.6
Female	28	42.4
Nutritional status		
Normal	27	40.9
Undernourished	22	33.3
Overweight/Obese	17	25.8
First seizure onset		
<1 year	31	47.0
1-5 years	26	39.4
6-10 years	8	12.1
11-18 years	1	1.5
Seizure type		
General tonic-clonic	39	59.1
Focal	20	30.3
Absence	7	10.6
Seizure frequency		
Everyday	9	13.6
>5 times/6 month	19	28.8
1-5 times/6 month	25	37.9
Seizure-free < 2 years	8	12.1
Seizure-free ≥ 2 years	5	7.6
Number of AED		
1 type	15	22.7
≥ 2 types	51	77.3
Treatment compliance		
Regular	52	78.8
Irregular	14	21.2

DISCUSSION

We carried out the present study to assess the incidence and the associated factors for hepatotoxicity in epileptic children receiving antiepileptic drugs. A total of 31 (46.9%) of the 66 children experienced hepatotoxicity. This study aligns with the findings of Hussein et al., who observed abnormal liver enzyme

TABLE 2. Bivariate analysis of risk factors for hepatotoxicity in children

Variable	Hepatotoxicity n (%)		*P*
	Yes	No	
Age when diagnosed			
<1 year	3 (42.9)	4 (57.1)	0.780
1-5 years	18 (47.4)	20 (52.6)	
6-10 years	5 (38.5)	8 (61.5)	
11-15 years	5 (62.5)	3 (37.5)	
Nutritional status			
Normal	14 (51.9)	13 (48.1)	0.530
Undernourished	11 (50.0)	11 (50.0)	
Overweight/Obese	6 (35.3)	11 (64.7)	
Epilepsy types and syndromes			
Frontal lobe epilepsy	0 (0.0)	1 (100.0)	0.824
Temporal lobe epilepsy	10 (62.5)	6 (37.5)	
Occipital lobe epilepsy	2 (66.7)	1 (33.3)	
Frontotemporal lobe epilepsy	2 (25.0)	6 (75.0)	
West syndrome	0 (0.0)	2 (100.0)	
Lennox-Gastaut syndrome	1 (50.0)	1 (50.0)	
Rolandic type epilepsy	1 (25.0)	3 (75.0)	
Rasmussen's encephalitis	2 (66.7)	1 (33.3)	
Hippocampal mesial	1 (50.0)	1 (50.0)	
Idiopathic generalized epilepsy	4 (57.1)	3 (42.9)	
Childhood absence epilepsy	1 (33.3)	2 (66.7)	
Other	7 (46.7)	8 (53.3)	
Intractable epilepsy			
Yes	6 (50.0)	6 (50.0)	1.0
No	25 (46.3)	29 (53.7)	

*Pearson Chi-Square test; Fisher's Exact Test, *p value <0.05: statistically significant*

TABLE 3. Bivariate analysis of risk factors for hepatotoxicity in children

Variable	Hepatotoxicity n (%)		*P*
	Yes	Tidak	
AED type			
Valproic acid	19 (40.4)	28 (59.6)	0.161
Carbamazepine	8 (61.5)	5 (38.5)	0.387
Clobazam	4 (40.0)	6 (60.0)	0.739
Clonazepam	0 (0.0)	1 (100.0)	1.0
Diazepam	4 (44.4)	5 (55.6)	1.0
Lamotrigine	0 (0.0)	1 (100.0)	1.0
Levetiracetam	7 (58.3)	5 (41.7)	0.581
Phenytoin	20 (71.4)	8 (28.6)	0.002*
Phenobarbital	11 (68.8)	5 (31.3)	0.086
Topiramate	1 (16.7)	5 (83.3)	0.202
AED treatment duration			
6-12 months	6 (33.3)	12 (66.7)	0.014*
13 months-5 years	16 (42.1)	22 (57.9)	
>5 months-10 years	7 (87.5)	1 (12.5)	
>10-15 years	2 (100.0)	0 (0.0)	
Number of AED			
1 type	4 (26.7)	11 (73.3)	0.134
≥ 2 types	27 (52.9)	24 (47.1)	

*Pearson Chi-Square test; Fisher's Exact Test, *p value <0.05: statistically significant*

levels in 51.9% of their study subjects. These subjects were categorized into three groups based on the type of antiepileptic drug (AED) used: carbamazepine, sodium valproate, and phenytoin [3]. Differences in reported incidence rates may result from several factors, including the application of slightly different

