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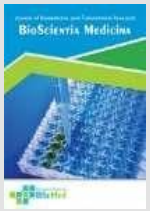

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Vitamin D Levels in Epilepsy Patients at the Neurology Polyclinic, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

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A B S T R A C T

Background: In epilepsy patients, treatment is often lifelong and anti-epileptic drugs (AEDs) can be divided into two general groups, namely drugs that affect cytochrome P-450 (CYP-450) such as carbamazepine, phenytoin, primidone, or valproic acid, and those that affect minimal cytochrome P-450 such as gabapentin, vigabatrin, levetiracetam, oxcarbazepine, or topiramate. AEDs include various drugs that can cause a decrease in vitamin D levels. Therefore, this study was aimed at examining vitamin D levels in epilepsy patients who took AEDs at the neurology polyclinic at Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia. **Methods:** This research is a descriptive study with a cross-sectional design using primary data obtained from the results of patient examinations using laboratory tests and secondary data from medical records. **Results:** As many as 78% (14 subjects) who received monotherapy had vitamin D levels below normal, and 16 subjects, or 76%, who received polytherapy had vitamin D levels below normal (p = 0.907). A total of 13 (72%) subjects who received phenytoin had vitamin D levels below normal, as well as 5 (63%) subjects who received carbamazepine and 12 (92%) subjects who received other therapies (p = 0.235). A total of 12 (67%) subjects who received therapy for 1-3 years and 18 (86%) subjects who received therapy > 3 years had vitamin D levels below normal (p = 0,406). **Conclusion:** Vitamin D deficiency is a crucial problem in epilepsy patients receiving AED therapy, where more than 75% of patients have vitamin D deficiency. In this study, vitamin D deficiency did not have a significant relationship with the type of therapy (monotherapy or polytherapy) or the type of drug used. used, duration of therapy, and frequency of sun exposure.

1. Introduction

Epilepsy is a disease characterized by seizures caused by disturbances in electrical activity in the brain and can be idiopathic or symptomatic.[1] The Epilepsy Study Group of the Association of Indonesian Neurologists (Pokdi Epilepsy PERDOSSI) stated in 2019 that there were 2,288 epilepsy patients, consisting of 487 new cases and 1,801 old cases. Several developing countries report that the peak incidence of epilepsy occurs in young adults, and the prevalence is higher in the first and second decades of life than in old age.[1,2] Treatment for epilepsy is often lifelong and anti-epileptic drugs (AEDs) can be divided into two general groups: influence CYP450s (such as carbamazepine, phenytoin, primidone, or valproic acid) and minimally

affecting CYP450s (such as gabapentin, vigabatrin, levetiracetam, oxcarbazepine, or topiramate). Antiepileptic drugs influence CYP450 may increase vitamin D catabolism.[3]

Vitamin D is a fat-soluble vitamin and plays a role as a prohormone in calcium homeostasis. Vitamin D levels can be monitored by monitoring 25-hydroxycholecalciferol (25-OHD), which has a fairly long half-life (around 2-3 weeks).[3] Vitamin D deficiency is a global public health problem, where around 50% of the population experiences vitamin D deficiency. Vitamin D itself can be obtained through endogenous synthesis and food intake, and vitamin D deficiency can be caused by decreased food intake or impaired absorption, reduced exposure to sunlight, decreased endogenous synthesis, and increased hepatic catabolism, which can be caused by drugs, including AEDs.[4,5] Until now, there have been many studies on the effect of AEDs on vitamin D levels, which occur through the induction of CYP450 in the liver. Vitamin D deficiency can be found in 22-79% of patients who receive AEDs for at least 1 year.[1,3,6] Therefore, this research was conducted to determine the description of vitamin D levels in epilepsy sufferers at the neurology polyclinic at Dr. Mohammad Hoesin General Hospital Palembang.

2. Methods

This research is a descriptive study with a cross-sectional design using primary data obtained from laboratory examination results and secondary data from medical records. This research involved all epilepsy sufferers who came for treatment to the neurology polyclinic of Dr. Mohammad Hoesin General Hospital Palembang for the period 1 August – 31 October 2023 and met the inclusion and exclusion criteria. The inclusion criteria set were patients who had been diagnosed with epilepsy, aged ≥ 18 years, and were willing to be involved in the research (proven through a form of informed consent). Patients with a history of chronic kidney disease or chronic liver disease before the diagnosis of epilepsy was made or patients who had taken anti-epileptic drugs for less than 1 year were excluded from the study. Patients who meet the inclusion and exclusion criteria will be offered their willingness to be involved in the research. After that, the patient underwent a blood draw to check vitamin D levels in the laboratory at Dr. Mohammad Hoesin General Hospital Palembang. The research data was processed using SPSS program version 24.

