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ORIGINAL ARTICLE

VITAMIN D LEVELS IN PEDIATRIC EPILEPSY PATIENTS ON THE ANTI-EPILEPTIC DRUGS AT TIKUR ANBESSA SPECIALIZED HOSPITAL, ADDIS ABABA, ETHIOPIA

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ABSTRACT

***Background**: Epilepsy is a common neurological disorder of childhood repeatedly necessitating prolonged use of anticonvulsants. This study was done to evaluate the status of vitamin D in epileptic children. We targeted to describe the prevalence and risk factors for vitamin D deficiency among children with epilepsy.*

***Methods**: A hospital-based descriptive cross-sectional study design with prospective data collection was used among children with epilepsy on anti-epileptic drugs attending the Pediatric Neurology Clinic and their primary caretakers. For this study, a sample of 226 children and adolescents were included in the study and a blood sample for the determination of serum vitamin D was taken. The participants were interviewed, and medical records were thoroughly reviewed. Descriptive statistics and binary logistic regression analysis was done to assess determinants of vitamin D deficiency. .*

***Results**: In this study, the prevalence of vitamin D deficiency was found to be 42%. Children on polytherapy (AOR = 4.3 (1.2 - 16)), 3 or more AEDs (AOR = 0.1 (0.0 - 0.8)), female sex (AOR = 1.8 (1.7 - 2.6)), age >15 years (AOR = 2.12 (1.0 - 1.5)), 4 months of exclusive breastfeeding (AOR = 5.6 (4.9 - 36)), family diet (AOR = 0.3 (0.1 - 0.8)) and non-ambulation (AOR = 1.7 (1.8 - 3.6)) were factors associated with being in the vitamin D deficiency group.*

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***Conclusion**: According to this study patients who take Anti-Epilepsy drugs are at a higher risk of a poor vitamin D status. Based on this finding, the need for timely and appropriate vitamin D supplementation and periodic follow-up seems to be very evident.*

Key Words: Anti-epilepsy drugs, Vitamin-D deficiency, Children, Ethiopia

INTRODUCTION

Vitamin D is essential for human health because it regulates calcium and bone metabolism. It helps the body absorb calcium and phosphorus from food and prevents parathyroid hormone from being released. Low levels of vitamin D can lead to bone problems such as rickets, osteopenia, and osteoporosis. Moreover, vitamin D deficiency may increase the risk of various diseases such as cancers, autoimmune disorders, hypertension, and infections (1,2).

Vitamin D3 levels below 30 ng/mL, which indicate insufficiency or deficiency, affect about one billion people worldwide (3). Anti-epileptic drug (AED) therapy in children is a known risk factor for impaired bone health (4–7). Hepatic CYP450 enzyme-inducing anti-seizure medication affects bone health by increasing the hepatic metabolism of vitamin D (8).

Other non–enzyme-inducing anti-epileptic drugs like sodium valproate can impact bone health via direct effects on bone cells, resistance to parathyroid hormone, and inhibition of calcitonin secretion (7,8). Anti-epileptic drug therapy, particularly long-term anti-epileptic drug therapy, and poly-therapy is known to be associated with Vitamin D Deficiency which negatively contributes to bone health (8–10).

Impaired bone health results in low bone mineral density and osteoporotic fractures in childhood and later adult life (11). Among Ethiopian adolescents aged 11 to 18 years, a study found that 42% had vitamin D deficiency ((25 OH) D below 50 nmol/l). Of these, 61.8% lived in urban areas and 21.2% lived in rural areas (12).

Particularly the occurrence of low bone density has been recognized as a risk factor for fractures in childhood (13–15). Augmenting vitamin D status by supplementation of Vitamin D during childhood can be the vital clinical approach to maximize peak bone density in children and with this improve bone mineral density and reduce fracture risk (16). It also has a significant effect on adult fracture rates (17). Several papers recommend episodic vitamin D level testing and vitamin D supplementation in children receiving long-term anti -epileptic drugs (8,18–20). This study aimed to assess Vitamin D status among children with epilepsy on anti-epileptic drugs in Addis Ababa, Ethiopia.

