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Original Research Article

Vitamin D Levels in Children on Antiseizure Medications: A Comparative Study of Monotherapy and Polytherapy

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Abstract:

Background: Epilepsy is a common chronic neurological disorder in children requiring long-term antiseizure medication (ASM) therapy. While ASMs are essential for seizure control, they may adversely affect vitamin D metabolism, thereby impacting bone health. Evidence regarding the comparative effect of monotherapy versus polytherapy on vitamin D levels in children remains limited, particularly in the Indian context.

Objectives: To assess serum vitamin D levels in children with epilepsy receiving ASM therapy and to compare the prevalence of deficiency between those on monotherapy and polytherapy.

Methods: A hospital-based cross-sectional study was conducted at a tertiary care center in Kerala over 18 months. Sixty-five children (aged 1–18 years) with epilepsy, on ASMs for at least six months, were enrolled. Demographic data, seizure history, and treatment details were recorded. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured and classified according to Indian Academy of Pediatrics guidelines. Comparative analyses between monotherapy and polytherapy groups were performed using appropriate statistical tests.

Results: Of the 65 participants, 60% (n=39) were on monotherapy and 40% (n=26) on polytherapy. Median serum vitamin D levels were higher in the monotherapy group (30.60 ng/mL, IQR: 22.00–44.70) than in the polytherapy group (25.75 ng/mL, IQR: 15.45–43.50), though this difference was not statistically significant (P = 0.194). However, vitamin D deficiency was significantly more common in the polytherapy group (42.3%) compared to the monotherapy group (12.8%) (P = 0.007). Among drug regimens, the Valproate + Carbamazepine combination was associated with the lowest median vitamin D levels (16.80 ng/mL, P = 0.009), while Valproate + Levetiracetam was associated with the highest levels (46.80 ng/mL).

Conclusion: Vitamin D deficiency is common among children with epilepsy, with significantly higher prevalence in those receiving polytherapy compared to monotherapy. These findings emphasize the need for routine monitoring of vitamin D levels and consideration of preventive supplementation, especially in patients on multidrug regimens or enzyme-inducing ASMs.

Keywords: Epilepsy, Antiseizure medications, Vitamin D deficiency, Monotherapy, Polytherapy, Pediatrics.

Introduction

Epilepsy is the most common chronic neurological disorder in children, affecting approximately 0.5% to 1% of the pediatric population worldwide [1]. It is characterized by recurrent, unprovoked seizures resulting from abnormal neuronal activity in the brain and can have significant impacts on a child's physical, cognitive, and psychosocial development. The reported prevalence of epilepsy in children varies considerably across regions, ranging from 3.2 to 5.5 per 1,000 in developed countries and from 3.6 to 44 per 1,000 in underdeveloped countries [2]. One in every 150 children is diagnosed with epilepsy within the first decade of life. In India, the prevalence among children aged 1 to 18 years is estimated at 6.24 per 1,000 population [3]. Such epidemiological variations are influenced by differences in diagnostic facilities, socioeconomic factors, healthcare access, and underlying etiological patterns. Understanding the burden of epilepsy in children is crucial for planning effective preventive strategies, early diagnosis, and appropriate management to improve long-term outcomes. Vitamin D is an essential nutrient that plays a pivotal role in maintaining calcium and phosphorus homeostasis in the human body. Beyond its classical functions in bone mineralization, vitamin D is involved in cellular differentiation and proliferation, modulation of immune function, and the prevention or mitigation of certain cancers, autoimmune disorders, and infectious diseases. Over the years, the combined benefits

of vitamin D and calcium have demonstrated significant impacts on the health, growth, and development of individuals across all age groups, from infancy to adulthood. Severe vitamin D deficiency manifests as rickets in children and osteomalacia in adults, both associated with impaired bone mineralization. In children, multiple factors contribute to hypovitaminosis D, including nutritional inadequacies, chronic kidney disease, limited sun exposure, and the use of certain medications such as anti-seizure medications (ASMs) [4]. Recognition of these risk factors is essential for timely prevention and management to reduce long-term morbidity.

