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CORRELATION BETWEEN THE DURATION OF ANTI-EPILEPTIC DRUGS THERAPY AND VITAMIN D LEVEL IN EPILEPTIC CHILDREN

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Abstract

Long-term use of antiepileptic drugs (AEDs) for epilepsy causes a decrease in vitamin D levels due to the activation of liver cytochrome P450 enzymes. The novelty of this study is due to researching about correlation between the duration of anti-epileptic drugs therapy and vitamin d level in epileptic children This cross-sectional study was conducted from October - December 2021in children with epilepsy aged 1 month to 18 years admitted to pediatric neurology polyclinic of DR Wahidin Sudirohusodo. They were divided into two groups: epileptic children receiving AEDs treatment ≤ 1 year and epileptic children receiving AEDs treatment > 1 year. Statistical analysis showed no significant relationship between the duration of AEDs use and the incidence of vitamin D deficiency in children with epilepsy.

Keywords: Vitamin D Deficiency; Antiepileptic Drugs; Epilepsy

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INTRODUCTION

Epilepsy is a central nervous system disorder characterized by spontaneous and periodic seizures (1). The incidence of epilepsy in children is reported from various countries with wide variations, around 4-6 per 1000 children, depending on the study design and the age group of the population. The World Health Organization (WHO) states, the incidence of epilepsy in developed countries is around 50 per 100,000 population, while in developing countries it is 100-190 per 100,000. In Indonesia, there are at least 700,000-1,400,000 cases of epilepsy with an increase of 70,000 new cases every year and it is estimated that 40%-50% occur in children (2)(3).

Vitamin D, which includes fat-soluble vitamins, is a prohormone that has the main function of regulating calcium balance for the body. Vitamin D status in the body is determined based on 25(OH)D levels (4)

Antiepileptic drugs (AEDs) effects on vitamin D levels have been studied for 40 years or more. Phenobarbital, phenytoin, carbamazepine, valproic acid, and oxcarbazepine are frequently studied for their effects on 25(OH)D levels. Most enzyme-inducing anticonvulsants (phenytoin, phenobarbital, primidone, and carbamazepine) are associated with low levels of vitamin D (5). The mechanism underlying low vitamin D levels in epilepsy patients has so far been based on two pathways. Antiepileptic drugs are associated with changes in bone metabolism and phosphate concentrations and thus also changes in calcium homeostasis in the body that affect vitamin D levels in the body. Another mechanism is based on decreased levels of active vitamin D, caused by induction of hepatic cytochrome P450 enzymes by antiepileptic drugs, leading to conversion to inactive metabolites in liver microsomes (6) (7).

AEDs are antiepileptic drugs that are widely used in Indonesia and are classified as drugs with a narrow therapeutic index that require monitoring of plasma drug levels and dose adjustments to prevent the effects of vitamin D deficiency. Epilepsy treatment is given for 2 years without seizures, which raises concerns about the effects. existing side. The exact duration of AEDs that cause vitamin D deficiency is not clear at this time. In a study by Cansu et al, vitamin D levels decreased significantly after 18 months of taking AEDs. In another study, 49% developed vitamin D3 deficiency

within 3 months of AEDs (6). Existing research still yields erratic results in explaining the relationship between vitamin D deficiency and AEDs use, particularly vitamin D levels, implying that additional study is necessary.

MATERIAL AND METHODS

Study Design

This is a cross-sectional study of children with epilepsy aged 1 month to 18 years enrolled at RSUP DR Wahidin Sudirohusodo in Makassar, South Sulawesi, from October to December 2021. Blood samples were examined at the Hasanuddin University Medical Research Center (HUMRC) Laboratory. Ethics approval has been obtained from the ethics committee for research in Humans of the Faculty of Medicine, Hasanuddin University.

The sampling method is using the consecutive sampling method. The research sample is all the affordable population that meet the research criteria. Furthermore, the calculation of the length of treatment with anti-epileptic drugs was carried out and resulted in two groups, namely the group of children with the use of anti-epileptic drugs for more than 1 year and less or equal to 1 year based on data from the neurology division and anamnesis from parents. Then in each group the levels of 25 (OH) D were checked using the Chemiluminescence Immune Assay method with Dia Sorin Liaison.

Statistical Analysis

The data analysis was using SPSS statistics for Windows, version 22.0 (IBM Co., Armonk, NY, USA). Data characteristics such as frequency, distribution, mean, median (range), and standard deviation, while Chi-square or Fisher Exact test was used to determine the significance of incidence of vitamin D deficiency and duration of use of AEDs. The risk factor was determined using Crude odds ratio (OR) analysis with 95% confidence interval (CI). Statistical significance was indicated with $P<0.05$.