MATERIALS AND METHODS

Study design and setting

The study was conducted at Tikur Anbesa Specialized Hospital, an 800-bed hospital that evaluates more than 100,000 patients annually. The hospital has 18 departments, including pediatrics, which has 180 beds for patients

aged one to 14 years. The pediatric neurology clinic is one of the clinics that sees 20 patients per day, of which 80% have follow-up visits for seizure disorders. This is cross-sectional study was carried out among patients who were on anticonvulsant treatment and were on follow up at neurologic clinic. Monthly case-load at the pediatric neurologic clinic is 320 patients, including those who came for repeated follow-up visits.

Study Period

The study was conducted over a one-year period between June 2019 and 2020.

Study Population

Our study group consisted of children aged 6 months to 16 years who had epilepsy and had been on antiepileptic drugs (AEDs) for at least six months.

Inclusion and exclusion criteria

The study included consenting pediatric patients who were on anti-epileptic drugs for the last six months at pediatric neurologic clinic The study excluded children who had medical conditions that affected bone metabolism, such as liver, kidney, metabolic, or hormonal disorders, or chronic diseases, such as cancer, diabetes, or GI tract issues, children who had moving disorders, or who took other medications that could cause neuromuscular diseases, such as Vitamin D/ Calcium supplements or corticosteroids.

Sample size and sampling technique

The sample size was calculated using the following formula and with p taken as 0.22 based on literature review in a setup with a similar context of pediatric patients on AEDs (21). Accordingly, 249 children were calculated for the current study.

$$N = \frac{Z^2 * p * (1-p)}{e^2} = \frac{1.96^2 * 0.22 * (1-0.22)}{0.05^2} \sim 264$$

However, with 14.4% of the collected data being incomplete made the sample size 226. All eligible participants, based on the inclusion and exclusion criteria, were invited to participate in the study. However, only a few parents of the patients consented to be part of the research. The lack of incentive was the main reason for the low number of participants. The study enrolled one patient per day on average until the calculated sample size was reached. A structured questionnaire, adapted from a previous study, was used for data collection (22). The quality of data collection was secured by the regular supervision of the primary investigator.

Blood sample collection procedure and measurements

We obtained 2 ml of peripheral venous blood from the participants after getting their informed consent. The pediatric nurses at the neurology clinic drew the blood using aseptic techniques. We immediately transported the blood to an outside hospital laboratory where we measured the serum 25(OH)D level.

Operational Definition

We diagnosed vitamin D deficiency when the serum 25(OH)D level was <20 ng/ml, vitamin D insufficiency when it was 20-30 ng/ml, and normal vitamin D status when it was 30-100 ng/ml (21,23).

Vitamin D Deficient Group: Defined as children with vitamin D insufficiency and deficiency.

Vitamin D Non-Deficient Group: Defined as children with a normal Vitamin D status.

Seizure: Defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (24).

Epilepsy: Defined as the clinical diagnosis requiring the occurrence of at least 1 unprovoked epileptic seizure with either a second episode or enough EEG and clinical information to convincingly demonstrate an enduring predisposition to develop recurrences (24).

Complete seizure control: Defined as complete remission of seizure for six months or more (24).

Partial seizure control: Defined as more than fifty percent reduction of frequency of seizure (24).

Poor seizure control: One or more seizure per month over period of 6 months or more and who had experienced trials of at least two different AEDs at optimum doses alone or in combination with adequate compliance (24).

Data Analysis

After data was cleaned and entered, analysis was completed using the Statistical Package for Social Sciences (SPSS) version 25. Descriptive statistics were done using frequency distribution tables, chi-square test was employed. Crude odds ratios and adjusted odds ratios with their corresponding 95% CI were calculated and a p-value of 0.05 was taken as statistically significant. Statistically significant associations were described using Odds ratio (OR) and Adjusted odds ratio (AOR) with CI for predictors deemed to be strongly associated to vitamin D status based on literature review.

