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Effect of Anti-Seizure Medication Monotherapy on Vitamin D Levels in Indian Children: A Longitudinal Cohort Study

Shatrishna Behera, MD[1], Devendra Mishra, MD[1], Bhawna Mahajan, MD[2], Mukta Mantan, MD[1], Shubham Bansal, MD[1]

[1]Department of Pediatrics, Maulana Azad Medical College & Associated Lok Nayak Hospital, Delhi; [2]Department of Biochemistry, GB Pant Institute of Medical Education and Research, Maulana Azad Medical College, Delhi, India

Background and Purpose: The timeline of alteration of vitamin D and calcium levels in those receiving anti-seizure medication (ASM) remains to be elucidated. To determine the changes in vitamin D levels over a period of 6 months among children receiving monotherapy with commonly used ASM.

Methods: The baseline serum levels of vitamin D, parathyroid hormone (PTH), calcium, alkaline phosphatase (ALP), phosphorus were measured in 32 children (median age 8 years) with newly diagnosed epilepsy. An appropriate ASM monotherapy was started. Those found to be deficient were treated with vitamin D supplementation. Children were reassessed after 90 days and 180 days for drug compliance and drug side-effects. All the baseline investigations were repeated.

Results: At baseline, 21.9% of children were vitamin D-deficient, with a median serum level of 19.8 ng/mL. For children who were not vitamin D-deficient (VDD) at baseline (n=25), the median (interquartile range [IQR]) vitamin D levels were found to be significantly lower than baseline after 90 days of ASM use (23.0 [18.0 to 28.9] vs. 22.0 [12.0 to 24.0]; p<0.001). After 90 days, ASMs caused notable decreases in vitamin D levels from baseline for children who were not VDD at baseline (n=25) (23.0 [18.0 to 28.9] vs. 22.0 [12.0 to 24.0]; p<0.001), alongside changes in calcium, phosphorus, PTH and ALP levels. Similarly, in children who were non-deficient at 90 days follow-up (n=20), median (IQR) vitamin D levels were found to be significantly lower at 180 days than at 90 days (24.5 [21.0 to 28.9] vs. 18.4 [13.6 to 20.6]; p<0.001).

Conclusions: The study noted vitamin D deficiency in children on ASM monotherapy for 3-6 months, emphasizing regular monitoring by clinicians. **(2024;14:73-80)**

Key words: Calcium, Epilepsy, Vitamin D, Antiepileptic drugs

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Corresponding author:
Shubham Bansal, MD
Department of Pediatrics, Maulana Azad Medical College & Associated Lok Nayak Hospital, Delhi 110002, India
Tel. +91-9013946483
Fax. +91-11-23231438
E-mail; drshubhambansal94@gmail.com

Introduction

Epilepsy is the most frequent chronic neurologic condition in children affecting 0.5% to 1% of children all over the world.[1] The prevalence of epilepsy in children is reported to range from 3.2 to 5.5 per 1,000 in developed countries and 3.6 to 44 per 1,000 in underdeveloped countries.[2] One out of 150 children is diagnosed with epilepsy during the first 10 years of life.[1] In India, the prevalence rate for epilepsy in children (1-18 years) is 6.24 per 1,000 population.[3]

Vitamin D is an essential nutrient that maintains the homeostasis of calcium and phosphorous levels in the body. Vitamin D is involved in cell-differentiation and proliferation, immune function, and the prevention and treatment of certain cancers, autoimmune and infectious diseases. A constellation of beneficial effects of vitamin D and calcium observed over the years has made a major impact on health, growth, and development of infants, children, adolescents, and adults. Severe deficiency results in rickets in children and osteomalacia in adults. There are multiple reasons for hypo-vitaminosis D identified in children like nutritional, renal diseases, lack of sun exposure, and drugs like anti-seizure medication (ASM).[4]

First reports on interference of ASM with calcium, phosphorus and vitamin D metabolism emerged about five decades ago.[5] Research over the years has reported the association of vitamin D deficiency (VDD) in pediatric patients with epilepsy on ASM.[6-8] Despite this in-

formation, no uniform recommendations exist regarding the need for prophylaxis with vitamin D in the various epilepsy management guidelines. It is also not clear after what duration of antiepileptic therapy does VDD occur [6] and when does it manifest. Moreover, there is limited Indian data on longitudinal changes in vitamin D levels with antiepileptic drugs usage among children with epilepsy.