3. Results

This research involved 39 subjects, where 29 (74%) subjects were aged between 18-45 years, and 10 (26%) subjects were aged 46-65 years. A total of 27 (69%) subjects were male and 12 (31%) subjects were female. A total of 6 subjects (26%) did not finish high school, and 33 (74%) graduated from high school. This data can be seen in Table 1.

Table 1. Distribution of epilepsy patients based on sociodemographic characteristics.

Characteristics	n (%)
Age	
18-45 years old	29 (74)
46-65 years old	10 (26)
> 65 years old	0 (0)
Gender	
Male	27 (69)
Female	12 (31)
Education	
Did not finish high school	6 (26)
Graduated from high school	33 (74)

A total of 46% (18) subjects received monotherapy, and the rest (21 subjects, 54%) received polytherapy. The most common type of drug used was phenytoin (18 subjects, 46%), followed by carbamazepine (8 subjects, 21%), and others (13 subjects, 33%). A total of 46% of subjects, or 18 people, received therapy for 1-3 years, and 54% (21 people) of subjects received therapy for more than 3 years. The results are in Table 2.

Table 2. Distribution of epilepsy sufferers based on pharmacological therapy in the form of number, type, and duration of treatment.

Pharmacological therapy	n (%)
Type of therapy	
Monotherapy	18 (46)
Polytherapy	21 (54)
Type of medication	
Phenytoin	18 (46)
Carbamazepine	8 (21)
Phenobarbital	0 (0)
Others	13 (33)
Length of treatment	
1-3 years	18 (46)
> 3 years	21 (54)

In Table 3, vitamin D levels are presented, which are categorized into normal (≥ 30 ng/mL) and abnormal (< 30 ng/mL). As many as 78% (14 subjects) who received monotherapy had vitamin D levels below normal, and 16 subjects, or 76%, who received polytherapy had vitamin D levels below normal (p = 0.907). A total of 13 (72%) subjects who received phenytoin had vitamin D levels below normal, as well as 5 (63%) subjects who received carbamazepine and 12 (92%) subjects who received other therapies (p = 0.235). A total of 12 (67%) subjects who received therapy for 1-3 years and 18 (86%) subjects who received therapy > 3 years had vitamin D levels below normal (p = 0,406).

Table 3. Distribution of 25(OH) D levels based on pharmacological therapy in the form of number, type, and duration of treatment.

Pharmacological therapy	Vitamin D < 30 ng/mL	Vitamin D ≥ 30 ng/mL	p-value
Type of therapy			
Monotherapy	14 (78%)	4 (22%)	0,907
Polytherapy	16 (76%)	5 (24)	
Type of medication			
Phenytoin	13 (72%)	5 (28%)	0,235
Carbamazepine	5 (63%)	3 (38%)	
Others	12 (92%)	1 (8%)	
Length of therapy			
1-3 years	12 (67%)	6 (33%)	0,406
> 3 years	18 (86%)	3 (14%)	

*Chi-square test, significant on p < 0,05.

In Table 4**,** it was seen that 21 (54%) subjects had vitamin D deficiency, 9 (23%) subjects had vitamin D insufficiency, and 9 (23%) subjects had vitamin D levels at normal levels. No subjects had vitamin D levels at the toxic threshold.

Table 4. Distribution of 25 (OH) D levels in epilepsy patients receiving AED therapy.

Vitamin D levels	n (%)
Deficiency	21 (54)
Insufficiency	9 (23)
Normal	9 (23)
Toxic	0 (0)

As many as 82% (18 people) of subjects exposed to sunlight less than 3 times a week had vitamin D levels below normal, while 71% (12 people) of subjects exposed to sunlight ≥ 3 times a week had vitamin D levels below normal (p = 0.409). This is presented in Table 5.

Table 5. Distribution of 25 (OH) D levels based on sun exposure.

Sun exposure	Vitamin D < 30 ng/mL	Vitamin D ≥ 30 ng/mL	p-value
< 3 times a week	18 (82%)	4 (18%)	0,409
≥ 3 times a week	12 (71%)	5 (79%)	

*Chi-square test, significant on p < 0,05.

4. Discussion

The principle of epilepsy management aims to reduce seizure recurrence, where currently, antiepileptic drugs are still the first choice. Anti-epileptic drugs (AEDs) work against seizures through various cellular targets so that they are able to stop the hypersynchronous activity that occurs in brain circuits to achieve the main effect of completing mechanism modifications. burst on neurons and reduces neuronal synchronization. The mechanism of action of AEDs can be categorized into four main groups: (1) modulation of voltage-gated ion channels (such as sodium, calcium, and potassium); (2) increasing GABA inhibition through reactions at the GABA-A receptor, GAT-1 GABA transporter, or GABA transaminase; (3) direct modulation of the synaptic release process; and (4) inhibition of excitatory synapses via ionotropic glutamate receptors (including AMPA receptors). Antiepileptic drugs can also inhibit it from firing abnormally in other areas so that in some seizures, for example, typical absence seizures are caused by thalamocortical synchronization. Most AED targets are sodium, potassium channels, and GABA-A receptors.[7]