The potential interference of anti-seizure medications with calcium, phosphorus, and vitamin D metabolism was first reported approximately five decades ago [5]. Since then, multiple studies have demonstrated an association between vitamin D deficiency (VDD) and pediatric epilepsy patients receiving long-term ASM therapy [6,7]. Despite this evidence, no uniform recommendations currently exist in epilepsy management guidelines regarding prophylactic vitamin D supplementation. Furthermore, uncertainties remain about the exact duration of ASM therapy after which VDD develops and the timeframe in which clinical manifestations appear. Data from India on the longitudinal changes in vitamin D levels among children with epilepsy on ASM are particularly scarce. Addressing these gaps is essential for informing clinical practice and optimizing bone health outcomes in this vulnerable population.

The Indian Council of Medical Research (ICMR) recommends vitamin D supplementation of 400 IU/day for populations with minimal sun exposure; however, no specific guidelines exist for individuals at higher risk of vitamin D deficiency [8]. Few studies have assessed vitamin D status in children receiving a ASDs, and even fewer have compared vitamin D levels in children on ASD monotherapy versus polytherapy. In India, routine supplementation of calcium or vitamin D for children on ASDs is not standard practice. Similarly, in the United Kingdom, only 3% of pediatric neurologists were reported to prescribe prophylactic calcium and vitamin D to children on anticonvulsants [9]. Given this gap in practice and evidence, the present study aims to assess serum 25-hydroxyvitamin D [25(OH)D] levels in children with epilepsy on ASM therapy and to compare levels between those receiving monotherapy and polytherapy.

Material & Methods

Study Setting: This study will be conducted in the Department of Paediatrics, and the Department of Developmental Paediatrics & Child Neurology, Malankara Orthodox Syrian Church Medical College Hospital Kolenchery.

Study Duration: The study will span a period of 1.5 years, commencing after obtaining clearance from the Institutional Review Board and Ethics Committee.

Study Population: The study population will comprise children aged 1 year to 18 years diagnosed with epilepsy, who have been on either monotherapy or polytherapy with ASMs for a minimum duration of six months. Monotherapy is defined as treatment with a single ASDs, while polytherapy refers to treatment involving two or more ASDs.

Sampling Technique

A consecutive sampling method will be employed. All patients who meet the eligibility criteria during the study period will be recruited.

Sample Size: Based on a proportion of 0.61 from a previous study by Sreelharan et al., the calculated sample size was 61; to account for potential dropouts or rounding, the final sample size used in the study was 65.

Study Design: This is a hospital-based cross-sectional study conducted at Malankara Orthodox Syrian Church Medical College Hospital, Kolenchery.

Inclusion Criteria: Children aged 1 year to 18 years who have been diagnosed with epilepsy and are on ASMs for a duration of at least six months will be included in the study. Epilepsy is defined as per the ILAE 2014 criteria: (1) two unprovoked (or reflex) seizures occurring more than 24 hours apart, (2) one unprovoked (or reflex) seizure with a high risk (≥60%) of recurrence over the next 10 years, or (3) a diagnosis of an epilepsy syndrome.

Exclusion Criteria: Children with the presence of systemic disorders such as hepatic, skeletal, renal, endocrine conditions, or malabsorption syndromes will be excluded. Additionally, those who have taken vitamin D supplements in the past six months or are on chronic medications (for more than one month) known to affect bone metabolism—such as bisphosphonates or glucocorticoids—will also be excluded from the study.

Study Tool: Data was collected using a structured data collection proforma designed specifically for the study.

Data Collection: The collected data covered several key domains: Demographic information (age, gender, and skin pigmentation); Anthropometric measurements (weight, height, and body mass index [BMI]); Epilepsy history (type and duration of epilepsy, seizure frequency per month, antiepileptic drugs used, and duration of therapy); Lifestyle factors (physical activity, average daily sunlight exposure, and dietary history); and Physical examination findings, including vital signs, anthropometric measurements, and clinical signs of vitamin D deficiency such as widened wrists, rickety rosary,

delayed closure of fontanelles, frontal bossing, chest and leg deformities (e.g., genu varum, genu valgum), kyphoscoliosis, and signs of hypocalcemia. Serum vitamin D levels were interpreted according to the Indian Academy of Pediatrics (IAP) guidelines: Normal levels are >20 ng/mL, Insufficient levels range from 12 to 20 ng/mL, and Deficient levels are <12 ng/mL. For the purpose of this study, vitamin D deficiency was defined as levels <20 ng/mL, and insufficiency was defined as levels between 21–30 ng/mL.