The pathogenesis associated with antiepileptic drugs and bone mineral disorder is multi-factorial and despite the advances in understanding the underlying mechanisms, the exact mechanisms are still unknown. Most commonly known association is that enzyme-inducing anticonvulsant drugs induce hepatic cytochrome P450 oxidase. Evidence suggests the main mechanism proposed is conversion of vitamin D3 into its polar inactive metabolites by the hepatic microsomal system.[9,10] Both enzyme inducing and non-enzyme inducing AEDs contribute to bone loss by direct inhibition of cation absorption from the intestine, inhibition of calcitonin secretion and inhibition of osteoblast cell growth.[9,10]

Pregnane X receptor (PXR) shares similarity in its structure with vitamin D receptor, and induces CYP24A expression. AEDs like phenytoin, phenobarbital, carbamazepine activate PXR and valproate is an inducer of this catabolic enzyme, which metabolizes active vitamin D3 into inactive products by hydroxylation at 24th position, thereby reducing its biological activity.[9]

We conducted this study to observe the longitudinal changes in vitamin D levels among children with epilepsy receiving antiepileptic monotherapy.

Methods

This descriptive cohort study was conducted in the Department of Pediatrics, of a referral public hospital in New Delhi, India after clearance from the Institutional Ethics Committee. The study site is at latitude 28.70° N. The study population included children aged 5-12 years with an episode of seizures, attending the outpatient or inpatient services of the department during the study duration.

Study subjects were eligible if they fulfilled the definition of epilepsy as per International League Against Epilepsy (ILAE) 2017 classification.[11] Among those included in the study, children with any of the following conditions were excluded: 1) known chronic renal or liver conditions; 2) those receiving or having received steroids or a ketogenic diet within the last 3 months, or likely to receive them during the study duration; 3) non-ambulatory children and/or children receiving tube feeding; or 4) children already diagnosed with rickets or hypocalcemia.

The study was conducted from April, 2017 to April, 2018; the last subject was enrolled on 17 October, 2017. Children with unprovoked seizures came either to pediatric emergency or to the outpatient department, and all the patients were managed as per a standard protocol. Once the seizures settled and the patient was comfortable, we approached the parents and the child and assessed them for eligibility for enrolment. Children not fulfilling the inclusion criteria were informed about the study, and the contents of the patient and parent information sheets were shared. Written informed consent was taken from parents/caregivers of eligible children. Assent was also taken from those 7 years and older.

After the participant was enrolled, a detailed medical history and clinical examination were conducted for all children, and the information was entered in the structured study proforma. Weight was recorded with minimal clothing to nearest 100 g using an electronic weighing machine. Height was recorded to the nearest 0.1 cm using a stadiometer. Body mass index was calculated using the standard formula. Sun exposure was estimated by calculating the ultraviolet light (UV) score,[12] which is determined by multiplying duration of exposure (in minutes) spent outdoors each day during the period of direct sunlight and the total body surface area (using the Lund and Browder[13] charts) exposed while wearing the routine clothing as minutes/m^2/day. UV exposure assessments was limited to baseline measurements only, as it was only considered as a baseline variable. It was not measured subsequently, as we did not expect any changes in it over the study duration, given the absence of any health education regarding the matter.

All the patients were treated for underlying epilepsy as per the decision of the treating physician. Seizures were classified based on parental description and/or any observed seizure according to ILAE-2017 classification[11] and epilepsy type was also classified as per ILAE-2017 classification. Antiepileptic drugs used for treatment were entered in the proforma. Working diagnosis was made based on history and clinical examination which was modified with further investigations (neuroimaging, electroencephalography, etc.) during follow-up.