TABLE 4. Analysis of AED treatment duration on hepatotoxicity incidence

Variable	*P* value	OR	95% CI	
			Min	Max
13 months-5 years	0.531	1.455	0.450	4.699
>5 years-10 years	0.025*	14.000	1.385	141.480
>10-15 years	0.999	-		

*Logistic regression test; *p value <0.05: statistically significant*

TABLE 5. Analysis of AED type on hepatotoxicity incidence

Variable	*P* value	OR	95% CI	
			Min	Max
Phenytoin	<0.001*	9.654	2.785	33.465
Phenobarbital	0.010*	6.573	1.579	27.360

*Logistic regression test; *p value <0.05: statistically significant*

TABLE 6. Analysis of liver function tests in the study subject

Parameter		Hepatotoxicity		*P*
		Yes	No	
ALT	Median	22	17	0,014*
	Min-Max	7.0-160.0	1.0-39.0	
GGT	Median	89	20,1	<0,001*
	Min-Max	31.5-1567.2	4.0-46.0	
ALP	Median	185	151	0,154
	Min-Max	61.0-728.0	56.0-326.0	

criteria for identifying hepatotoxicity, disparities in study populations, age at diagnosis, and the type of antiepileptic drugs utilized in healthcare settings. However, this requires further study to accurately determine the cause of liver injury by assessing the level of AED toxicity in blood serum.

In this study, it was observed that among children with epilepsy and hepatotoxicity, 26.7% were using a single type of antiepileptic drug (AED), while 52.9% were using more than two types of AEDs. Additionally, the majority of these patients (78.8%) demonstrated good medication adherence. The number of AEDs did not significantly increase the risk of hepatotoxicity in children with epilepsy (P>0.05). These findings contrast with previous research, which noted a higher incidence of hepatotoxicity among critically ill children: 55.6% of those taking phenobarbitone, 75% of those on phenytoin monotherapy, 70% of those on phenytoin/phenobarbitone, and other combinations of AEDs. This previous research reported hepatotoxicity either as a hepatocellular injury or liver biochemical test abnormalities. A comparable number of subjects administered with each of the previously described AEDs also demonstrated increased GGT levels [5].

In this study, the majority of people with epilepsy were 1-5 years old (47.4%). The proportion of epilepsy cases in a previous study at Dr. Soetomo General Academic Hospital from January to December 2013 reported that most patients were in the age range of 1-5 years (45.63%) [6,7]. However, Suwarba et al. stated that pediatric epilepsy incidence was found to be similar at the 1-5 years age group (42%) and in the younger age

group (<1 year) with 46% of patients [2]. The age at diagnosis was not a risk factor for hepatotoxicity.

One of the risk factors for drug interactions that induce liver damage is age. This study's results contradict Yuan's (2013) previous research, which showed an increase in AED-related liver damage risk in children under 24 months [8]. A similar study found that younger age is a major risk factor for valproate-induced severe hepatotoxicity, especially in children under 2 years of age undergoing polytherapy [9,10]. A population-based study in the United States found that AED was the fourth most common cause of drug-induced acute necrotic liver injury, which led to liver transplantation. As age increases, liver damage incidence arises. People over 40 years old are more vulnerable to liver injury due to concurrent changes in medication, drug excretion, and intake. In addition, older people tend to experience more cholestatic-type damage, and younger populations (aged ≥10 years) tend to experience hepatocellular-type damage [11, 12]. Nevertheless, this study did not collect sample data from patients under the age of one, thereby preventing the examination of risk factors in this specific age group.

In this study, most subjects had normal nutritional status in both the hepatotoxicity (51.9%) and non-hepatotoxicity (48.1%) groups. However, it was found overweight/obese nutritional status was more prevalent in the non-hepatotoxicity group (64.7%). Further bivariate analysis revealed that nutritional status was not a risk factor for hepatotoxicity in epileptic children. Malnutrition is very common in patients with liver disease and has a linear correlation with the severity of liver disease. Malnutrition negatively impacts the liver, leading to an inability of the liver to release and store nutrients (water-soluble vitamins) properly. Therefore, loss of nutrient storage capacity in the liver could exacerbate micronutrient deficiencies due to low and unbalanced food intake. Malabsorption and impaired nutrient synthesis might occur, reducing the patient's energy requirement [13,14].