Results

Sociodemographic characteristics

Of the 226 patients studied, 83 (36.7%) participants were between 5-10 years, while the other 56 patients accounting for 24.3% were in the age group of 10 - 15 years. 35.8% of the participants were between the age range of 6 months to 15 years. More than half or 138 (60.6%) of the participant were males, making the male-to-female ratio 1.5:1. Most of the study participants meaning 156 (69%), were residents of Addis Ababa (Table 1).

Table 1. Descriptive characteristics of children with seizure disorder attending follow-up at Pediatrics Neurologic Clinic in TASH, 2020.

Characteristics	**Category**	**N (%)**
Age	6 months - 5 years	81 (35.8)
	5 - 10 years	83 (36.7)
	10 - 15years	55 (24.3)
	≥ 15years	7 (3.1)
Sex	Female	89 (39.4)
	Male	137 (60.6)
Birth Order	First	122 (54)
	Second	44 (19.5)
	Third	31 (13.7)
	More	29 (12.8)
Family Size	Two	25 (11)
	Three	53 (23.5)
	Four	52 (23)
	Five	43 (19)
	Six and above	53 (23.5)
Address	Addis Ababa City	156 (69)
	Oromia Region	48 (21.2)
	Amhara Region	13 (5.8)
	SNNPR	7 (3.1)
	Others	2 (0.9)
Religion	Muslim	58 (25.7)
	Orthodox	139 (61.5)
	Catholic	3 (1.3)
	Protestant	25 (11.1)
	Other	1 (0.4)
Primary Care Giver	Mother	97 (42.9)
	Father	33 (14.6)
	Both parents	82 (36.3)
	Adult relatives	12 (5.3)
	Nonrelatives	1 (0.4)
	Orphanage	1 (0.4)
Marital Status	Single	19 (8.4)
	Married	182 (80.5)
	Divorced	21 (9.3)
	Widowed	4 (1.8)
Primary caregiver level of education	Can't read or write	13 (5.8)
	Can read or write	17 (7.5)
	Attended Grade 1 – 8	76 (33.6)
	Attended Grade 9 - 12	61 (27)
	College Level Education	59 (26.1)

Child feeding and related characteristics.
Out of the 226 mothers, 24 (10.6%) practiced breastfeeding at the time of data collection, while 157 (69.5%) had exclusively breast-fed for six months in the past.

Table 2. Child feeding and related characteristics of children with seizure disorder attending follow-up at Pediatrics Neurologic Clinic in TASH, 2020

Characteristics	Category	N (%)
Mode of child feeding at the time of data collection	Exclusive Breast Feeding	24 (10.6)
	Formula Milk	8 (3.5)
	Cow milk	7 (3.1)
	Combination of Breast and Formula Milk	8 (3.5)
	Combination of Breast and Cow Milk	5 (2.2)
	Family Diet	172 (76.1)
	Others	2 (0.9)
Historical Months of Exclusive Breast Feeding	One Month	18 (8)
	Two Months	7 (3.1)
	Three Months	24 (10.6)
	Four Months	11 (4.9)
	Five Months	9 (4)
	Six Months	157 (69.5)
Frequency of Sunlight exposure per week	One Day	28 (12.4)
	Two Days	38 (16.8)
	Three or more days	151 (66.8)
	No exposure	9 (4)
Average Duration of Sunlight exposure	Less than 20 minutes	55 (24.3)
	20 to 30 minutes	88 (38.9)
	More than 30 minutes	83 (36.7)
Use of skin Ointments	Yes	97 (42.9)
	No	129 (57.1)
Ambulation Status	Ambulating	158 (69.9)
	Not Ambulating	68 (30.1)

Serum Vitamin D level of respondents
The mean vitamin D level of the participants was 24.8 ng/mL (SD ± 12.7), and the median was 21.5 with an Interquartile range between 16.4 and 31.4, the minimum and maximum serum Vitamin-D levels determined were 3.8 ng/mL and 70ng/ml, respectively. 41.6% of participants were found to be in the deficient group. (Figure 1)

