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Original Research Paper

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THE ASSOCIATION OF ANTIEPILEPTIC DRUGS WITH VITAMIN D STATUS IN CHILDHOOD EPILEPSY

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ABSTRACT

Background: Epilepsy is a common neurological disorder of childhood requiring long term of antiepileptic drugs that has been associated with low 25-hydroxyvitamin D (25(OH)D) status and high prevalence of vitamin D deficiency. However, studies on the effect of long term antiepileptic drugs use on vitamin D had inconsistent results.

The aim of this study was to analyze the association of antiepileptic drugs (AED) with vitamin D status in childhood epilepsy.

Methods: A cross sectional study was conducted from February to April 2019 at children outpatient clinic Haji Adam Malik Hospital. One hundred and two epileptic children taking antiepileptic drug were enrolled consecutively. All cases who met inclusion criteria, underwent test for serum 25(OH)D that were categorized as normal (≥30 ng/ml) and abnormal (<30 ng/ml). Antiepileptic drugs were categorized based on their enzyme inducing properties, polytherapy combination and monotherapy.

Results: From 102 patients, 77 children (75.5%) had abnormal vitamin D with average level of 25(OH)D was 24.37 ng/ml (SD 9.23). The mean of age was 9.26 years (SD 4.96), 57.8% were boy and 79.4% on monotherapy. Association between enzyme inducing vs non-inducing properties, monotherapy vs polytherapy and duration of therapy with vitamin D status were non significance with *p* value 0.277, 0.713 and 0.728 respectively. Sodium Valproate was the most common AED used in mono therapy (87.7%) and combination of Sodium Valproate-Topiramate in polytherapy (42.9%). The differences of an abnormal vitamin D in those on AED as monotherapy were not significant ($p=0.713$). Similarly in polytherapy, there were non-significant difference of vitamin D level in each combination of AED ($p=1$).

Conclusion: There was no significant association of antiepileptic drugs with vitamin D status in childhood epilepsy.

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KEYWORDS : epilepsy, antiepileptic drugs, vitamin D

1. INTRODUCTION

Epilepsy is one of the most common neurological disorders in children. It was estimated that 6 of 1,000 children worldwide suffer from epilepsy, and it is estimated that it is twice as frequent in children as adults.[1] Epilepsy incidence is estimated to be more in developing countries than in industrialized countries. In developing countries, the incidence of childhood epilepsy from birth to 16 years is estimated at around 40 out of 100,000 children per year.[2]

Vitamin D plays an important role in many different physiological functions. Vitamin D has an important role during brain development, proliferation, differentiation, neurotrophic and neuroprotective.[3] Studies showed that vitamin D deficiency is a risk factor for neurological diseases such as Alzheimer's, Parkinson's, multiple sclerosis, depression, schizophrenia, autism and epilepsy.[4,5]

Management of epilepsy is by giving antiepileptic drugs. Antiepileptic drugs (AEDs) are usually given long term and use a combination of several drugs to control seizures, so we must pay attention to the side effects of each drug used. The use of AEDs can cause vitamin D deficiency, through the induction of cytochrome P450 that will increase the catabolism of vitamin D.[6,7,8] In Indonesia, there were less study about the effect of long term AEDs administration on vitamin D. Because of the limited data, this study aim to determine the association of antiepileptic drugs with vitamin D status in childhood epilepsy.

2. METHODS

The design of this study was concecutive, cross sectional study. This study was conducted in outpatient pediatric neurology clinic Haji Adam Malik Hospital, Medan, North Sumatera. This study was held from February to April 2019. The study was approved by the Research Ethics Committee of the University of Sumatera Utara Faculty of Medicine. Inclusion criteria were defined as epileptic children, aged 0-18 years who had been used antiepileptic drugs. We excluded children with obesity, impaired liver function, renal failure and those who consumed vitamin D supplements.

All cases who meet inclusion criteria underwent test for 25(OH)D level. Blood specimen were taken from all the subjects after obtaining parental consents. Abnormal vitamin D was defined as 25(OH)D level less than 30 ng/ml, whereas normal vitamin D level as ≥ 30 ng/ml. There are 4 types of drugs used as antiepileptic drugs, namely phenobarbital, valproic acid, carbamazepine and topiramate. Antiepileptic drugs were categorized based on their enzyme inducing properties, polytherapy combination and monotherapy. Type of antiepileptic drugs, number of AEDs, duration of therapy and using of first and second line AEDs as monotherapy and polytherapy combination were analyzed. First line AEDs define as using phenobarbital, valproic acid or carbamazepine as therapy meanwhile topiramate as second line therapy.