Data Analysis: Data was coded and entered into Microsoft Excel, then rechecked and analyzed using SPSS version 22. The normality of distribution was assessed using the Shapiro-Wilk test. For quantitative variables, data was summarized using the mean ± standard deviation (SD) if the distribution was normal, or the median and interquartile range if the distribution was non-normal.

Categorical variables were represented using frequency and percentage. The following statistical tests were used: the Mann-Whitney U test and Kruskal-Wallis test to test differences in means between groups (non-parametric tests); the Pearson Chi-square test and Fisher's Exact test to compare categorical variables between groups; and binary logistic regression to identify independent factors associated with vitamin D deficiency. A p-value of <0.05 was considered statistically significant.

Results

A total of 65 children were included in the study. Of these, males comprised the majority, accounting for 60% (n=39), while females represented 40% (n=26).

Age Distribution: The age distribution of study participants is shown in Table 1. The largest group consisted of children older than 5 years (58.5%, n=38). The next most common group was 3–4 years (15.4%, n=10), followed by 2–3 years (9.2%, n=6) and 4–5 years (9.2%, n=6). The smallest category was 1–2 years (7.7%, n=5). This indicates that the majority of participants belonged to the older age group.

Table 1: Age group distribution of study subjects (N=65)

Age Range	Frequency (n)	%
1–2 years	5	7.7
2–3 years	6	9.2
3–4 years	10	15.4
4–5 years	6	9.2
>5 years	38	58.5

Antiseizure Medication Use: The distribution of antiseizure medications is illustrated in Figure 1. Valproate (Valparin) was the most frequently prescribed (70.8%, n=40), followed by Carbamazepine (38.5%, n=25) and Levetiracetam (24.6%, n=16). Other medications—including Clobazam, Zonisamide, Lacosamide, and Topiramate—were used in much smaller proportions (1.5–3.1%). These results suggest a strong preference for Valproate and Carbamazepine in clinical practice.

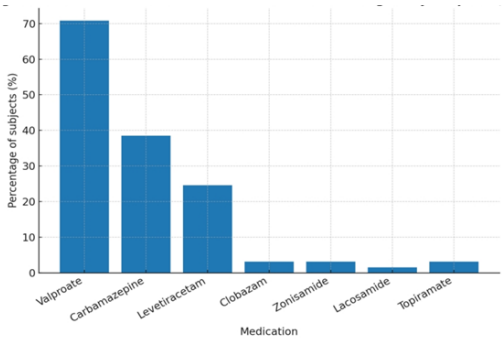

Figure 1: Distribution of antiseizure medications among study subjects (N=65)

Monotherapy vs. Polytherapy: As shown in Figure 2, 60% of children were on monotherapy, while 40% received polytherapy, indicating that single-drug therapy was the predominant approach.

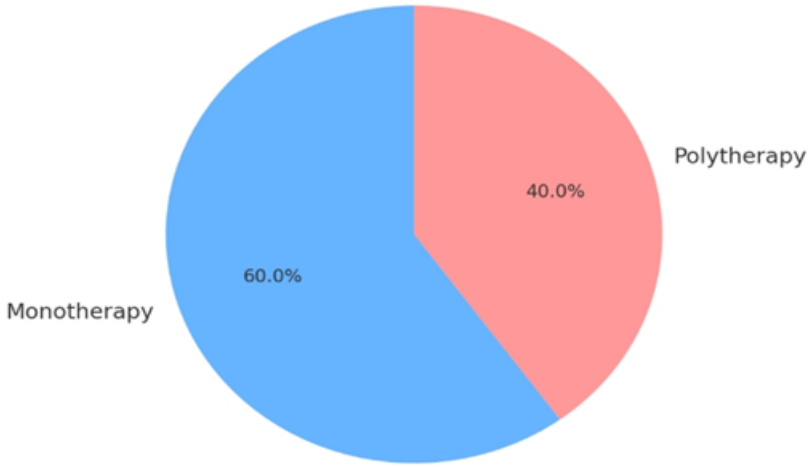

Figure 2: Proportion of children on monotherapy and polytherapy

Vitamin D Levels: Monotherapy vs. Polytherapy: Comparison of serum vitamin D levels between groups is summarized in Table 2. The median vitamin D level was higher in the monotherapy group (30.60 ng/mL, IQR: 22.00–44.70) compared to the polytherapy group (25.75 ng/mL, IQR: 15.45–43.50). However, the difference was not statistically significant (P = 0.194). This suggests that the number of antiseizure drugs used may not independently influence vitamin D levels, with other factors (drug type, duration of therapy, diet) likely contributing.