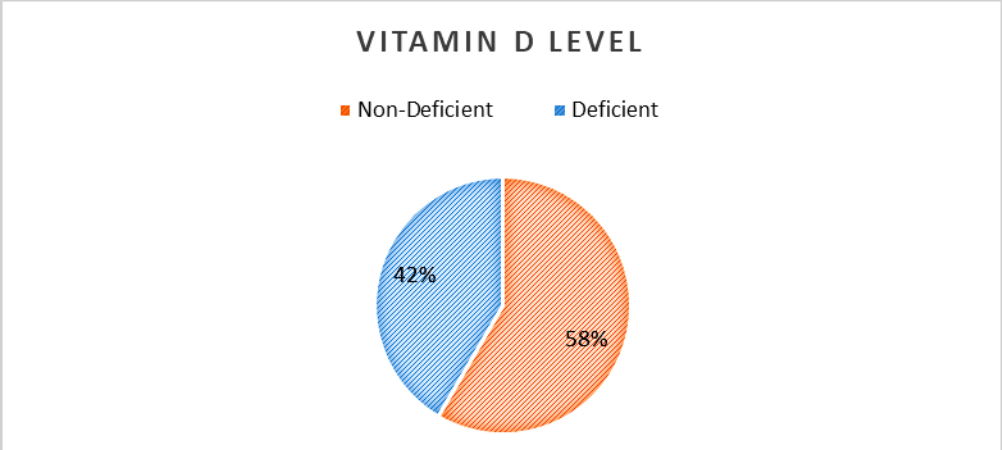

Figure 1. Results of Vitamin D level in children taking AEDs in TASH, Pediatric Neurologic Clinic August 2020

Table 3 shows that of the 89 female participants 42 (47%) were in the Vitamin D Deficient group while only 52 (38%) of the 138 male participants were in the vitamin D deficient group. Furthermore, 71 (45%) of the 156 participants from Addis Ababa were in the Vitamin D Deficient group while only 23 (33%) of the 70 participants from outside of Addis Ababa were. (Table 3)

Table 3. Comparison of Vitamin D Deficient and Non-Deficient groups of children on AEDs attending and followed at TASH, pediatric neurology clinic August 2020.

Characteristics	Category	Frequency (%)	Vitamin D status, N (%)	
			Deficient	Non-Deficient
Age	6 month-5yrs	81 (35.8)	29	52
	5-10 years	83 (36.7)	35	48
	10-15years	55 (24.3)	24	31
	>=15years	7 (3.1)	6	1
Sex	Female	89 (39.4)	42	47
	Male	138 (60.6)	52	85
Address	Addis Ababa	156 (69.0)	71	85
	Out of Addis Ababa	70 (31%)	23	47

Seizure-related information and vitamin D level

The majority of the study participant that is 146 (64.6%) had a Generalized Tonic Clonic (GTC) type of seizure while focal seizures were observed in 73 (32.3%) of the participants. Regarding the type of AEDs and vitamin D deficiency, most participants, 139 (61.5%) were on monotherapy.

As shown in Table 4, among the 146 participants who had GTC type seizure 55 (38%) were in the vitamin D deficient group. While among the 73 participants who had focal seizure 36 (49%) were in the vitamin D deficient group. Furthermore, of the 87 participants who were on polytherapy 35 (40%) were in the vitamin D deficient group. While among the 139 participants who were on monotherapy 59 (42%) were in the vitamin D deficient group.

One hundred fifty-two (67.3%) of the participants used Enzyme Inducing AEDs (EI-AEDs), and among these 67 (44%) were in the vitamin D deficient group. Of the 43 participants consuming Non-Enzyme Inducing AEDs (NEI-AEDs), 16 (37.2%) were in the vitamin D deficient group. Finally, among the 31 participants using a combination of both groups of drugs 35.5% were in the vitamin D deficient group. (Table 4)

Table 4. Seizure-related findings of children on AEDs attending and followed at TASH, pediatric neurology clinic 2020.