Pharmacokinetic interactions between AEDs lead to changes in absorption, metabolism, protein binding, and excretion processes. The study identified phenytoin (71.4%), valproic acid (40.4%), and phenobarbital (68.8%) as the most common antiepileptic drugs used in the hepatotoxicity group. A multivariate analysis showed that phenytoin (P<0.001, OR 9.654, 95% CI 2.785–33.465) and phenobarbital (P=0.010, OR 6.573, 95% CI 1.579–27.360) were both major risk factors for hepatotoxicity. A study conducted by Vidaurre (2017) revealed that hepatotoxicity is more commonly associated with phenytoin, valproic acid, and felbamate, whereas the latest generation of antiepileptic drugs (AEDs) is less likely to cause hepatotoxicity [15].

Phenytoin is known as an enzyme inducer, causing asymptomatic GGT elevation. Liver microsomal enzymes may also elevate ALP, although it remains lower than GGT. Approximately 25% of patients experience temporary and asymptomatic increases in ALT. The risk of hepatotoxicity due to phenytoin is similar in both genders. Most patients experience symptoms of phenytoin-induced hepatotoxicity two to eight weeks after the start of treatment, followed by hypersensitivity reactions such as fever (75% of cases), rash (62%), eosinophilia (89%), facial edema, and lymphadenopathy [16].

Most patients in the hepatotoxicity group received AED for 13 months to 5 years (42.1%) followed by AED use for more than 5 years (87.5%). In contrast, in the non-hepatotoxicity group, most patients received AED for 6 months to 12 months (66.7%). Bivariate and multivariate analysis revealed that AED treatment duration was a significant risk factor for the occurrence of hepatotoxicity in epileptic children, where AED treatment of >5 years-10 years was found to have a significant influence on hepatotoxicity occurrence (P=0.025). Using AED for >5-10 years led to a 14-fold risk of hepatotoxicity compared to using AED for 6-12 months in this study.

Haque et al. reported similar findings, showing that different types of AEDs and the duration of treatment resulted in various patterns of liver damage. Their research indicated that using valproic acid for one to six months led to hepatocellular or mixed damage, elevated ammonia levels, and occasional acidosis. Conversely, treatment with phenytoin and carbamazepine for zero to three months resulted in hepatocellular, cholestatic, or mixed damage along with immuno-allergic reactions [17,18]. Another study noted a significant increase in average liver enzyme levels at 3-, 6-, and 12-months following phenobarbital administration [19].

In this study, intractable epilepsy was only found in 12 patients (18.2%). The proportion of intractable epilepsy was found to be similar in both groups, hence intractable epilepsy incidence was not a risk factor for hepatotoxicity in children (P>0.05). In a population-based study conducted in Western Europe, approximately 22.5% of epilepsy patients had refractory or drug-resistant epilepsy. Only about 2/3 of epilepsy could be controlled with AEDs, leaving 1/3 uncontrolled, which resulted in high morbidity and mortality [20, 21]. In the management of intractable epilepsy, the burden of drug side effects such as hepatotoxicity is an important issue that has received little attention. Complex drug interactions might increase the risk of side effects and affect drug efficacy, especially drugs that are metabolized in the liver via the cytochrome P450 system [22].

Our enzyme analysis revealed a significant difference in GGT levels between the groups (P<0.001). This finding aligns with the observed patterns of liver injury in our study, where cholestatic injury was predominant (80.6%), followed by mixed (12.9%) and hepatocellular (6.5%) patterns. However, the lack of serum AED level data prevented definitive attribution of liver injury to specific AED agents. Notably,

liver dysfunction can vary depending on the type of AED used. As in the case of hepatotoxicity due to carbamazepine, very high GGT and ALP values are often found, giving rise to suspicion of the rare condition of ductopenia, which is characterized by loss of small bile ducts and the risk of jaundice and impaired liver function. In addition, carbamazepine produces a variety of liver pathologies that vary across individuals. Carbamazepine also affects the central nervous system and liver side effects may occur due to carbamazepine overdose [4]. GGT itself is a sensitive marker for detecting various types of hepatocellular and hepatobiliary disorders. Serum GGT level might increase early and remain high if cell damage continues to progress [23].

