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Risk factors for hepatotoxicity in children with epilepsy

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ABSTRACT

Background and objectives. The use of antiepileptic drug (AED) is often required for a long period in pediatric patients. However, there is a risk of hepatotoxicity due to its use. This study aimed to identify the risk factors that affect liver disorder occurrence in pediatric patients with epilepsy who received AED.

Materials and methods. This case control study was conducted at the Pediatric Neurology outpatient clinic of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia between May and July 2023. Children with epilepsy aged 1-18 years who had received AED (monotherapy or polytherapy) for at least six months had their blood drawn to measure alanine transaminase, gamma-glutamyl transferase, and alkaline phosphatase levels. Risk factors were obtained through history and clinical examination. Risk factor analysis was conducted using bivariate and multivariate analysis.

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

Conclusions. Treatment period and phenytoin and phenobarbital use are risk factors for hepatotoxicity in epileptic children.

Keywords: Hepatotoxicity, antiepileptic drugs, epilepsy, children

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Abbreviations:

AED – antiepileptic drug

ALP – alkaline phosphatase

ALT – alanine transaminase

AST – aspartate transaminase

GGT – gamma-glutamyl transferase

INTRODUCTION

The number of epilepsy patients in children is expected arise continuously due to increasing life expectancy throughout the world. Globally, it is estimated that approximately 10.5 million children under 15 years of age suffer from active epilepsy, representing approximately 25% of the world's epilepsy population [1]. In Indonesia, epilepsy case reached at least 700,000-1,400,000 cases with an increase of 70,000 new cases every year, and it is estimated that around 40-50% of cases occurred in children [2].

Hepatotoxicity is a common side effect among conventional antiepileptic drugs (AEDs), with reactions ranging from mild, transient changes in hepatic enzymes, to severe liver failure [3]. Hepatotoxicity prevalence that was associated with AED use was found to be only around 2-4% in Europe. Although paracetamol intoxication is the most common cause of hepatotoxicity leading to liver transplantation, antiepileptic drugs are known to be the third cause of liver toxicity in 15% of cases [4].

There are still few studies regarding risk factors that affect hepatotoxicity occurrence in epileptic children in Indonesia, including at our hospital. Identification of risk factors that affects liver disorder occurrence is necessary during long-term treatment, hence acute liver toxicity could be avoided and improves outcome in children with epilepsy. This study aimed to determine the risk factors for hepatotoxicity in pediatric patients with epilepsy at our hospital, one of the tertiary referral centers in Indonesia.

MATERIALS AND METHODS

This was an analytical, observational, case control study to determine the risk factors for hepatotoxicity in epileptic children. The population in this study were all children with epilepsy who were undergoing treatment at the Pediatric Neurology Outpatient Clinic, Department of Child Health, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia from May to July 2023. The samples in this study were some of the selected epilepsy patients who met the criteria. The inclusion criteria for this study were children aged 1 to 18 years, epilepsy patients who received AED treatment, either as monotherapy or polytherapy, for a minimum of 6 months at the Pediatric

Neurology Outpatient Clinic, Department of Child Health, Dr. Soetomo General Academic Hospital, and parents or guardians of the patient gave written consent to participate by signing a written consent form after being given informed concerns regarding this study. The exclusion criteria in this study were children with epilepsy who had a history of liver disorders before receiving AED and experienced seizures defined as status epilepticus in the last 3 months. The sampling technique was conducted using consecutive sampling. Every subject with epilepsy who met the inclusion criteria was included as study sample. The sample search was stopped when the sample size was met.

Each child underwent a routine history and physical examination. Basic data was collected which included age, gender, nutritional status, epilepsy type and syndrome, intractable epilepsy incidence, AED type that had been given, duration of AED treatment, and data on previous liver disorders and other important disorders. Blood tests was conducted which included liver function tests (alanine transaminase [ALT], gamma-glutamyl transferase [GGT)], and alkaline phosphatase [ALP]). The examination was conducted at the Clinical Pathology Laboratory, Central Diagnostic Center Building, Dr. Soetomo General Academic Hospital, Surabaya. If the laboratory results were inconclusive, corrections were made. The obtained study data were collected, processed, and analyzed further.

