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Original Research Article

Study of vitamin D levels in pediatric patients on antiepileptic monotherapy

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ABSTRACT

Background: Epilepsy affects nearly 50 million people worldwide, with childhood onset common. Long-term antiepileptic drug (AED) therapy, including valproate (VPA), carbamazepine (CBZ), and levetiracetam (LEV), may adversely influence vitamin D metabolism, impacting bone and neurological health. With limited pediatric data and no supplementation guidelines, this study investigates the association between AED monotherapy, vitamin D status, and biochemical outcomes in children. The aim of this study is to evaluate if CBZ, VPA and LEV as monotherapy is associated with vitamin D deficiency among children with epilepsy.
Results: In 86 pediatric patients (52.3% female), VPA (43%) and CBZ (24.4%) significantly reduced Vitamin D3 to 22.7 ng/ml and calcium to 9.1 mg/dl at 6 months, while elevating ALP to 281.4 IU/L and 267.7 IU/L, respectively. LEV (32.6%) showed milder effects (28.7 ng/ml, 202.5 IU/L).
Methods: After ethics approval, children aged 5-18 years with epilepsy at Umaid/MDM Hospital were screened. Baseline serum vitamin D3, calcium, phosphate, and ALP were measured using chemiluminescence. Patients with normal vitamin D3 (>20 ng/ml) were enrolled and initiated on VPA, LEV, or CBZ, with follow-up monitoring for biochemical changes. Statistical tool used is SPSS v.22.
Conclusions: VPA and CBZ were associated with significant declines in vitamin D and calcium levels, along with elevated ALP, indicating adverse effects on bone health in pediatric epilepsy patients. LEV showed comparatively milder effects. Routine monitoring and proactive management of bone health are crucial for all children on long-term AED therapy.

Keywords: Antiepileptic drug, Vitamin D levels, Monotherapy, Alkaline phosphatase, Pediatric epilepsy patients, Levetiracetam

INTRODUCTION

A seizure is a transient event caused by abnormal, excessive, or synchronous neuronal activity in the brain.[1] Epilepsy is defined as a predisposition to generate seizures with associated neurobiological, cognitive, psychological, and social consequences. Diagnosis generally requires at least one unprovoked seizure with recurrence or EEG/clinical evidence of predisposition. Globally, about 50 million people live with epilepsy (0.5% burden). In developing nations, prevalence may reach 10/1,000 children, with nearly half of all cases beginning in childhood.[2]

AEDs such as CBZ, VPA, phenytoin, LEV, and phenobarbitone are widely used. They are classified into

10 groups: barbiturates, deoxybarbiturates, benzodiazepines, succinimides, hydantoins, iminostibenes, aliphatic carboxylic acids, phenyltriazines, cyclic GABA analogues, and newer AEDs.[1] Long-term therapy is often necessary but may cause adverse effects such as gingival hyperplasia, osteomalacia, marrow toxicity, hepatotoxicity, nephrotoxicity, teratogenicity, and altered vitamin D metabolism.[3]

Vitamin D, a pro-hormone, regulates calcium and phosphorus balance, supports immunity, cell growth, and cancer prevention. It protects neurons against oxidative stress, aids brain development, modulates mood via serotonin, supports cognition, and regulates neurotransmission through calcium homeostasis. Serum 25-hydroxyvitamin D (25-OH D) is the main marker; levels <20 ng/ml indicate deficiency, which impairs bone mineralization and increases fracture risk.[4] Indian populations generally have suboptimal vitamin D compared to US guidelines.[5]

Although VPA, lamotrigine, and oxcarbazepine are considered to have minimal enzyme-inducing effects, studies show VPA may induce CYP3A4 and CYP24A1, promoting vitamin D catabolism.[6] Data on newer AEDs (gabapentin, lamotrigine, oxcarbazepine, LEV, lacosamide, etc.) and vitamin D in children remain limited. LEV is favored for efficacy and tolerability. No clear guidelines exist for vitamin D supplementation in children on AEDs; in India it is uncommon, and in the UK, only 3% of pediatric neurologists use prophylactic supplementation.[7]

This study aims to evaluate whether CBZ, VPA, and LEV monotherapies are linked to vitamin D deficiency in epileptic children.

METHODS

Type of study

It was a prospective observational study.

Place of study

The study conducted at department of pediatrics, Dr. S. N. medical college, Jodhpur, Rajasthan (Umaid/MDM Hospital).

Population

Children aged 5-18 years with epilepsy, normal serum vitamin D levels, initiated on monotherapy (CBZ/VPA/LEV), recruited from OPD, Wards, PICU, and neuroclinic.

Study duration

Total duration of the study was 6months from start of the study

Inclusion criteria

Children aged 5-18 years with epilepsy (diagnosed by ILAE), normal serum vitamin D (>20 ng/mL), started on monotherapy (VAL/LEV/CBZ) were included in the study.