Table 2: Serum vitamin D levels in monotherapy vs. polytherapy groups

Number of ASDs	Median Serum Vitamin D (IQR)	P value
Monotherapy	30.60 (22.00–44.70)	0.194
Polytherapy	25.75 (15.45–43.50)	

Vitamin D Deficiency in polytherapy and monotherapy with antiseizure medications: The association between polytherapy and monotherapy with antiseizure medications and vitamin D deficiency is presented in Table 3. Among monotherapy patients, only 12.8% (n=5/39) had deficiency, while 87.2% (n=34/39) had normal levels. In contrast, 42.3% (n=11/26) of polytherapy patients were deficient, with 57.7% (n=15/26) maintaining normal levels. This difference was statistically significant (P = 0.007), indicating that polytherapy is associated with a higher risk of vitamin D deficiency.

Table 3: Association of therapy type with vitamin D deficiency

Number of ASDs	Vitamin D Deficiency (n=16)	Vitamin D Normal (n=49)	P value
Monotherapy	5 (12.8%)	34 (87.2%)	0.007
Polytherapy	11 (42.3%)	15 (57.7%)	

Drug-Specific Associations: Figure 3 illustrates the relationship between individual antiseizure drugs and vitamin D levels.

Among monotherapy regimens (Valproate, Carbamazepine, Levetiracetam), median vitamin D levels ranged between 27.40–31.20 ng/mL, with no significant differences observed. Non-Carbamazepine users had the highest levels (31.20 ng/mL). However, combination therapy revealed notable differences. The Valproate + Carbamazepine regimen showed the lowest median vitamin D level (16.80 ng/mL, P = 0.009), indicating a significant reduction. In contrast, the Valproate + Levetiracetam combination was associated with the highest vitamin D levels (46.80 ng/mL), suggesting a potential protective effect. These findings indicate that polytherapy, especially regimens involving enzyme-inducing drugs like Carbamazepine, significantly increases the risk of vitamin D deficiency. This underscores the need for regular monitoring and supplementation in children receiving such therapies to prevent long-term complications.

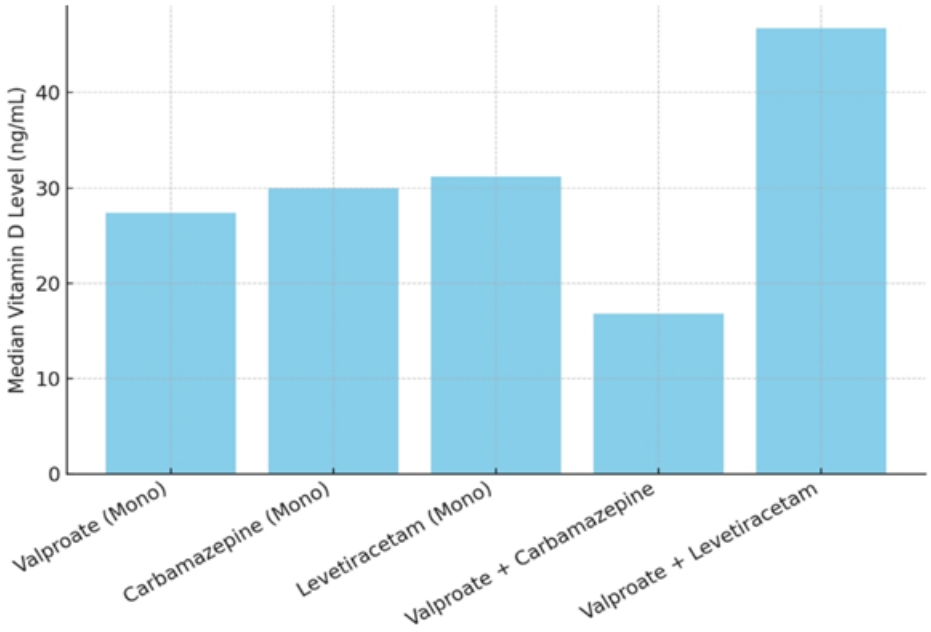

Figure 3: Association between antiseizure drug regimens and serum vitamin D levels

Discussion

The relationship between antiseizure medications (ASMs) and vitamin D status in children has been widely studied, with evidence showing variable results depending on patient populations, drug regimens, and study designs. Our findings, which demonstrate a higher prevalence of vitamin D deficiency among children on polytherapy compared to monotherapy, are in line with many recent reports, though some earlier studies have presented contrasting observations.