Characteristics	**Category**	**Frequency (%)**	**Vitamin D status, N (%)**	
			Deficient	Non-Deficient
Seizure Types	Generalized	146 (64.6)	55	91
	Focal	73 (32.3)	36	37
	Unknown onset	7 (3.1)	3	4
Number of AEDs used	Monotherapy	139 (61.5)	59	80
	Polytherapy	87 (38.5)	35	52
Address	Addis Ababa	156 (69.0)	71	85
	Out of Addis Ababa	70 (31%)	23	47
Type of AED	Enzyme Inducing AEDs	152 (67.3)	67	85
	Non-Enzyme Inducing AEDs	43 (19)	16	27
	Combination of EI-AEDs and NEI-AEDs	31 (13.7)	11	20
Seizure control	Well controlled	91 (40.3)	39	52
	Partial controlled	112 (49.6)	46	66
	Poor controlled	23 (10.2)	9	14

Vitamin D level and clinical signs

Half of the participants who were taking AEDs for more than 3 years were in the vitamin D deficient group. Majority 214 (94.7%) of participants who were in the vitamin D deficient group did not have clinical manifestation.

Table 5. Vitamin D level of children on AEDs attending and followed at TASH, pediatric neurology clinic 2020

Characteristics	**Category**	**Frequency (%)**	**Vitamin D status, N (%)**	
			Deficient	Non-Deficient
Duration of therapy	6 month-2 years	89(39.4)	31	58
	2-3 years	40(17.7)	15	25
	>3 years	97(42.9)	48	49
Clinical signs of rickets	Yes	12(5.3)	5	7
	No	214(94.7)	89	125
Signs of Rickets	Frontal bossing	2	1	1
	Wrist widening	8	3	5
	Rachitic rosary	3	1	2

Factors predicting vitamin D status.

In the bivariate and multivariable logistic regression analysis of potential risk factors of being in the vitamin D deficiency group were sex, age, number of AEDs, duration of AEDs treatment, ambulatory status, and duration of daily sun exposure showed a statistically significant association ($p < 0.04$) with being in the vitamin D deficient group. Female participants had statistically significant risk of having vitamin D deficiency ($P < 0.03$). Non ambulating participants has a higher chance of being in the vitamin D deficiency group ($P < 0.04$). The participants who received poly antiepileptic drugs had significant odds of being in the vitamin D deficiency group ($P <0.03$). A significant odd of being in the vitamin D deficiency group ($p = 0.01$) was observed in participants whose age was greater than 15 years. (Table 6)

Table 6. Results of bivariate and multivariate regression model of risk factors for being in the vitamin D deficiency group in children taking AEDs in TASH, Pediatric Neurologic Clinic 2020

Characteristics	**Category**	**COR (95% CI)**	**P - value**	**AOR (95% CI)**	**P - value**
Age	6 month - 5 years	1		1	
	5 - 10 years	1.4 (0.8 - 2.7)	0.25	0.1 (0.1 - 1.2)	0.07
	10 - 15 years	1.3 (0.7 - 2.7)	0.41	0.2 (0.1 - 1.8)	0.14
	≥ 15 years	10.8 (1.2 - 93)	0.03	2.12 (1.0 - 1.5)	0.01
Sex	Female	1.5 (0.87 - 2.5)	0.14	1.8 (1.7 - 2.6)	0.03
	Male	1		1	