Three milliliter of venous blood sample was withdrawn at enrollment for baseline biochemical assessments (serum calcium, ionized calcium, serum phosphate, alkaline phosphate [ALP], 25 hydroxyvitamin D [25(OH) vitamin D], and parathyroid hormone [PTH] levels). After separation of serum, vitamin D and PTH levels were determined by electrochemoluminescence on a Cobas E411 analyzer (Roche Diagnostic, Indianapolis, IN ,USA). Ionic calcium was measured by direct ion se-

lective electrode (ISE method). Phosphate was measured by photometric assay using molybdate UV, and ALP using ALP buffer method photometrically on Roche Cobas system (Roche Diagnostic).

We defined VDD when serum vitamin D levels were below 15 ng/mL, insufficiency between 15-19.9 ng/mL and sufficiency above 20 ng/mL, as per the institute of medicine guidelines.[14] Children found to be vitamin D-deficient were treated according to global consensus recommendations,[15] which included an intramuscular injection of 100,000 IU of vitamin D3, followed by oral vitamin D3 at 400 IU once daily, and an oral syrup containing calcium and vitamin D3 (5 mL=250 mg elemental calcium and 125 IU vitamin D3) twice daily for 90 days. No further supplementation was given.

Follow-up

The study subjects were followed up in the outpatient clinics as per the appointments given at the time of enrolment. Those missing the follow-up date were contacted telephonically, and appointment was re-scheduled on a convenient date within 1 week of the missed date. At 90±7 and 180±7 days, another 3 mL venous sample was withdrawn, and a similar analysis as at baseline was performed, with the results recorded. Treatment for VDD was similar to that used at baseline. The primary outcome of the study was a change in the vitamin D levels in comparison to baseline serum vitamin D levels over the follow-up period of 6 months.