Bilge et al. (2025) from Turkey highlighted that both the type and number of ASMs significantly influenced vitamin D levels in pediatric epilepsy patients. Children on monotherapy had higher concentrations compared to those on combined therapy, and a clear dose-dependent relationship was evident: vitamin D levels progressively decreased with two or more ASMs. These findings emphasize that polytherapy is a major risk factor for deficiency and support preventive supplementation, consistent with our results [10].

Behera et al. (2024) demonstrated that even monotherapy leads to a progressive decline in vitamin D levels over time, with reductions occurring as early as 3–6 months after treatment initiation. Alterations in calcium, phosphorus, parathyroid hormone, and ALP levels reinforced the impact of ASMs on bone metabolism. Although polytherapy was not assessed, this study highlights the early and sustained effects of ASM exposure [11]. Varghese et al. (2024) from Kerala showed that nearly half of patients developed adverse drug reactions, the majority of whom were on monotherapy. This underscores that even single-drug regimens carry risks, reinforcing the need for close monitoring regardless of the number of medications prescribed [12]. Bezboruah et al. (2023) from Assam reported Valproate as the most frequently prescribed ASM, with a significant proportion of vitamin D deficiency noted in children receiving Valproate alone or in combination. Importantly, polytherapy was associated with significantly lower vitamin D levels than monotherapy, and treatment duration further influenced deficiency rates [13].

Similarly, Gunavan et al. (2023) from Indonesia demonstrated a markedly higher prevalence of deficiency among children on polytherapy (53%) compared to monotherapy (13%), further confirming the adverse impact of multidrug regimens on bone health [14]. Fathima et al. (2021) from Tamil Nadu found both deficiency and insufficiency to be more prevalent among children receiving long-term ASM therapy compared to controls. Polytherapy was associated with a significantly higher prevalence of deficiency than monotherapy (16% vs. 4%). Their observation that over 40% of children on ASMs had insufficient vitamin D despite medical supervision highlights the need for routine biochemical monitoring and supplementation [15]. Azad et al. (2020) from Chandigarh, however, did not observe significant differences in vitamin D deficiency prevalence between monotherapy and polytherapy groups (53% vs. 51.5%, p=0.79). This contrasts with many later studies and suggests that the cumulative metabolic effects of ASMs may vary with geographic, dietary, or lifestyle factors [16]. Nagarjunakonda et al. (2015) from Andhra Pradesh also failed to show a clear association between ASM use and vitamin D deficiency.

They reported a high prevalence of deficiency in both epileptic and non-epileptic groups, suggesting

that environmental and lifestyle factors such as limited sun exposure, sedentary habits, and poor diet may play a dominant role in determining vitamin D status [17]. Taken together, more recent studies consistently demonstrate that polytherapy significantly increases the risk of vitamin D deficiency in children with epilepsy, while earlier studies reported mixed findings.

Our results add to the growing body of evidence highlighting the cumulative and dose-dependent effects of ASMs, particularly in multidrug regimens. These findings underscore the importance of routine monitoring and preventive supplementation in children with epilepsy, with special attention to those on polytherapy.

Conclusion

This study showed that vitamin D deficiency is common among children with epilepsy. Although vitamin D levels were lower in those receiving polytherapy compared to monotherapy, the difference in distribution was not statistically.

These discrepancies may be attributed to variations in geographic location, sunlight exposure, dietary patterns, sample size, and treatment regimens. Nevertheless, the trend toward lower vitamin D status in children on multiple antiseizure medications supports concerns raised in previous studies.

Recommendations

- Routine screening of vitamin D status should be incorporated into the management of pediatric epilepsy patients, particularly those on long-term or multiple ASMs.
- Preventive supplementation should be considered to maintain adequate vitamin D levels and minimize the risk of bone health complications.
- Awareness programs for caregivers and clinicians should emphasize the importance of vitamin D monitoring in epilepsy care.
- Further multicenter, longitudinal studies are recommended to better define the relationship between ASM use and vitamin D metabolism across different populations and to establish evidence-based supplementation protocols.

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