Birth order	First	1		1	
	Second	2.4 (0.9 - 5.9)	0.07	1 (0.5 - 2.5)	0.85
	Third	2.6 (0.9 - 7.4)	0.07	1.3 (0.5 - 3.2)	0.63
	Fourth or more	3.3 (1.1 - 10)	0.03	0.4 (0.1 - 1.1)	0.08
Mode of Feeding	Breast milk	1		1	
	Formula milk	0.8 (0.2 - 4.4)	0.81	1.3 (0.2 - 8.3)	0.79
	Cow milk	0.4 (0.1 - 2.1)	0.26	0.2 (0.1 - 1.6)	0.13
	Breast milk and Formula milk	0.2 (0.1 - 1.2)	0.05	0.1 (0.1 - 1)	0.07
	Breast milk and Cow milk	0.3 (0.1 - 2.4)	0.28	0.3 (0.0 - 5.3)	0.43
	Family diet	0.3 (0.1 - 0.8)	0.01	0.3 (0.1 - 0.8)	0.02
	Others	****			
Month of exclusive feeding	1 month	1.5 (0.6 - 3.9)		1.1 (0.3 - 3.6)	0.86
	2 months	1.1 (0.2 - 5.0)	0.92	0.9 (0.2 - 5.5)	0.95
	3 months	0.7 (0.2 - 1.8)	0.53	0.7 (0.3-1.9)	0.49
	4 months	6.6 (1.4 - 3.6)	0.02	5.6 (4.9 - 36)	0.04
	5 months	0.7 (0.2 - 3)	0.67	1.1 (0.2 - 6.5)	0.90
	6 months	1		1	
Duration of sunlight exposure	< 20 min	2.4 (1.5 - 2.9)	0.03	0.8 (0.3 - 1.9)	0.64
	20-30 min	0.7 (0.4 - 1.2)	0.18	0.6 (0.3- 1.4)	0.24
	>30 min	1		1	
Skin ointment application	Yes	0.8 (0.5 - 1.4)	0.46	1.0 (0.5 - 1.9)	0.96
	No	1		1	
Ambulation status	Ambulating	1		1	
	Not ambulating	1.7 (0.9 - 3)	0.07	1.7 (1.8 - 3.6)	0.04
Seizure type	Generalized	1		1	
	Focal	1.5(.84-2.6)	0.17	1.6 (0.8 – 3.0)	0.19
	Unknown	1.2(.25-5.4)	0.84	2 (0.3 - 12.6)	0.43
Number of AEDs used	One	1		1	
	Two	0.9 (0.6 - 1.8)	0.97	0.4 (0.1 - 1.2)	0.09
	≥ Three	0.7 (0.2- 2.3)	0.52	0.1 (0.0 - 0.8)	0.03
Duration of therapy	6 months - 2 years	1		1	
	2 - 3 years	1 (0.5 - 2.3)	0.86	1.5 (0.6 - 3.6)	0.42
	> 3 years	1.8 (1.9 - 3.2)	0.01	1.6 (0.7 - 3.6)	0.26
AEDs based on drug generation	EI-AEDs	1		1	
	NEI-AEDs	0.9 (0.4 - 1.9)	0.85	0.9 (0.4 - 2.2)	0.86
	EI -AEDs & NEI-AEDs	0.8 (0.3 - 1.7)	0.48	0.6 (0.2 - 1.9)	0.33
AEDs based on drug combination	Monotherapy	1		1	
	Poly-therapy	1.4 (0.7 - 2.4)	0.28	4.3 (1.2 - 16)	0.03

DISCUSSION

We conducted a observational study with prospective data collection to examine the effect of anticonvulsants on vitamin D levels. We found that patients who had used anticonvulsants for more than 3 years had significantly lower vitamin D levels. Out of 226 participants, 95 had vitamin D deficiency. This prevalence was lower than that reported in India (25), but higher than that reported in Iraq and other countries (21,23,25,26). We also observed that the age group of above 15 years had the highest percentage of being in the vitamin D deficiency group. This finding was inconsistent with the studies from India (25) and Iraq (26), where the highest proportion occurred in younger age groups. Moreover, we found that the duration of antiepileptic drug use was a risk factor for poor vitamin D status.

Female sex was associated with a nearly twofold higher risk of being in the vitamin D deficiency group than male sex (AOR 1.8 and 95% CI= 1.7, 2.6). This finding was consistent with the studies in India, Iraq, Malaysia, and others (21,23,25–27), but not with Ramya's study (28). We could not explain this difference, but another study (29) reported lower vitamin D levels in healthy girls. This could be due to the less sun exposure and outdoor activities of girls than boys.