Exclusion criteria

Children with prior AED use, multiple/other AEDs, recent vitamin D supplements, glucocorticoids, malnutrition, CKD/CLD, rickets, hypoparathyroidism, or non-ambulatory due to neurological/orthopedic disorders were excluded from the study.

Vitamin D3 interpretation

D3 levels in blood refers to<12 ng/mL=deficiency; 12-20 ng/mL=insufficiency; >20 ng/mL=sufficient.

Sample size

Sample size was calculated using formula $N=z^2\alpha/2\ P(100-P)/d^2$, with Z=1.96, P=68%, α=95%, d=allowable error, giving required sample size of 86 patients.

Procedure

Ethics approval obtained, informed consent taken, baseline serum vit. D3, calcium, phosphate, alkaline phosphatase, renal function tested via chemiluminescence, and only children with normal vit. D included.

Follow-up

At 3 months compliance was assessed with repeat labs, and at 6 months final labs were repeated and results analyzed.

Ethical approval obtained

Participants informed of rights, voluntary participation, confidentiality, withdrawal option; data collected, analyzed, and securely stored.

Statistical tool

SPSS v.22 was used for statistics.

RESULTS

The study (n=86) showed 48.8% <10 years, 32.6% aged 10-13, and 18.6% ≥14; females 52.3%, males 47.7%. Vitamin D3 was highest with CBZ (31.1), lowest at 6 months with CBZ / VPA (22.7, $p<0.001$). ALP peaked in VPA (281.4, $p<0.001$). Vitamin D insufficiency was 14.3% (<10), 28.6% (10-13), 12.5% (≥14), and higher with VPA use.

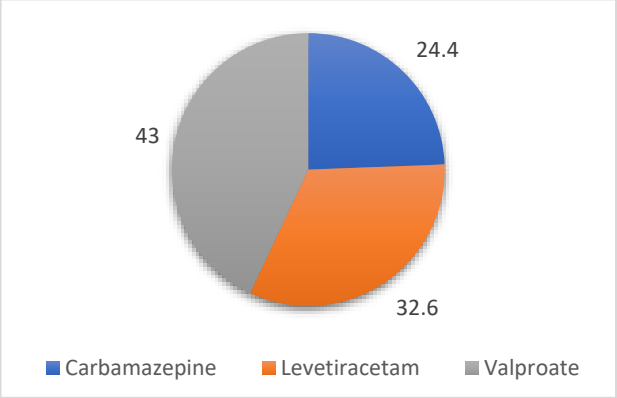

Figure 1: Distribution of patients according to type of AEDs used (n=86).

The use of AEDs among the patients showed that 43% were on VPA, 32.6% on LEV, and 24.4% on CBZ. This distribution reflects a preference for VPA and LEV, which may be due to their effectiveness or side effect profiles in this patient population.

Younger patients (<10 years) mostly received LEV (71.4%), while ages 10-13 predominantly used VPA (54.1%). For ≥14 years, CBZ (42.9%) was most common. Overall, AED prescription varied significantly with age, showing a strong association between patient age and drug choice (p<0.001).

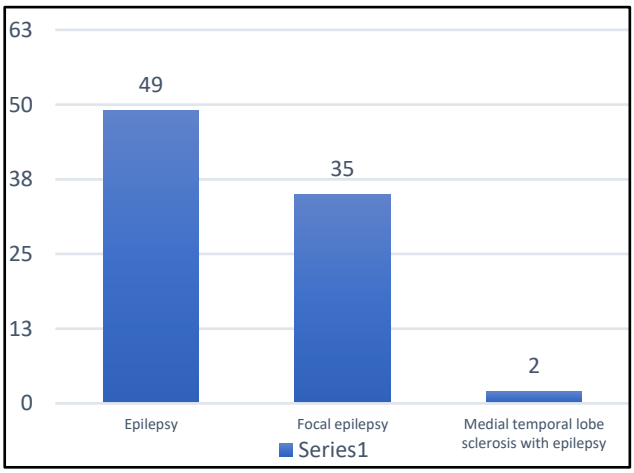

Figure 2: Distribution of patients according to diagnosis, (n=86).

In the cohort, 57% were diagnosed with epilepsy, 40.7% with focal epilepsy, and 2.3% with medial temporal lobe sclerosis with epilepsy.

Table 1: Distribution of patients according to type of AED used as per their age, (n=86).

Age groups (in years)	CBZ, n=21	LEV, n=28	VPA, n=37	Chi-square value	P value
<10	10 (47.6%)	20 (71.4%)	12 (32.4%)	23.842	<0.001
10-13	2 (9.5%)	6 (21.5%)	20 (54.1%)		
14+	9 (42.9%)	2 (7.1%)	5 (12.5%)		
Total	21 (100%)	28 (100%)	37 (100%)		

Table 2: Change of with the laboratory parameter measurement at presentation and 6 months, (n=86).