Data were analyzed by using IBM SPSS Statistics version 22.0. Mean and standard deviation (SD) were estimated for various variables. Categorical variables were presented as

chi-square or Fischer's exact test for cells value <5 to evaluate the factors that associate with AEDs using and the association with vitamin D status. A value of p<0.05 was considered as statistically significant with 95% confidence interval (CI).

3. RESULT

Subject's characteristics

A total of 102 epileptic children with epilepsy who were treated at the paediatric neurology outpatient clinic Haji Adam Malik Medan from February to April 2019 who had met the inclusion criteria. Characteristics of research subjects are presented in table 1. The majority of research subjects were male (57.8%) with an average age of 9.26 years. Epilepsy with generalized seizures is more common than focal seizures (77.5%) while the most common cause of seizures is idiopathic (54.9%).

Table 1. Characteristics of the study subjects

Characteristics	n (%)
Gender	
Male	59 (57.8)
Mean Age (SD), years	9.28 ± 4.96
Type of epilepsy	
Generalized	79 (77.5)
Focal	23 (22.5)
Etiology of epilepsy	
Idiopatic	56 (54.9)
Symptomatic	46 (45.1)
Number of antiepileptic drug	
Monotherapy	81 (79.4)
Polytherapy	21 (20.6)
Type of antiepileptic drug	
Enzyme inducer	18 (17.6)
Non-enzyme inducer	84 (82.4)
Type of AED in monotherapy	
First line	77 (95.1)
Second line	44 (4.9)
Type of AED combination in politherapy	
First line + First line	10 (47.6)
First line + Second line	11 (52.4)
Status of 25(OH)D	
Normal	25 (24.5)
Abnormal	77 (75.5)
Mean Vitamin D level (SD), ng/ml	24.33 ± 9.08
Duration of therapy	
< 2 years	52 (51)
≥ 2 years	50 (49)
Mean duration of AED (SD), months	26.28 ± 23

Monotherapy is the most type of therapy (79.4%) with valproic acid as the most AED used as monotherapy (87.7%). The average serum vitamin D level was 24.37 ng / ml where most subjects had abnormal vitamin D levels (75.5%) consisting of insufficiency in 43 subjects (42.2%) and deficiency in 34 subjects (33.3%). Only 25 subjects (24.5%) had normal vitamin D levels. The average duration of treatment with AED was 26.28 months.

Tabel 2. Associations between vitamin D status and type of AED, number and duration of therapy

	Vitamin D status		PR (95% CI)	p value
	Abnormal	Normal		
Type of AED				
Enzyme inducer	16	2	0.3	0.23[b]
Non-enzyme inducer	61	23	(0.07-1.56)	
Number of AED				
Monotherapy	60	21	1.5	0.71[a]
Polytherapy	17	4	(0.45-4.92)	
Duration of therapy				
< 2 years	38	14	1.3	0.73[a]
≥ 2 years	39	11	(0.53-3.24)	

[a] *Chi Square*, [b] *Fischer's Exact*

Tabel 2 shows that there was no significant association between the type and duration of therapy and type of AEDs with serum vitamin D levels in the study subjects with p values of 0.227, 0.713 and 0.728, respectively.

Table 3. Association between vitamin D status and type of AED in monotherapy

Antiepileptic drug	Vitamin D Status		PR (95%CI)	p value
	Abnormal	Normal		
First line	56	21	0.7	0.57
Second line	4	0	(0.63-0.83)	

The analysis used to assess the relationship between AEDs types of first and second line monotherapy is the Chi square test. Types of AEDs monotherapy are divided into two groups namely first line (phenobarbital, valproic acid, and carbamazepine) and second line (topiramate). Table 3 shows that there was no significant difference in vitamin D between groups using first-line AEDs and groups using second-line AEDs with *p* value >0.05.