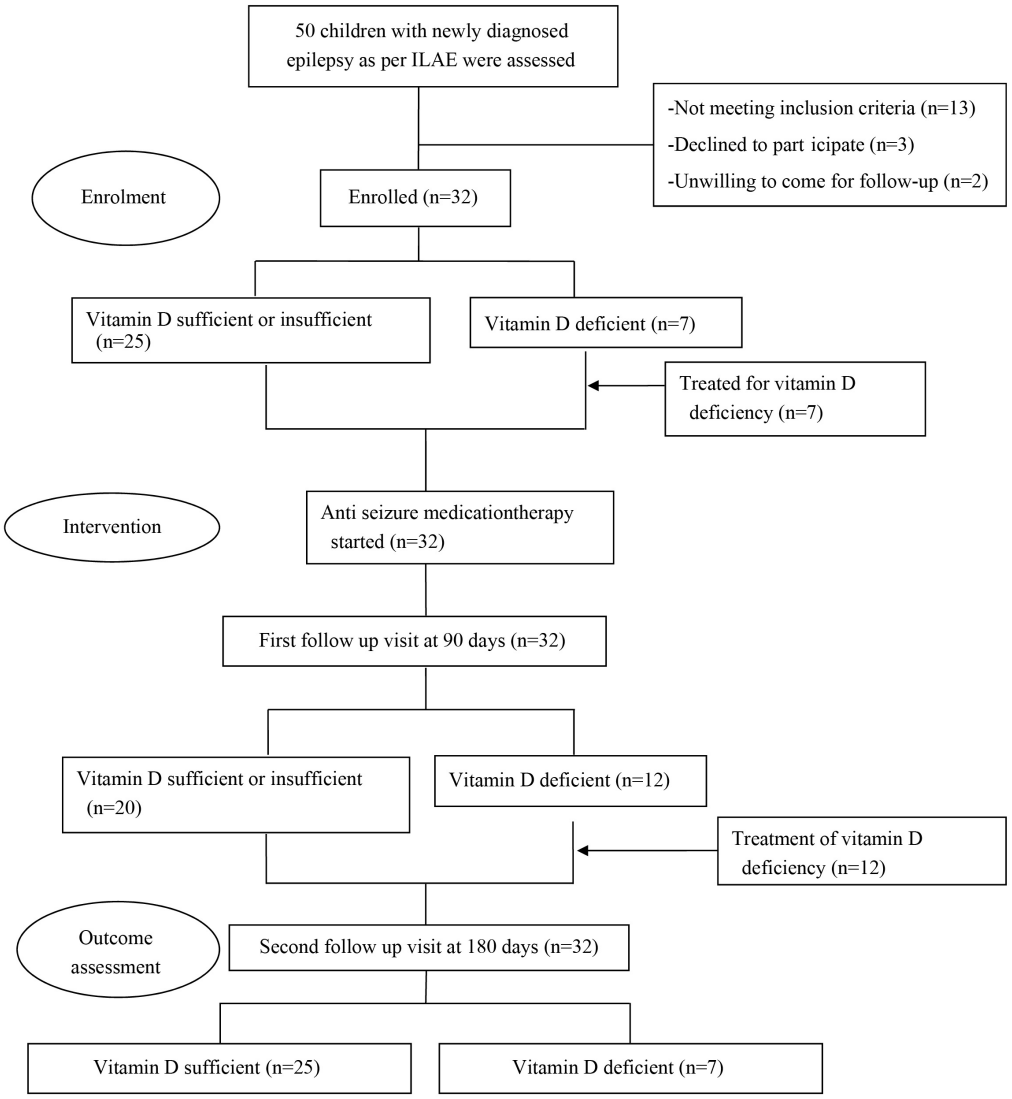

Figure 1. Study flow-chart. ILAE, International League Against Epilepsy.

Sample size

A previous study in children showed a fall of mean (standard deviation [SD]) vitamin D levels from 31.1 ng/mL (14.7) to 20.2 ng/mL (14.9) after a mean (SD) anti-seizure medication usage of 1.8 years (0.8).[6] To detect a similar difference between baseline and follow-up values with a sensitivity of 95% and power of 80%, a sample size of 29 is needed at baseline and follow-up. As we expected a 10% loss to follow-up, we enrolled 32 patients in the study.

Statistical analysis

The data was coded and entered into Microsoft Excel spreadsheet and rechecked for discrepancies. A test of normality was performed for vitamin D levels at baseline and at each follow-up. As the distribution was non-normal, we have used non-parametric tests for comparison. We used the Social Science Statistics online software (http://www.socscistatistics.com/) for carrying out the statistical analysis. Values of continuous variables (serum vitamin D levels, parathyroid hormone levels, etc. before and after ASM use) were com-

Table 1. Baseline characteristics of the study participants (n=32)

Characteristic	Value
Age (years)	8.0 (6.0 to 10.2)
Males	17 (53.1)
Weight (kg)	20.0 (16.1 to 25.1)
Z score	-0.2 (-1.0 to 0.74)
Height (cm)	125.9 (111.4 to 130.2)
Z score	0.2 (-0.8 to 0.6)
BMI (kg/m^2)	13.9 (12.5 to 15.2)
Z score	0.0 (-0.9 to 0.9)
Vitamin D (ng/mL)	19.8 (15.0 to 28.0)
Vitamin D status	
Sufficient (≥20 ng/mL)	16 (50.0)
Insufficient (15.0-19.9 ng/mL)	9 (28.1)
Deficient (<15 ng/mL)	7 (21.9)
Parathyroid hormone (pg/mL)	17.9 (9.0 to 30.6)
Total calcium (mg/dL)	9.1 (8.5 to 9.5)
Serum phosphorus (mg/dL)	4.9 (4.6 to 5.3)
Alkaline phosphatase (U/L)	229.5 (181.2 to 262.0)

Values are presented as median (interquartile range) or number (%).