Variables	CBZ			LEV			VPA		
	Presentation	3 months	6 months	Presentation	3 months	6 months	Presentation	3 months	6 months
Vit D3 (ng/ml)	31.1± 2.7	27.1± 3.3	22.7± 4.3	29.3± 5.3	29.1± 5.1	28.7± 5.1	29.5± 5.1	26.3± 4.9	22.7± 4.9
P value	<0.001*			0.213			<0.001*		
Serum calcium (mg/dl)	9.9± 0.4	9.6± 0.3	9.1± 0.4	9.8± 0.3	9.7± 0.3	9.6± 0.4	10.1± 0.4	9.6± 0.4	9.1± 0.6
P value	0.011*			0.001*			0.001*		
Serum phosphorus (mg/dl)	4.1± 0.4	4.1± 0.4	4.1± 0.4	3.9± 0.4	3.9± 0.2	3.8± 0.2	4.0± 0.4	4.0± 0.4	4.0± 0.4
P value	1			0.842			1		
ALP (IU/L)	220.8± 77.9	234.8± 84.9	267.7± 78.9	190.1± 57.3	195.9± 60.7	202.5± 55.4	255.2± 67.7	233.7± 71.3	281.4± 68.6
P value	0.001*			<0.001*			<0.001*		

*P value significant.

Vitamin D3 declined with CBZ (31.1→27.1→22.7 ng/ml, p<0.001) and VPA (29.5→26.3→22.7, p<0.001), but stable with LEV (29.3→29.1→28.7). Serum calcium decreased with CBZ (9.9→9.6→9.1, p=0.011) and VPA (10.1→9.6→9.1, p<0.001). Phosphorus remained stable (4.1, 3.9–3.8, 4.0). ALP increased notably with VPA (255.2→233.7→281.4, p<0.001) and CBZ (220.8→234.8→267.7, p=0.001), less with LEV (190.1→195.9→202.5).

DISCUSSION

In our study, VPA (43%) was most used, followed by LEV (32.6%) and CBZ (24.4%). Durá-travé et al found VPA (59) prescribed more than LEV (31), with deficiencies 24.1% and 35.5%.[8] Chaudhuri et al reported VPA deficiency 45% and CBZ 27%.[9]

In our study, 57% had epilepsy, 40.7% focal epilepsy, and 2.3% medial temporal lobe sclerosis. Nearly half (48.8%) were under 10 years. Abdullah et al reported mean age 7.57±3.62 years with 56% well-controlled cases, while Sreedharan et al observed median age 8.6 years on monotherapy.[10,11]

In our study, 57% had epilepsy, 40.7% focal epilepsy, and 2.3% medial temporal lobe sclerosis. Distribution mirrored Abdullah et al who reported 82% generalized and 18% partial seizures.[10]

General examination showed 24.5% with pallor, without icterus, cyanosis, or edema, suggesting a possible association between pallor and epilepsy requiring further research.

Study showed significant reductions in vitamin d3 and calcium with elevated alp in VPA and CBZ users over six months. Durá-travé et al reported lower calcium and 25-hydroxyvitamin d levels in VPA users (mean 22.7 ng/ml) with deficiency risks.[8] Chaudhuri et al similarly found 45% deficiency and elevated alp in these groups.[9]

Our study found no significant association between sex and vitamin D levels at six months. Among females, 17.8% had levels <20 ng/ml, 62.2% between 20-30 ng/ml, and 20% between 31-70 ng/ml, while in males, the corresponding values were 19.5%, 70.7%, and 9.8%, respectively. Multivariate logistic regression confirmed the non-significant relationship between sex and vitamin D levels. Similar findings were reported by Sreedharan et al, Iragamreddy et al and Vijayakumar et al all of whom observed vitamin D deficiency among pediatric epilepsy patients without significant gender differences.[11-13]

Overall, children on antiepileptic monotherapy, particularly VPA and CBZ, exhibit reduced vitamin D3 and calcium levels with elevated ALP over time, underscoring the importance of regular bone health monitoring irrespective of age or sex.

Limitations

This study has limitation, including a small sample size, absence of a healthy control group, and lack of data on confounders such as diet, sun exposure, and physical activity. Its observational design also limits causal interpretation. Larger, controlled, and longitudinal studies are required to better understand the effects of AED therapy on vitamin D status and the bone health in children.

CONCLUSION

This study assessed AED monotherapy effects on pediatric bone health. VPA and CBZ caused significant reductions in vitamin D and calcium with elevated ALP, while LEV showed milder effects. Vitamin D deficiency was more prevalent in VPA and CBZ users. Age and sex had minimal influence, highlighting the need for routine monitoring to prevent long-term complications in children on AED therapy.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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