Our study agreed with Teagarden et al. (30) that patients with epilepsy who used enzyme-inducing antiepileptic drugs had higher odd of being in the vitamin D deficiency group than those who used non-enzyme-inducing antiepileptic drugs. This could be because old antiepileptic drugs induce cytochrome P450 enzymes, which alter vitamin D metabolism, while new antiepileptic drugs do not or do so minimally. Most of our patients used old antiepileptic drugs, which could explain the poorer vitamin D status.

The most common antiepileptic drugs in our study were Enzyme Inducing AEDs such as phenytoin (29%), phenobarbital (21%), sodium valproate (14.9%), and carbamazepine (3.9%). We found that phenytoin (50%), sodium valproate (35%), and phenobarbital (30.6%) were significantly associated with vitamin D deficiency. This finding differed from other studies (31–35).

Lee et al. (36) conducted a longitudinal study of 143 epileptic children who were exposed to AEDs for 2 years and found that a high proportion of them had hypovitaminosis D. Our study also revealed that having a poor vitamin D status was more prevalent among children with seizure therapy >3 years, adolescent age >15 years old, and non-ambulating status. These findings are consistent with earlier studies (25,26,37,38) .

Rauchenzauner et al (39) reported that non-enzyme inducing AEDs did not cause vitamin D deficiency in healthy children on monotherapy. Our study found that polytherapy increased the risk of a poorer vitamin D status compared to monotherapy. This finding agreed with one study (31) but disagreed with another study by Ramya et al. (28).

In our study, we found hundred forty-six patients had generalized seizures, and 74 suffered from partial seizures of these a decreased vitamin D level was observed in patients with generalized seizures. It was in agreement with the study done in India (25). In the current study, we have found that vitamin D levels ranged between 3.8, and 70 nmol/L, with a mean of 24.8 nmol/L, which was lower than the findings in the Malaysian and Australian studies (21,23).

Limitation of the study

We acknowledge some limitations of our study: we conducted it in one tertiary hospital, which may limit its generalizability and may not be representative of the national burden. We did not measure the baseline vitamin D levels before starting the treatment. We also did not consider other risk factors for vitamin D deficiency, such as dietary intake of vitamin D and calcium. Moreover, we did not distinguish between insufficiency and deficiency in our analysis, which makes our conclusion and recommendations less specific, as they require different interventions.

CONCLUSION

Poor vitamin D status including insufficiency and deficiency was found to be highly prevalent among children with epilepsy on AEDs. Almost half of the children with AEDs were at risk of poor vitamin D status. Increased duration of AEDs therapy lower daily sunlight exposure, female gender, and poor ambulation was associated with a higher risk of a poor vitamin D status. Based on this finding, the need for timely and appropriate vitamin D supplementation and periodic follow-up seems to be very evident.

Availability of data and material

The data used for analysis for the current study are available from the corresponding author.

Abbreviations

AED: Anti-epileptic Drugs

CYP450: Cytochrome P450

EI-AED: Enzyme Inducing Anti-epileptic Drugs.

GTC: Generalized Tonic Clonic Seizure

SPSS: Statistical Package for Social Sciences

TASH: Tikur Anbessa Specialized Hospital

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Ethical Clearance

The research and publication committee of the department of pediatrics and child health approved the Ethical Clearance. The ethical approval number was DRPC/008/12 and it was approved on April 23 2019. The study participant parents, and children older than 12 years

gave their informed consent and assent respectively after learning about the purpose, significance, and blood sample of the study. It is a routine practice to take a blood sample for a patient who is on an antiepileptic drug. Furthermore, the participants were informed that they had the right to opt out of the study at any time. The data collection was done anonymously, and the information was protected and confidential.

Competing interests

There is no competing interest with all authors.

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Funding was secured from the university of postgraduate program.

Authors' contributions

MM – Proposal development, and manuscript writing

AM – Data collection and analysis

MT - Advised on proposal development, oversaw study implementation, and manuscript writing.

ML – Data analysis

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