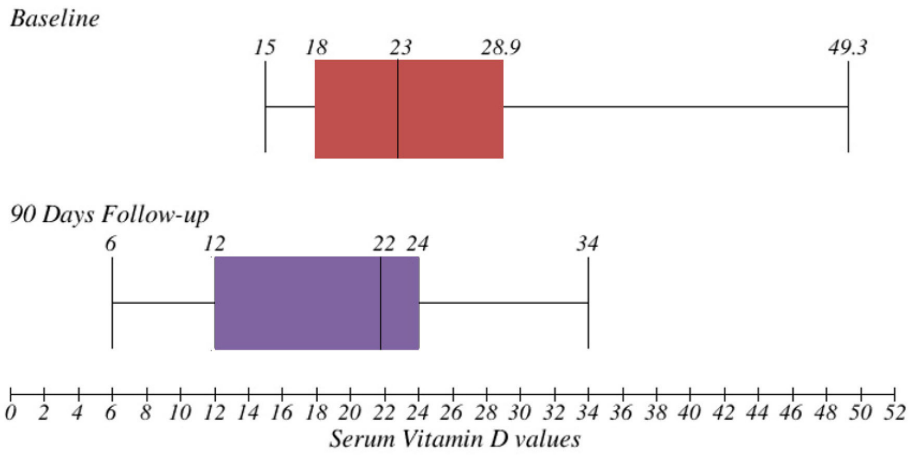

Figure 2. Box-plot showing baseline and day-90 serum vitamin D values in children who were non-deficient at baseline.

pared with Wilcoxon signed-rank test. Categorical variables (e.g., proportion of children with hypocalcemia and hypovitaminosis D) were compared using the McNemar test.

Results

During the study period, we assessed consecutive patient cohort of 50 children for eligibility for enrolment. Among them, 13 children did not meet the inclusion criteria, parents of three children declined to participate in the study, and remaining two parents expressed their inability to come for follow-up visits due to long distance involved in travel. There was no child fulfilling any of the exclusion criteria. Thus, a total of 32 patients were enrolled in the study. They were followed-up on a 3-weekly basis over a period of 180 days. All the children who were enrolled completed their 180 days follow-up. The study flow chart is depicted in Fig. 1. The baseline variables of the study population are shown in Table 1.

The sun exposure was calculated at baseline by estimating the UV score. The median (interquartile range [IQR]) UV score was 10.9 (9.6 to 15.3), and it was higher among non-deficient children than for vitamin D-deficient children at baseline (12.24 [10.5 to 15.8] vs. 5.8 [5.4 to 10.1]; p=0.002]. Focal seizures were seen in 14 (43.8%). ASM used in the study were valproate 21 (65.6%), phenytoin seven (21.9%), and carbamazepine four (12.5%). All the patients were on monotherapy throughout the study period. The doses of antiepileptic drugs were increased in nine children during the study period for better control of seizures, and the drugs were changed in four children (changed to carbamazepine).

All the 32 children enrolled in our study at baseline were re-tested for biochemical variables at 90±7 days follow-up visit. When median values at baseline and 90 days were compared, it was observed there was a decline in vitamin D, total calcium and phosphorus levels, and an increase was seen in PTH and alkaline phosphatase level. The data was further analyzed after excluding those who received vitamin D supplementation (deficient; n=7), and the median (IQR) vitamin D levels were found to be significantly lower than baseline after 90 days of antiepileptic drug use (23.0 [18.0 to 28.9] vs. 22.0 [12.0 to 24.0]; p<0.001) (Fig. 2). Similarly, in children who were non-deficient at 90 days follow-up (n=20), comparing median vitamin D values at 90 days and 180 days showed a significant reduction (24.5 [21.0 to 28.9] vs. 18.4 [13.6 to 20.6]; p<0.001) (Table 2, Figs. 2, 3).