RESULTS

Table 1. The characteristic sample based on the duration of AEDs

Characteristics	The duration of AEDs		P value
	> 1 year	≤ 1 year	
Gender			
Male	25 (62.5%)	23 (48.9%)	0.205*
Female	15 (37.5%)	24 (51.1%)	
Age			
1 month - ≤ 7 years	28 (70%)	33 (70.2%)	
> 7 - ≤ 12 years	9 (22.5%)	8 (17%)	1.000**
> 12 years	3 (7.5%)	6 (12.8%)	
Nutrition state			
Malnutrition	19 (47.5%)	19 (40.4%)	0.507*
Good nourished	21 (52.5%)	28 (59.6%)	

* *Chi-square*
** *Kolmogorov Smirnov*

Table 2. The characteristic sample based on vitamin D status

Characteristics	Vitamin D status		P value
	Abnormal	Normal	
Gender			
Male	32 (54.2%)	16 (57.1%)	0.799 *
Female	27 (45.8%)	12 (42.9%)	
Age			
1 month - ≤ 7 years	34 (57.6%)	27 (96.4%)	0.001*
> 7 - ≤ 12 years	16 (27.1%)	1 (3.6%)	
> 12 years	9 (15.3%)	0 (0%)	
Nutrition state			
Malnutrition	28 (47.5%)	10 (35.7%)	0.302*
Good nourished	31 (52.5%)	18 (64.3%)	

* *Chi-square*

Table 3. Analysis of vitamin D levels in the group with duration of AEDs more than 1 year and less or equal to 1 year in epilepsy children

Duration of AEDs	Vitamin D levels (ng/ml)		P Value
	Median	(Min-Max)	
> 1 Year	13.92	0.58-150.53	0.618***
≤ 1 year	15.78	1.03-132.75	

** *Mann Whitney*

Table 4. Analysis of vitamin D status in the group with duration of AEDs more than 1 year and less or equal to 1 year in epilepsy children.

Duration of AEDs	Vitamin D state				P value
	Normal		Abnormal		
	N	%	N	%	
> 1 year	13	46.4%	27	45.8%	0.954
≤ 1 year	15	53.6%	32	54.2%	

** Chi-square*

A total of 87 children with epilepsy were classified into the group with AEDs use >1 year there were 40 (46%) children and in the group with AEDs use ≤1 year there were 47 (54%) children. In the group with duration of use of AEDs for more than 1 year the number of boys was 25 (62.5%) and girls were 15 (37.5%). In the group with duration of use of AEDs less than or equal to 1 year the number of boys was 23 (48.9%) and girls were 24 (51.1%). Statistical analysis showed that there was no significant difference in the distribution of sex with the duration of use of AEDs in children with epilepsy, with p value=0,205 (p>0,05). In the group with duration of use of AEDs less or equal to 1 year the number of children aged less than 7 years were 33 (70.2%), 7 to 12 years were 8 (17%) and > 12 years were 6 (12.8%). In the group with duration of use of AEDs for more than 1 year, the number of children aged less than 7 years were 28 (70%), 7 to 12 years were 9 (22.5%) and > 12 years were 3 (7.5%). Statistical analysis showed that there was no significant difference in the distribution of age and duration of use of AEDs in children with epilepsy, with p value=1,000 (p>0.05). In the group with duration of use of AEDs less or equal to 1 year, the number of children with malnutrition was 19 (40.4%) and 28 (59.6%) with good nutrition. In the group with duration of use of AEDs for more than 1 year, the number of children with malnutrition was 19 (47.5%) and 21 (52.5%) with good nutrition. Statistical analysis showed that there was no significant difference in the distribution of nutritional status with the duration of use of AEDs in children with epilepsy, with p value=0.507 (p>0.05).

In the group of abnormal vitamin D levels, the number of boys was 32 (54.2%) and girls were 27 (45.8%). In the

group with normal vitamin D levels, 16 (57.1%) boys and 12 girls (42.9%). Statistical analysis showed that there was no significant difference in the distribution of sex with vitamin D deficiency in children with epilepsy, with p value =0.799 (p>0.05). In the group with abnormal vitamin D levels the number of children aged less than 7 years was 34 (57.6%), 7 to 12 years was 16 (27.1%) and > 12 years was 9 (15.3%). In the group without vitamin D deficiency, the number of children aged 1 to 7 years was 27 (96.4%) and 7 to 12 years was 1 (3.6%). Statistical analysis showed that there was a significant difference in the distribution of age with vitamin D deficiency in children with epilepsy, with p value=0.001 (p<0.05). In the group with abnormal vitamin D levels, 28 (47.5%) children with malnutrition and 31 (52.5%) with good nutrition. In the group with normal vitamin D levels, there were 10 (35.7%) malnourished children and 18 (64.3%) with good nutrition. Statistical analysis showed that there was no significant difference in the distribution of nutritional status with vitamin D deficiency in children with epilepsy, with p value = 0.302 (p>0.05).

In the group for duration of use of AEDs more than 1 year, the median vitamin D levels was 13.92 ng/ml, with a minimum - maximum value of 0.58 - 150.53 ng/ml. Meanwhile, in the group with duration of use of AEDs for less than 1 year, the median value of vitamin D levels was 15.78 ng/ml, with a minimum – maximum value of 1.03 – 132.75 ng/ml. The results of statistical tests showed that there was no significant difference in median vitamin D levels with duration of use of AEDs in children with epilepsy with p value = 0.618 (p> 0.05).

