SERUM LEVEL OF 25-HYDROXYVITAMIN D IN CHILDREN WITH EPILEPSY RECEIVING LONG-TERM ANTIEPILEPTIC TREATMENT COMPARED TO HEALTHY CHILDREN

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ABSTRACT

Background: Long-term treatment with antiepileptic drugs (AED) requires monitoring of potential side effects, one of them is the decreasing in serum vitamin D level. Low serum vitamin D level is also a global health problem in healthy children. There are conflicting results regarding the low serum vitamin D level in epileptic children due to treatment with AED. **Purpose:** This study aimed to compare serum vitamin D level between healthy children and children with epilepsy receiving long-term AED treatment in Soetomo General Hospital. **Methods:** This was a cross-sectional study conducted in the pediatric neurology clinic of Soetomo general academic hospital from August 2018 to July 2019. Subjects are children ages 2-18 years with epilepsy receiving AED treatment for over 6 months (n=22), with healthy children as control (n=22). Peripheral serum 25-hydroxyvitamin D level were measured using enzyme-linked fluorescence assay (ELFA) method. The differences of those groups were analyzed by comparing the mean of 25-hydroxyvitamin D level of both groups using Anova and T-test (95% CI). **Results:** Low serum vitamin D level were identified in 27% children with epilepsy and 13% healthy children. The mean of serum 25-hydroxyvitamin D level in children with epilepsy and healthy children was 21.5 ng/ml (SD 8.41) and 34.3 ng/ml (SD 10.09), respectively. There was a significant difference between groups ($p<0.05$). **Conclusion:** Children with epilepsy receiving long-term AED treatment have lower level of serum 25-hydroxyvitamin D than healthy children.

Keywords: epilepsy, antiepileptic drugs, 25-hydroxyvitamin D.

INTRODUCTION

Epilepsy is one of the pediatric neurology health problem in Indonesia. The incidence of new epilepsy cases in Soetomo academic hospital is 103 cases in 2013.[1] Long-term treatment with antiepileptic drugs (AED) requires monitoring of potential side effects, one of them is the decreasing in serum vitamin D level.[2] Low serum vitamin D level is also a global health problem. Long-term consumption of AED is considered as a risk factor for vitamin D deficiency.[3] Vitamin D has been known to have an important role in bone growth.[4] Deficiency or insufficiency of vitamin D in children results in impaired linear bone growth. Several studies have shown decrease in vitamin D level due to the administration of antiepileptic drugs that affected growth of the children.[5] Body height is a results of complex process of chondrocyte proliferation, chondrocyte hypertrophy, and endochondral ossification of bone growth plates which are influenced by various factors, such as vitamin D.[6]

Short stature is significantly more prevalent in children with epilepsy undergoing long-term antiepileptic treatment than the normal population.[7] Short stature in children is big problem due to the risk of psychological and economic problem in the future.[8] According to the stunting syndrome theory, a child with short stature will give birth to a baby with a low body length and small head circumference, causing a decline in intelligence in the next generation.[6] Thus, low serum vitamin D level in children with epilepsy may affect the quality of the next generation in the future.[6,8]

The aim of this study is to compare serum vitamin D level between healthy children and children with epilepsy receiving long-term AED treatment in Soetomo general hospital.

PATIENTS AND METHODS

This is a comparative cross-sectional study conducted from August 2018 to July 2019 in Soetomo General Hospital, Surabaya. The protocol was approved by Ethics Committee of Health Research Soetomo General Hospital Surabaya.

Subjects are children ages 2-18 years with epilepsy receiving AED treatment for over 6 months (n=22). The patients were excluded if they were overweight, obese, wasted, severely wasted, had moderate or severe malnutrition, bone mineralization disease, poor compliance on AED, and severe neurological dysfunction. Patients with vitamin D supplementation were also excluded. The family member of pediatric resident was recruited as healthy children on control group. Comprehensive informed consent was obtained from each legal representative of the patient.

Measurement of Serum 25-Hydroxyvitamin D Level

Serum 25-hydroxyvitamin D level from peripheral blood was measured using enzyme-linked fluorescence assay (ELFA) method with VIDAS® reagent. Vitamin D status is determined based on serum 25-hydroxyvitamin D level according to the Endocrine Society (deficiency <20 ng/ml, insufficiency 20-29 ng/ml, and deficiency >29 ng/ml).

Statistical Analysis

SPSS version 21.0 was used for statistical analysis. Chi-Square was used to evaluate data comparison between groups. Saphiro-Wilk test was used to assess data distribution. Anova and T-test were used for comparison of mean serum 25-hydroxyvitamin D level and vitamin D status between groups (p-value <0.05).