VDD was noted in seven children (21.9%) at baseline, but after 90

Table 2. Change in biochemical parameters of the children at 180 days (n=32)

Parameter (normal range)	Baseline	90 days	180 days
Vitamin D (15-50 ng/mL)	19.8 (15.0 to 28.0)	19.6 (12.7 to 25.8)	21.4 (16.5 to 34.8)
PTH (15-65 pg/mL)	17.9 (9.0 to 30.6)	23.7 (8.5 to 34.3)	17.1 (6.2 to 30.8)
Total calcium (8.8-10.8 mg/dL)	9.1 (8.5 to 9.5)	8.9 (8.7 to 9.5)	9.2 (9.0 to 9.5)
Serum phosphorus (3.3-5.4 mg/dL)	4.9 (4.6 to 5.3)	4.8 (4.5 to 5.2)	5 (4.5 to 5.4)
Alkaline phosphatase (100-320 U/L)	229.5 (181.2 to 262.0)	256.0 (232.3 to 284.5)	278.5 (234.3 to 325.8)

Values are presented as median (interquartile range).
PTH, parathyroid hormone.

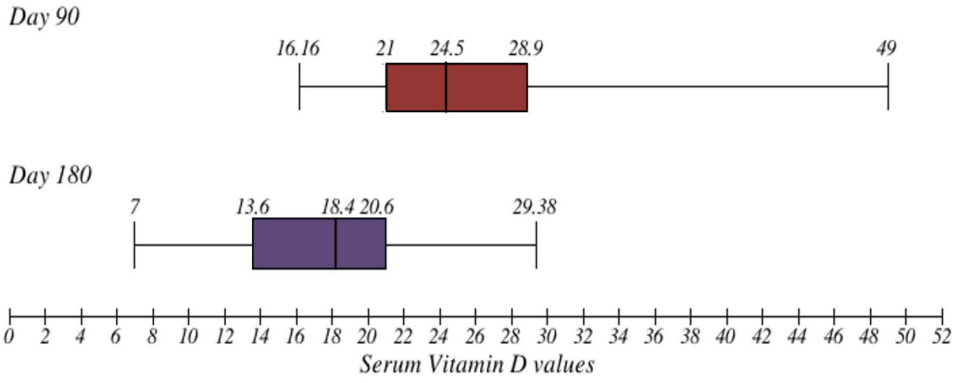

Figure 3. Box-plot showing day-180 serum vitamin D values in children who were non-deficient at day-90.

days of ASM, vitamin deficiency was noted in 12 children (37.5%) (Table 3). Moreover, of the 16 patients who had sufficient vitamin D at baseline, four (25.0%) were deficient and two (12.5%) had become insufficient in their vitamin D levels after 90 days of ASM (Table 3). Of the nine children who were in the insufficient vitamin D category at baseline, seven (77.8%) had become vitamin D-deficient after 90 days of ASM (Table 3). Of the 16 children who were in the sufficient group at 90 days, 25% became deficient at 180 days follow-up, whereas three (75.0%) of the four insufficient children became deficient over the same period (Table 4, Fig. 4). A total of 25 children were treated for VDD during the study period: seven (21.9%) at baseline, 12 (37.5%) after 90 days of ASM use, and seven after 180 days of ASM use. One child had to be treated twice for deficiency, with documented normalization of vitamin D levels after the second dose. None of our study subjects reported any side-effects due to vitamin D.

Table 3. Vitamin D status of the study population at 90 days follow-up visit (n=32)

Baseline vitamin D status	Vitamin D status at 90 days		
	Sufficient	Insufficient	Deficient
Sufficient (n=16)	10 (62.5)	2 (12.5)	4 (25.0)
Insufficient (n=9)	0 (0.0)	2 (22.2)	7 (77.8)
Deficient (n=7)*	6 (85.7)	0 (0.0)	1 (14.3)
	16 (50.0)	4 (12.5)	12 (37.5)

Values are presented as number (%).
*Received megadose vitamin D at baseline and oral vitamin D and calcium for 90 days.

Table 4. Vitamin D status of study participants at 90 days and 180 days (n=32)

90 days	180 days		
	Sufficient	Insufficient	Deficient
Sufficient (n=16)	8 (50.0)	4 (25.0)	4 (25.0)
Insufficient (n=4)	0 (0.0)	1 (25.0)	3 (75.0)
Deficient (n=12)*	12 (100.0)	0 (0.0)	0 (0.0)

Values are presented as number (%).
*Received mega-dose vitamin D at 90 days and oral vitamin D+calcium for 3 months.