Vitamin D is a fat-soluble vitamin, a prohormone whose main function is to regulate the body's calcium balance. It is divided into two main forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D3 is the only form found naturally in humans and other animals and can be obtained from oily fish, egg yolks, or milk enriched with vitamin D. Apart from being sourced from animal ingredients, vitamin D3 can also be produced by the body through exposure to ultraviolet light. B (UVB) at a wavelength of 290-320 nm, which comes from sunlight. Sun exposure will convert 7-dehydrocholesterol in the skin into pre-vitamin D3. AAP and the Institute of Medicine (IOM) define vitamin D deficiency as a calcidiol (25-OH-D) concentration < 20 ng/mL in children.[3,4]

In this study, no significant relationship was found between the type of therapy (monotherapy or polytherapy), the type of drug given, the duration of therapy, and the frequency of exposure to sunlight (Table 3 and Table 5). Theoretically, several factors could influence the level of vitamin D deficiency in subjects with AEDs. In this study, vitamin D deficiency was found in 77% of subjects (Table 4). The prevalence of vitamin D deficiency in epilepsy patients who receive anticonvulsant agents alone is known to be above 50% because anticonvulsant drugs (phenytoin, phenobarbital, and carbamazepine) can interfere with vitamin D metabolism. These drugs work at the liver microsomal level by inducing enzyme activity. CYP450 hydroxylase increases vitamin D catabolism while decreasing active vitamin D activity.

Nevertheless, CYP450 induction is only one of the factors associated with vitamin D deficiency. Other factors that can reduce vitamin D levels in epilepsy patients are polytherapy as well as the duration of anticonvulsant therapy (79% of cases of vitamin D deficiency and insufficiency have been observed with more than 2 years of treatment),[8,9] as seen in Table 3 in this study.

Although there were no subjects in this study who received phenobarbital, phenobarbital is known to be associated with clinical symptoms of vitamin D deficiency in children due to CYP450 induction. The observed changes are caused by impaired calcium transport in the intestine, which results in hypocalcemia, as well as mobilization of calcium from the bones, which in turn causes a decrease in the level of bone mineralization. In one study, hypocalcemia and osteopenia occurred in patients receiving anticonvulsant therapy even though mean serum vitamin D levels were within normal limits.[8,10]

Phenytoin is an epilepsy medication that changes the movement of sodium ions across neuron cell membranes. Phenytoin itself has been associated with several metabolic abnormalities in bone, such as hypocalcemia and hypophosphatemia caused by induction of hepatic CYP450 in a similar manner to phenobarbital.[8,10] Another epilepsy therapy, carbamazepine, is used to treat focal seizures and seizures focal-to-bilateral in adults and children. Carbamazepine primarily acts on sodium channels that are maintained in an inactive state. Carbamazepine does not affect calcium metabolism directly but acts through its effect on CYP450, which accelerates vitamin D catabolism. Several studies in adults and children have shown that carbamazepine treatment can induce a decrease in calcium metabolism. bone marrow density in the lumbar vertebrae, femoral neck, antecubital, and calcaneus; however, there are conflicting results, especially in studies involving children.[10]

Valproic acid is a broad-spectrum antiepileptic drug that has been used as a first-line agent for generalized seizures. Valproic acid can block voltage-dependent sodium channels (voltage-gated sodium channels) and modify the conductance of calcium and potassium. Administration of valproic acid can increase the activity of the glutamate decarboxylase enzyme, which plays a key role in GABA synthesis and acts as an inhibitor of GABA transaminase. Several studies of valproic acid therapy in children and adults failed to find differences in mean cervical BMD values, while several other authors have found significant reductions in BMD with long-term use of valproic acid. In particular, studies in children with epilepsy found lower BMD values compared with control femoral neck, fingers, and lumbar vertebrae.[11]

This research has several weaknesses. The limited level of subject participation in this study reduces the opportunity for extrapolation of the study on a broader scale. Furthermore, the prevalence of vitamin D deficiency in this study was quite high (77%), thereby reducing the number of subjects who had normal vitamin D levels and could act as controls. Therefore, other research is needed on a wider scale to look at the prevalence of vitamin D deficiency and the relationship between AED therapy and vitamin D deficiency and its impact on BMD in epilepsy sufferers.

5. Conclusion

Vitamin D deficiency is a crucial problem in epilepsy patients receiving AED therapy, where more than 75% of patients have vitamin D deficiency. In this study, vitamin D deficiency did not have a significant relationship with the type of therapy (monotherapy or polytherapy), type of drug used, duration of therapy, and frequency of sun exposure.

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