RESULTS

46 children were participated in this study, but wo children were excluded because of technical difficulty on blood sample collection and insufficient of blood sample volume. Subjects were divided into two groups, children with epilepsy receiving AED for more than 6 months (n=22) and healthy children group (n=22). There was no difference in age, sex, milk consumption, mother educational background, and serum calcium level between groups. There was significant difference of hemoglobin level between groups. Based on Saphiro-Wilk test, data distribution between groups was normal (p>0.05). The characteristics of subjects are shown in Table 1.

Table 1. Baseline Characteristics of the Subjects

Characteristic	Children with Epilepsy	Healthy Children	p*
Mean age (year ± SD)	8.5 ± 3.87	8.2 ± 3.79	0.429
Sex (boy:girl)	15:7	15:7	0.627
AED (n/%)			-
Phenytoin	5/23	0	
Phenobarbital	1/4	0	
Valproic acid	5/23	0	
Phenytoin + phenobarbital	6/27	0	
Phenytoin + valproic acid	1/4	0	
Phenobarbital + valproic acid	4/19	0	
Milk consumption per day (n)			0.326
<200 ml	9	4	
200-<500 ml	6	8	
500-<1000 ml	7	9	
≥1000 ml	0	1	
Mother educational background (n/%)			0.533
Junior high school	6/27	3/14	
Senior high school	11/50	13/59	
University	5/23	6/27	
Mean duration of AED (month ± SD)	13.5 ± 5,67	0	-
Mean hemoglobin level (Z score ± SD)	-1.5 ± 0.93	-0.8 ± 1.91	0.016
Mean serum calcium level (mg/dl ± SD)	9.0 ± 0.55	9.4 ± 0.49	0.342

* Statistical analysis using Chi-Square test

Serum 25-hydroxyvitamin D level was measured in Clinical Pathology Laboratory of Soetomo General Academic Hospital. There was a significant difference in serum 25-hydroxyvitamin D level and vitamin D status between groups ($p < 0.05$). The results of serum 25-hydroxyvitamin D level and vitamin D status in both groups are shown in Table 2.

Table 2. The Mean of Serum 25-Hydroxyvitamin D Level

Characteristic	Children with Epilepsy	Healthy Children	p
Mean of 25(OH)D level (ng/ml ± SD)	21,5±8,41	34,3±10,09	0.000*
Vitamin D status (n/%)			0.001**
Sufficient	2/9	14/64	
Insufficient	14/64	5/23	
Deficient	6/27	3/13	

Statistical analysis with *T-test and **Anova test

DISCUSSION

Low level of serum vitamin D are one of the health problems in children. Previous study examined serum 25-hydroxyvitamin D level at 48 districts in Indonesia to determine the prevalence of vitamin D deficiency and insufficiency in child population. Vitamin D insufficiency occurs in 38.76% children, while vitamin D deficiency occurs in 1.08% children.[9] The result of this study showed that vitamin D insufficiency and deficiency are more prevalent in children with epilepsy receiving long-term AED treatment than in the healthy subjects in control group.

There are still different of opinions regarding the decrease of vitamin D level in children with epilepsy who are given long-term antiepileptic drugs. Several studies have concluded that the use of antiepileptic drugs is associated with low serum vitamin D level. However, other studies have produced different conclusions which stated that there is no association between the consumption of antiepileptic drug and serum 25-hydroxyvitamin D level.[10] As seen in this study, there was a significant difference of serum 25-hydroxyvitamin D level between children receiving long-term AED treatment and control group.

Fong compared serum 25-hydroxyvitamin D level in children with epilepsy receiving long-term AED treatment and healthy children in Malaysia. The study proved that there was significant difference between groups.[3] Vitamin D level are influenced by several factors, one of them is the process of vitamin D degradation. Long-term administration of antiepileptic drugs activates pregnane X receptors which increase the enzyme activity of CYP24A1 and CYP3A4. The increasing activity of CYP24A1 and CYP3A4 enzymes results in higher vitamin D catabolism rate. Several studies have suggested that many antiepileptic drugs affect the activity of CYP24A1 and CYP3A4, thus increasing their activity.[11] This enzyme inducing process thereby reducing vitamin D level in the blood.[12]

Study by Babayigit study showed different results. The study also compared serum 25-hydroxyvitamin D level in children with epilepsy receiving long-term AED treatment and healthy children. Data found that administration of long-term AED in children with epilepsy was not significantly reduce serum vitamin D level compared to healthy children. It is suspected that compensation mechanism of vitamin D catabolism preserve the serum 25-hydroxyvitamin D level in normal range.[10]

There were several limitations of this study, such as relatively small number of subjects. But from this study we can conclude that children with epilepsy receiving long-term AED treatment have lower level of serum 25-hydroxyvitamin D than healthy children.

Conflicts of Interest

No potential conflict of interest in this study.

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