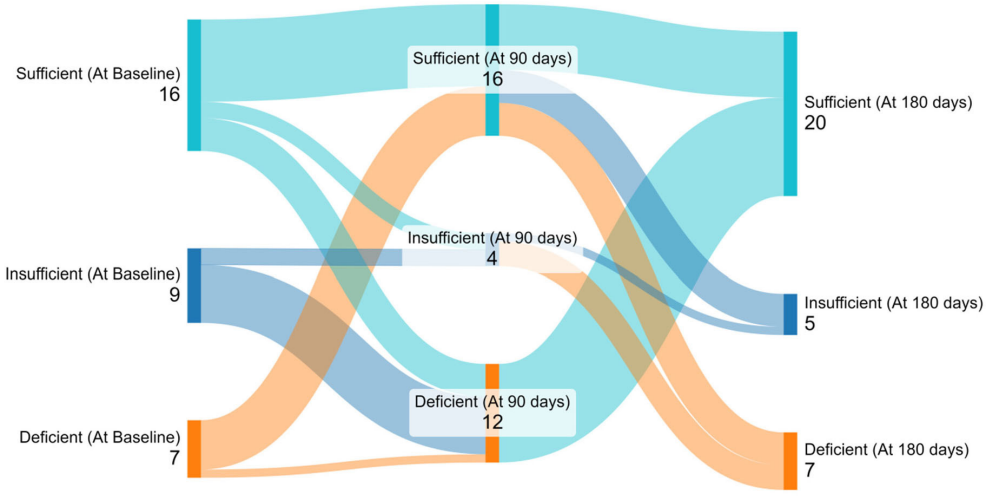

Figure 4. Sankey chart showing vitamin D status at baseline, at day-90 & at day-180.

Discussion

On prospectively following 32 drug-naïve children started on ASM in a tropical country setting, serum vitamin D levels were noted to decrease at 90 days and 180 days follow-up in those who were non-deficient at baseline. From among those who were non-deficient at baseline, 72% (18/25) developed hypo-vitaminosis D during the 180 days of ASM therapy.

We found 50% of the study children to be vitamin D-sufficient (≥20 ng/mL) at enrolment, with median serum values of 19.2 ng/mL. Vitamin D status similar to our study was reported from a hospital-based cross-sectional study which involves children of 1-16 years old, who visited the outpatient clinics of a teaching trust hospital of Kolkata, India.[16] They found 53% of the children to be vitamin D-deficient, and the median (IQR) serum 25(OH) vitamin D were also similar at 19 ng/mL (11 to 28). Misra et al.[17] also reported lower baseline vitamin D levels in pediatric epilepsy patients (n=47) from Delhi, India. The mean age was 6.72±2.22 years SD (mean serum vitamin D, 14.45 ng/mL). Some studies have shown the prevalence of VDD in the pediatric epilepsy population in tropical countries like Malaysia and Thailand to vary from 22.5% to 23.2%.[18,19] These studies enrolled children of age 1-19 years. This matches with the proportion of 21.9% seen in the epileptic children in our study.

Although, studies detailing vitamin D levels in patients of epilepsy abound, very few have followed newly diagnosed pediatric epilepsy longitudinally and measured vitamin D levels.[6,17] Misra et al.[17] measured baseline serum vitamin D, calcium, PTH and alkaline phosphatase levels in 47 drug-naïve pediatric patients with focal epilepsy and followed them longitudinally for a period of 6 months. Vitamin D levels reduced significantly over the 6 months of carbamazepine therapy in the 32 that were evaluated.[17] The mean PTH and serum alkaline phosphatase values also increased after 6 months of ASM, which is similar to our findings after 3 months of ASM. Lee et al.[6] enrolled 143 epileptic children and followed them for a mean follow-up duration of 1.8 years (0.8) and measured their vitamin D levels at the start of therapy and 6 to 12 monthly for a period of 2 years. Similar to our findings, they showed a significant decline in vitamin D levels and increase in proportion of children who were vitamin D-deficient. However, as they had not treated the vitamin D-deficient patients identified at baseline, it is difficult to compare our results with them.