Every patient with epilepsy who met the inclusion criteria had their blood drawn for 3-5 ml via a peripheral vein using a 5 ml Terumo® brand disposable syringe and a 23.5 G needle. The blood was put into a tube with a yellow cap containing acid-citrate-dextrose. The data was input into the data collection sheet for further statistical analysis.

Processing and analysis of data was conducted using the SPSS version 24 statistical software. Data was presented in tabulated and narrative form. Descriptive analysis was conducted using statistical measures (mean, standard deviation, and frequency distribution table). The correlation between two variables (age, nutritional status, epilepsy type and syndrome, intractable epilepsy, AED type, and treatment duration on hepatotoxicity incidence was analyzed using the Chi-square test. To determine the analyzed risk factors, logistic regression analysis was used to determine the dominant factors that affects liver disorder occurrence.

The study had as received approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia with registration number: 0652/KEPK/IV/2023.

RESULTS

In this study, a total of 70 pediatric patients were diagnosed with epilepsy and received AED for at least 6 months. A total of 4 patients were excluded because they refused to undergo blood tests. The remaining 66 patients met the inclusion criteria, 31 patients experienced

hepatotoxicity, and 35 patients did not experience hepatotoxicity. The characteristics of the study subjects revealed that there were 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). The initial onset of seizures was most common 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/6 months (37.9%). Temporal lobe epilepsy was the most common type associated with hepatotoxicity (62.5%). Meanwhile, epilepsy related to post-infection (53.3%) dominated the non-hepatotoxicity epilepsy group, followed by frontotemporal lobe epilepsy (75%). More than half of the study subjects used >2 types of AEDs (77.3%) and more than half of the study subjects had good medication compliance (78.8%).

Treatment duration (P= 0.014) was proven to be a significant risk factor for hepatotoxicity in children (Table 2). For AED type, a separate analysis was conducted for each type of drug because the majority of subjects in this study used more than 2 types of AED. Based on the results of bivariate analysis, it was found that phenytoin was a significant risk factor for hepatotoxicity in epileptic children (P=0.002) (Table 3).

Only AED types and treatment duration were conducted multivariate analysis (P<0.25). Logistic regression analysis was conducted for each of these variables to determine the dominant factors that affected liver disorder occurrence in children with epilepsy. Treatment duration of 6-12 months was used as a comparison. Based on the results of the analysis, it was found 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 fourteenfold in patients with treatment duration of >5 years-10 years compared to patients who underwent treatment for 6-12 months. AED types was also analyzed using the backward method to identify AED type that had the greatest effect on hepatotoxicity. In this study, 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).

In this study, liver function tests were conducted in epileptic children with and without hepatotoxicity. Only median GGT level that showed a significant difference (p<0.001) between patients with (89 [31.5-1567.2]) and without (20.1 [4.0-46.0]) hepatotoxicity (Table 6).

DISCUSSION

In this study, most patients with epilepsy were in the age range 1-5 years (47.4%). The proportion of epilepsy cases in previous study at Dr. Soetomo General Academic Hospital from January to December 2013 reported that most patients were at the age range of 1-5 years (45.63%)

[5,6]. However, Suwarba et al. which 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].

One of the risk factors for drug interactions that induce liver damage is age. The risk of AED-related liver damage increases in children aged <24 months [7]. Younger age is a major risk factor for valproate-induced severe hepatotoxicity, especially in children under 2 years of age undergoing polytherapy [8,9]. In a population-based study in the United States, AED was the fourth most common cause of drug-induced acute necrotic liver injury leading to liver transplantation. As age increases, liver damage incidence arises. Population aged >40 years are more susceptible to liver injury due to changes in medication, drug excretion and intake at the same time. In addition, older people tend to experience more cholestatic type damage and younger populations (aged ≥10 years) tend to experience hepatocellular-type damage [10,11].