This is different from the ALP level which has no diagnostic value in the incidence of hepatotoxicity in children. There are changes of ALP activity in the human body during various phases of life and development because it is a marker of osteoblast activity, hence the ALP level will increase during the childhood and adolescence of the bone mineralization process and turnover is higher. ALP plays an important role in DNA synthesis and resolving inflammation, and is also a useful serum biochemical marker for liver diseases, especially cholestatic disease. Total ALP levels in serum reach their highest point in the first six months of life, then gradually decrease until reaching a relatively stable level. Levels increase again after 9 years of age, with a peak at puberty, although this peak is not as high as that observed in infancy [24]. Therefore, ALP level in this study did not have a significant value in the occurrence of hepatotoxicity in children.

Limitations

This study utilized a minimal sample size, resulting in a less powerful analysis and an inability to accurately describe the actual incidence of hepatotoxicity. The study was unable to establish a definite causal correlation between the incidence of hepatotoxicity and the use of each AED due to the absence of preliminary data on the status of liver enzymes prior to drug administration. One of the weaknesses of case-control studies is the difficulty in confirming the history of different risk factors in each group of cases and controls, which can be attributed to memory bias and subjective confusion. Furthermore, the therapeutic range and level of drug toxicity in each patient remain uncertain due to the lack of measurements of antiepileptic drug levels in blood serum.

CONCLUSION

In summary, a retrospective case-control study of pediatric patients with epilepsy conducted at Dr. Soetomo General Academic Hospital Surabaya found that hepatotoxicity exhibits a significant prevalence of 46.9% among children with epilepsy. Notably, conventional demographic characteristics including age at diagnosis and patient gender were not found to be risk factors for hepatotoxicity in pediatric patients with epilepsy. In addition, factors such as nutritional status, epilepsy type and syndrome, and intractable epilepsy incidence were excluded as potential contributors to the probability of hepatotoxicity. Nevertheless, the use of phenytoin and phenobarbital increases the risk of hepatotoxicity by 9.6 and 6.5 times respectively compared to epileptic children who do not take these drugs. AED treatment duration of 6-10 years is also a risk factor for hepatotoxicity in epileptic children compared to AED treatment for less than a year. This outcome underscores the importance of including routine liver function panel assessments every 3 months during AED therapy in the risk stratification of hepatotoxicity in pediatric patients with epilepsy. Further randomized controlled trials with larger sample sizes are needed to confirm the association between the specific duration of antiepileptic therapy and the occurrence of hepatotoxicity in epileptic children.

Authors' contributions:

Christina Silalahi, Sunny Mariana Samosir, Rendi Aji Prihaningtyas, Prastiya Indra Gunawan, Bagus Setyoboedi Conceptualization – Christina Silalahi and Bagus Setyoboedi; methodology – Bagus Setyoboedi and Prastiya Indra Gunawan; software – Christina Silalahi; validation – Bagus Setyoboedi and Prastiya Indra Gunawan; formal analysis – Christina Silalahi, Sunny Mariana Samosir, Rendi Aji Prihaningtyas and Prastiya Indra Gunawan; investigation – Christina Silalahi, Sunny Mariana Samosir and Rendi Aji Prihaningtyas; resources – Christina Silalahi; data curation –Christina Silalahi and Bagus Setyoboedi; writing-original draft preparation – Christina Silalahi; writing-review and editing – Bagus Setyoboedi and Prastiya Indra Gunawan; visualization – Christina Silalahi; supervision – Christina Silalahi.