Tabel 4. Association between vitamin D status and type of AED combination in polytherapy

AED combination	Vitamin D status		PR (95%CI)	p value
	Abnormal	Normal		
First line + First line	8	2	1.1	1
First line + Second line	9	2	(0.13-0.94)	

The association of AEDs combination in politherapy with vitamin D in table 4 was analyzed using the Fischer exact test showing the value of *p* (1), so it can be concluded that there is no association between AEDs combination with vitamin D.

4. DISCUSSION

Epilepsy is a long-term neurological disorder that is most often found in childhood. Most epilepsy sufferers need long-term, even lifelong AEDs, which has the potential to experience undesirable metabolic side effects.[9] Given that adequate vitamin D is important for various health functions, making the effect of AEDs on vitamin D metabolism very interesting.[10] One cause of vitamin deficiency D is a long-term use of anticonvulsants in epileptic children. The anticonvulsant effect on vitamin D levels has been studied for more than 40 years. The prevalence of vitamin D deficiency in people with epilepsy varies depending on the definition of vitamin D deficiency, anticonvulsant type, amount and duration of administration and place of study.[11]

In this study the prevalence of abnormal vitamin D levels (<30 ng/ml) was 75.5% with an average value of 24.37 ng/ml. Assessment of abnormal vitamin D levels (<30 ng/ml /) based on the Endocrine Society and the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI). This definition is more consistent with the classification used in adults based on the occurrence of bone health disorders and increased levels of parathyroid hormone at vitamin D levels up to 32 ng / ml.[12,13]

The same prevalence with the result of research conducted in Germany, in epileptic children aged 5-12 years, that it was more than 75%.[10] However, it had a wide different when compared with the national prevalence of vitamin D deficiency in healthy children. Cross sectional study, a part of the South East Asian Nutrition Survey (SEANUT) conducted in 48 districts in Indonesia in healthy children aged 2 to 12.9 years reported that no children had vitamin D deficiency. There were 45.1 % experienced insufficiency and 49.3% with adequate status, while only 5.6% have enough vitamin D levels. The vitamin D classification used as follows, vitamin D

deficiency if serum 25 (OH) D levels <25 nmol/L (<10 ng / ml), insufficiency between 25-49 nmol/L (10-19.6 ng / ml), this is strong 50-74 nmol/L (20-29.6 ng / ml) and desirable status if ≥ 75 nmol/L (30 ng/ml).[14]

Study in Sri Lanka, India, Korea, Malaysia reports that the incidence of vitamin D deficiency in epileptic children is 53.7%, 45%, 9.1% and 22.5% .[15,16,17,18] This may be due by the different definitions of vitamin D deficiency used, the duration of AEDs administration, the method, ethnicity of the research subject, and the place / environment of the study. In these 4 studies, the criteria for the research subjects were epilepsy patients who had consumed AEDs for 1 year or more, whereas in this study the minimum time limit for AEDs use was not determined. This can lead to a higher prevalence of abnormal vitamin D levels in this study.

Until now there has been no consensus on the definition of vitamin D status in children and adolescents.[19] Globally, levels of 25 (OH) D below 10 ng / ml are considered the lowest cut off for vitamin D status. Endocrine Society Task Force publishes a guideline that defines adequate vitamin D if serum 25 (OH) D levels >30 ng/ml, 20-30 ng / ml insufficiency and deficiency <20 ng/ml.[20] Serum 25 (OH) D levels are recommended between 30-100 ng/ml to avoid health problems. Level 25 (OH) D 40-60 ng/ml is considered the best. Vitamin D poisoning occurs when serum 25 (OH) D levels> 150 ng/ml. [21]

Sun exposure is the main source of vitamin D (> 90%) through synthesis in the skin facilitated by ultraviolet B.[22] The amount of vitamin D synthesized by the skin depends on various factors such as individual age, geographical location, use of sunscreen, and skin pigmentation. [12,23] Children, especially infants, need less sun exposure than adults to produce adequate concentrations of vitamin D because of the ratio of body surface to volume and the ability to increase vitamin production which is greater than that of adults.[24]However, until now there has been no recommendation to determine the appropriate duration of sun exposure for a pediatric population, there are variations in vitamin D synthesis between individuals so it is difficult to determine recommendations.[13] In this study the duration of sun exposure was not assessed.