In this study, most subjects had normal nutritional status in both hepatotoxicity (51.9%) and non-hepatotoxicity (48.1%) group. However, it was found overweight/obese nutritional status was more prevalent in 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 inability of 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 [12, 13].

Pharmacokinetic interactions between AEDs lead to changes in absorption, metabolism, protein binding, and excretion processes. The association of AEDs with hepatotoxicity is more commonly associated with phenytoin, valproic acid, and felbamate, whereas the latest generation of AEDs are more unlikely to cause hepatotoxicity [14]. Phenytoin is known as an enzyme inducer, inducing asymptomatic GGT elevation. Liver microsomal enzymes might also increase ALP, even though it is still lower than GGT. Asymptomatic elevations in ALT and aspartate aminotransferase (AST) might also occur. The risk of hepatotoxicity due to phenytoin is similar in both sexes. Most patients experience symptoms of phenytoin-induced hepatotoxicity 2-8 weeks after the start of treatment, followed by non-specific symptoms such as fatigue, fever, rash, facial edema, and lymphadenopathy [15].

Most patients in hepatotoxicity group received AED for 13 months-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 years-10 years led to a 14-fold risk of hepatotoxicity compared to using AED for 6-12 months in this study.

A study reported that different types of AEDs and duration of treatment cause different patterns of liver damage. In valproic acid treatment for 1-6 months, hepatocellular or mixed damage, increased ammonia, and occasional acidosis were found. Meanwhile, phenytoin and carbamazepine treatment for 0–3 months causes hepatocellular, cholestatic, or mixed damage, as well as immuno-allergic reactions [16, 17]. This is different from this study, where the mean liver enzyme levels increased significantly at 3, 6, and 12 months after phenobarbital administration [18].

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 [19, 20]. 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 [21].

In terms of enzyme analysis, only GGT level that was a significantly difference between groups (p<0.001). Liver function disorders 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 [22]. This is different from 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 ALP level will increase during the childhood and adolescence of 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 level in serum reach their highest point in the first 6 months of life, then gradually decrease until they reach a relatively stable level, and increase further after the age of 9 years, with a peak at puberty, although

not as high as ALP level detected in infancy [23]. Therefore, ALP level in this study did not have a significant value in the occurrence of hepatotoxicity in children.

This study used a minimal sample size, causing the analysis to be less powerful and unable to describe the actual incidence of hepatotoxicity. This study also did not have preliminary data on liver function examinations before the patients received AED, hence it was not possible to clearly determine the causal correlation between each AED and hepatotoxicity incidence.

One of the weaknesses in case-control studies is the difficulty for confirming the history of different risk factors in each group of cases and controls due to memory bias and confusing subjectivity. In addition, blood AED level in this study was not measured, hence it is not known for certain the therapeutic range and level of drug toxicity in each patient.

CONCLUSION

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.

Conflict of interest: The authors do not have any financial or personal relationships that might bias the content of this work.

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. All authors have read and agreed to the published version of the manuscript.

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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. https://www.saripediatri.org/index.php/sari-pediatri/article/download/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.1600-0404.2008.01009.x

5. 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. https://saripediatri.org/index.php/sari-pediatri/article/view/9/22

6. 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

7. 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

8. Perucca P, Gilliam FG. Adverse effects of antiepileptic drugs. Lancet Neurol. 2012;11(9):792–802. doi: 10.1016/S1474-4422(12)70153-9

9. 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

10. 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

11. 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

12. 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

13. 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

14. 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

15. 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/

16. 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

17. 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

18. 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

19. 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

20. 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

21. Marvanova M. Pharmacokinetic characteristics of antiepileptic drugs (AEDs). Mental Health Clinician. 2016;6(1):8–20. doi: 10.9740/mhc.2015.01.008

22. Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci. 2001;38(4):263–355. doi: 10.1080/20014091084227

23. 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

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FIGURES, TABLES AND SCHEMES

TABLES

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

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 (continued)

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

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	