In the group with normal vitamin D levels, 13 (46.4%) children with duration of use of AEDs more than 1 year and 15 (53.6%). In the group with abnormal vitamin D levels, 27 (45.8%) children with duration of use of AEDs more than 1 year and 32 (54.2%) use of AEDs less than or equal to 1 year. Statistical analysis showed that there was no significant difference in vitamin D status. with the duration of use of AEDs in children with epilepsy, with p value=0.954 (p>0.05).

DISCUSSION

According to this study, there was no relationship between duration of use of AEDs with vitamin D levels as well as

vitamin D deficiency or hypervitaminosis. In the duration of use of AEDs for more than one year, the average level of vitamin D was 29.99 ng/ml which was much higher than the duration of use of AEDS less than 1 year which was 29.96 ng/ml.

This is in line with the Saket study (2021) in 120 children with epilepsy who took AEDS for more than 6 months, there was no significant difference based on the duration of AEDS use with vitamin D levels (8). In the Attilakos study (2018) in children with epilepsy who compared children before taking AEDS and those who were more than 12 months had no significant difference in vitamin D levels with p value = 0.345 (9). In Lee's (2015) study on 198 children with epilepsy in Chenon, Korea. They compared the duration of children taking AEDS and vitamin D levels which did not find a significant difference with p value = 0.534 (10).

This study is different from several studies, namely according to research by Chaudhuri et al (2017) using a prospective method with a mean patient age of 14 years proving that 25-hydroxyvitamin D levels were significantly lower in cases of using anti-epileptic drugs (18.3 ± 6.2) compared to with controls (27.7 ± 3.9) (P < 0.0001) (6). In Abdullah et al's study, using a case-control study method with a mean age of 7.57 years showed that patients taking anticonvulsants had lower levels of vitamin D than children without anticonvulsant use (p=0.001) (11). In a cross-sectional study conducted by Pohan et al, found an association between long-term use of anticonvulsants (one year or more), decreased 25(OH)D levels, and vitamin D status. Epileptic children with a mean age of 9.1 years taking anticonvulsants for at least 1 year experienced an 18.4% decrease in mean 25(OH)D levels compared to the control group, and they had a higher prevalence of vitamin D deficiency (5).

The prevalence of vitamin D deficiency in epileptic children receiving anticonvulsant agents is above 50%. Phenytoin, phenobarbital, and carbamazepine interfere with vitamin D metabolism. These drugs act at the liver microsomal level by inducing the activity of the cytochrome P450 hydroxylase enzyme, thereby leading to accelerated vitamin D and metabolite catabolism and reduced activity; however, the inducer of the enzyme is only one of the factors associated with vitamin D deficiency (12). Enzyme-inducing AEDSs can induce

CYP450 to accelerate vitamin D degradation, contribute to hypocalcemia, reduced bone density, and a higher risk of fracture. Phenytoin can also induce CYP450 expression, which increases the degradation of available vitamin D, decreases intestinal calcium absorption, decreases serum calcium and phosphate levels, and increases parathyroid hormone. Carbamazepine can induce CYP450 to decrease vitamin D levels (13). Valproic acid inhibits the 25-hydroxylase activity of vitamin D in liver mitochondria without inhibiting the cytochrome P450 component of the mono-oxygenase system (6) (7).

The above mechanism has been associated with AEDS which is an inducer of the cytochrome P450 enzyme system (phenobarbitol, phenytoin and carbamazepine). Other mechanisms include decreased intestinal calcium absorption (phenytoin), impaired response to parathyroid hormone (phenobarbitone). and phenytoin), hypovitaminosis K (phenytoin), and calcitonin deficiency. The exact mechanism by which sodium valproate causes similar abnormalities of bone mineral metabolism is unclear but may be mediated by inhibition of different liver enzymes. Polytherapy therapy is associated with a higher risk of bone mineral metabolism abnormalities than monotherapy (6).

CONCLUSION AND RECOMMENDATION

There is no significant difference in vitamin D levels with the duration of AEDs use in this study because there are other factors that affect vitamin D levels besides the use of AEDs, namely the age of the child, the use of the type of AEDs which in this study was not divided, the use of monotherapy and polytherapy, which in this study were analyzed. which is one of the uses of AEDs and the initial value of vitamin D levels is unknown.

The limitation of this study is that the method used is cross sectional so that the examination of vitamin D levels is only carried out once, so it is not known whether the vitamin D levels have decreased with the duration of AEDs use and there are other factors that greatly affect vitamin D levels cannot be controlled such as sun exposure and diet that can affect vitamin D levels. The results of this study can contribute to data regarding vitamin D levels with duration of use of AEDs in patients with epilepsy, which can later be continued with further studies by taking vitamin D levels twice at the beginning and end of the study. Thus,

the resulting data are able to provide a clearer picture of the role of prolonged use of AEDs on the incidence of vitamin D deficiency in epilepsy patients.

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