The average age of epilepsy sufferers (9.26 ± 4.96 years) which is a school age group causes their chance to play in the sun and physical activity outside the home has begun to decrease and more activity is done indoors. Limited mobility and disability of epileptic children also play a major role in reducing the synthesis of vitamin D in children due to rarely being outside the house.[1,25]

Antiepileptic drugs are used to prevent the recurrence of seizure. Long last seizure can cause damage until the death of brain cells. The principle of epilepsy treatment is starting from monotherapy, because most of patients are successfully managed with the first or second line monotherapy.[26,27] Although the use of first-line AEDs (valproic acid, phenobarbital, carbamazepine and phenytoin) is quite large compared to second-line AEDs, but from statistical tests there is no significant association.

If it fails with monotherapy, another AED (polytherapy) can be added. It is estimated that 35% of epilepsy patients do not respond to monotherapy, and are candidates for the use of polytherapy.[28,29] The administration of polytherapy with a lower dose AEDs or is being selected as the management of refractory patients who have received a maximum dose of monotherapy AEDs.[27] In the polytherapy group used combination of 2 or more drugs. The group of epilepsy patients receiving polytherapy in this study was 20.6% and the combination of valproic acid and topiramate was the most widely used AED as polytherapy (42.9%). There were no significant differences in levels of 25 (OH) D between the groups of patients taking monotherapy compared to the groups using polytherapy or between each AEDs combination used as polytherapy. Likewise with the results of research in Korea by Baek et al, Ramya and Nagarjunakond in India that there were no differences in vitamin D levels between patients receiving monotherapy and polytherapy.[17,30,31] In contrast, research by Nettekoven et al in Germany, Fong et al in Malaysia stated that polytherapy is one of the risk factors for decreasing vitamin D levels in people with epilepsy.[10,48] This difference may be caused by the existence of various complex interactions between various AEDs to the metabolism of vitamin D.[30]

Some studies report that the long use of AEDs will affect the decrease in vitamin D levels in epilepsy sufferers. The exact duration of use of AEDs which can cause vitamin D deficiency is unclear.[16] Research by Baek et al in Korea states that 25 (OH) D levels were significantly lower in patients who received AEDs for more than 2 years.[17] In this study, no significant association was found between AEDs use <2 years and AEDs use ≥2 years on vitamin D levels of epilepsy sufferers.

Inactivation of vitamin D by AEDs occurs mainly due to induction of liver enzymes and due to activation of pregnane X receptors (PXR), steroids and xenobiotic receptors (SXR).[32,33] Activation of vitamin D (D2 and D3) initially occurs in the liver where hydroxylation occurs to 25 (OH) D by CYP27A. Antiepileptic drugs combine and activate SXR and subsequently join the retinoid X receptor (RXR), which then activates the 24-hydroxylase enzyme by interacting with the vitamin D element which is responsive to 24-OHase. This will increase the destruction of 25 (OH) D and 1,25 (OH) 2D.[34,35]

However, several studies reported no difference between enzyme-inducing and non-enzyme-inducing AEDs on vitamin D. status.[36] A systematic review was conducted by Robien et al. did not find sufficient evidence to explain that AEDs affect serum vitamin D levels.[37] This is consistent with the results of this study where there is no significant relationship between enzyme-inducing AEDs (phenobarbital and carbamazepine) and non-inducing enzyme AEDs (valproic acid and topiramate).

Hypovitaminosis D can cause decreased intestinal calcium absorption. Thus, a low dietary calcium intake, hypovitaminosis D induced by vitamin D will cause a detrimental effect on bone mineral metabolism. Genetic factors can also influence an individual's susceptibility to the effects of AEDs on vitamin D and bone metabolism.[38,39] Feldkamp et al bbserved that a decrease in bone cell proliferation due to the direct effect of AEDs on bone cells which plays a role in causing skeletal damage.[40] Furthermore, either AED is induced or non-enzyme induction also plays a role in bone mass loss because it inhibits intestinal calcium absorption and vitamin D activation.[41] In this study, calcium and Bone Mineral Density (BMD) tests were not carried out so we cannot see the effect of decreasing vitamin D levels on health bone.

Limitations of this study are the absence of data on vitamin D levels in healthy subjects and vitamin D levels before the use of AED, making it difficult to determine whether vitamin D levels are abnormal (<30 ng / ml) purely due to AED use or not. This research is a cross sectional study so that it cannot see a causal relationship.

4. CONCLUSION

There was no significant association of antiepileptic drugs with vitamin D status in childhood epilepsy.

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