At 180 days out of all the non-deficient children at baseline, 56% became vitamin D-deficient at one point or the other during the course of ASM treatment of 6 months. Lee and Yu[8] in their study of 198 epileptic children found 54.4% of vitamin D-replete participants to become vitamin D-deficient after an ASM therapy of 2 years. However, as the mean vitamin D levels at baseline were higher (39.5 ng/mL) in that study compared to ours (23.0 ng/mL), the reason for this difference is not clear, even though multiple studies have shown that up to 64% children in India have insufficient vitamin D levels. A recent multi-centric community study showed the mean (SD) vitamin D concentration was 18.32 ng/mL (9.56).[20] However, the course of vitamin D-deficient children in the two studies is similar, with decrease in vitamin D levels and increase in proportion of vitamin D-deficient children. In another pediatric study, over a mean follow-up of 1.8 years of ASM therapy, the proportion of vitamin D deficient children significantly increased from 20.3% to 61.5% among 143 drug-naïve children.[6] Even though, none of the previous studies have provided separate data for children with insufficient levels of vitamin D (15-19.9 ng/mL) at baseline, we found 3/4th of such children to develop VDD after 3 months of ASM use, which is expected in line with the reduction in vitamin D levels noted with ASM use.

Our study has certain limitations; not all participants in the study received the same antiepileptic drug, and since various drugs have different actions on vitamin D levels,[9,10,21] this could have affected our results. Moreover, due to the side-effects experienced by some of the participants, ASM had to be changed midway during the study. However, all children were on monotherapy with the commonly used pediatric antiepileptic drugs, which is a strength of the study, as ASM polytherapy is itself a risk factor for VDD.[6] For ease of statistical analysis, their data was combined with those with sufficient levels, which may make our findings less reliable, though this was done due to the small numbers in this group.

Sun-exposure of participants was assessed calculating a UV light score,[22] rather than a solarimeter/UV dosimeter, which has been shown to have a better reliability.[23,24] We did not consider changes in sun exposure subsequent to AED medication, which directly affects vitamin D levels, potentially constituting a limitation of the study. We did not physically check for the remaining tablets/syrup with the participant to confirm compliance with the ASM and/or the calcium and vitamin D prescribed; however, we did verify drug compliance verbally with each participant's family at each follow-up.

The major strength of our study is that it is a prospective follow-up study without any loss to follow-up, measuring the longitudinal change in serum markers of VDD. We treated all VDD patients identified during the study, which was both ethically justified and likely to be more closely reflecting the actual situation in clinical practice. An

estimation of baseline vitamin D levels was done in all patients, which has been a shortcoming in many of the previous cross-sectional studies. Similarly, most previous studies have compared vitamin D status in children with varying duration of exposure to ASM, which was not done in this study where drug-naïve patients were enrolled at baseline. We measured UV exposure data at baseline and excluded non-ambulatory children and those with motor disabilities to ensure a relatively homogenous participant group for the study, minimizing any factors that may affect the vitamin D levels.

This descriptive cohort study found VDD in a high proportion of vitamin D-replete ambulant children receiving anti-epileptic drug monotherapy over a period of 3 to 6 months. Given the important role of vitamin D in bone health, the study results indicate that clinicians managing pediatric epilepsy should consider measuring vitamin D status at baseline and repeat screening after 3-6 months for these children. Those diagnosed to be deficient should be treated as per standard management guidelines. Further, possibility of routine vitamin D supplementation for those receiving ASM may be considered, if these results are confirmed by larger studies in different settings.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Statement

Ethical clearance was taken from the IEC of MAM College (No. 2016/113 dated 04.11.2016).

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