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REFERENCES

1. Gadze ZP. Childhood age epilepsy and family. In: Epilepsy in children - clinical and social aspects. Croatia: InTech; 2011. p. 147–55.
2. Suwarba IGNM. Insidens dan karakteristik klinis epilepsi pada anak. *Sari Pediatri.* 2011;13(2):123–8. Available from: https://www.saripediatri.org/index.php/sari-pediatri/article/view/468/406.
3. Hussein RRS, Soliman RH, Abdelhaleem Ali AM, Tawfeik MH, Abdelrahim MEA. Effect of antiepileptic drugs on liver enzymes. *Beni Suef Univ J Basic Appl Sci.* 2013;2(1):14–9. doi: 10.1016/j.bjbas.2013.09.002.
4. Björnsson E. Hepatotoxicity associated with antiepileptic drugs. *Acta Neurol Scand.* 2008;118(5):281–90. doi: 10.1111/j.1600-0404.2008.01009x.
5. Sridharan K, Daylami AA, Ajjawi R, Ajooz HAM. Drug-induced liver injury in critically ill children taking antiepileptic drugs: A retrospective study. *Curr Ther Res.* 2020;92:100580. doi: 10.1016/j.curtheres.2020.100580.
6. Andrianti PT, Gunawan PI, Hoesin F. Profil epilepsi anak dan keberhasilan pengobatannya di RSUD Dr. Soetomo tahun 2013. *Sari Pediatri.* 2016;18(1):34–9. Available from: https://saripediatri.org/index.php/sari-pediatri/article/view/9/22.
7. Gunawan PI, Noviandi R, Samosir SM. First unprovoked seizure in Indonesian Children. *J Med Chem Sci.* 2023;6:1909–14. doi: 10.26655/JMCHEMSCI.2023.8.19.
8. Yuan L, Kaplowitz N. Mechanisms of drug-induced liver injury. *Clin Liver Dis.* 2013;17(4):507–18. doi: 10.1016/j.cld.2013.07.002.
9. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. *Lancet Neurol.* 2012;11(9):792–802. doi: 10.1016/S1474-4422(12)70153-9.
10. Raspall-Chaure M, Neville BG, Scott RC. The medical management of the epilepsies in children: Conceptual and practical considerations. *Lancet Neurol.* 2008;7(1):57–69. doi: 10.1016/S1474-4422(07)70324-1.
11. Shehu AI, Ma X, Venkataramanan R. Mechanisms of Drug-Induced Hepatotoxicity. *Clin Liver Dis.* 2017;21(1):35–54. doi: 10.1016/j.cld.2016 08.002.
12. Andrade RJ, Aithal GP, Björnsson ES, Kaplowitz N, Kullak-Ublick GA, Larrey D, et al. EASL Clinical Practice Guidelines: Drug-induced liver injury. *J Hepatol.* 2019;70(6):1222–61. doi: 10.1016/j.jhep.2019.02.014.
13. Chapman B, Sinclair M, Gow PJ, Testro AG. Malnutrition in cirrhosis: More food for thought. *World J Hepatol.* 2020;12(11):883–96. doi: 10.4254/wjh.v12.i11.883.
14. Saunders J, Brian A, Wright M, Stroud M. Malnutrition and nutrition support in patients with liver disease. *Frontline Gastroenterol.* 2010;1(2):105–11. doi: 10.1136/fg.2009.000414.
15. Vidaurre J, Gedela S, Yarosz S. Antiepileptic drugs and liver disease. *Pediatr Neurol.* 2017;77:23–36. doi: 10.1016/j.pediatrneurol.2017.09.013.
16. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK547852/.
17. Haque T, Sasatomi E, Hayashi PH. Drug-induced liver injury: pattern recognition and future directions. *Gut Liver.* 2016;10(1):27–36. doi: 10.5009/gnl15114.
18. Gunawan PI, Rochmah N, Faizi M. Comparison of 25-hydroxy vitamin D serum levels among children with epilepsy in therapy with single versus multiple antiseizure medications. *Epilepsy Behav Reports.* 2023;24:1–4. doi: 10.1016/j.ebr.2023.100620.
19. Mujgan Sonmez F, Demir E, Orem A, Yildirmis S, Orhan F, Aslan A, et al. Effect of antiepileptic drugs on plasma lipids, lipoprotein (a), and liver enzymes. *J Child Neurol.* 2006;21(1):70–4. doi: 10.1177/08830738060210011301.
20. Laxer KD, Trinka E, Hirsch LJ, Cendes F, Lang J, Delanty N, et al. The consequences of refractory epilepsy and its treatment. *Epilepsy Behavior.* 2014;37:59–70. doi: 10.1016/j.yebeh.2014.05.031.
21. Nugroho RA, Gunawan PI, Utomo B. Risk factors for drug-resistant epilepsy (DRE) in children and a model to predict development of DRE. *Rom J Neurol Rev Rom Neurol.* 2023;22:5–10. doi: 10.37897/RJN.2023.1.1.
22. Marvanova M. Pharmacokinetic characteristics of antiepileptic drugs (AEDs). *Mental Health Clinician.* 2016;6(1):8–20. doi: 10.9740/mhc.2015.01.008.
23. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci.* 2001;38(4):263–355. doi: 10.1080/20014091084227.
24. Cannalire G, Pilloni S, Esposito S, Biasucci G, Di Franco A, Street ME. Alkaline phosphatase in clinical practice in childhood: Focus on rickets. *Front Endocrinol* (Lausanne). 2023;14(February):1–7. doi: 10.3389/fendo.2023.1111445.