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# Vitamin D Levels in Children Aged 1-12 Years on Anti Epileptic Drugs

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**A B S T R A C T**

Vitamin D is an essential nutrient which has pivotal role in calcium homeostasis. bone mineral metabolism and fundamental biological functions. Also vitamin D is known to have anti epileptogenic activity and hence its deficiency in children with seizure disorder is associated with difficulty in seizure control. It has been postulated that AEDs result in low vitamin D levels by varying mechanisms. Our study aims to find out the relation between AEDs and vitamin D levels.

**OBJECTIVES**

1. To estimate the levels of vitamin D in children on Antiepileptic drugs.
2. To study the associated risk factors of vitamin D deficiency in children on Antiepileptic drugs.

**MATERIALS AND METHODS:** A cross sectional study done in 100 children aged 1-12 years on AEDs for >1 year. Vitamin D levels along with type of AEDs used were assessed. Vitamin D deficiency classified according to U S Endocrine society classification.

**RESULTS:** Vitamin D deficiency was found in 74 %, 15% had insufficiency and 11 % had sufficiency. Patient on Monotherapy 84% and polytherapy 16 % although not associated with vitamin D deficiency. Vitamin D deficiency associated with longer duration of anticonvulsant, shorter seizure free period, developmental delay, increased BMI.

**CONCLUSIONS:** Vitamin D deficiency was prevalent (74%) among our study subjects on antiepileptic drugs. It was observed that vitamin D deficiency was significantly associated with duration of antiepileptic, seizure free period, BMI and developmental delay.

Vitamin D deficiency in our study was found in both enzyme inducing and non enzyme inducing antiepileptic drug usage.

**Keywords:** Vitamin D, Anti Epileptic Drugs, Bone Health, Epilepsy, Bmi.

## INTRODUCTION

Epilepsy is a common neurological disorder which involves all ages and is most prevalent non-communicable diseases of the world with incidence of which is 3% in lifetime, more than half of which occur in childhood.[1,2] Seizure is transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain whereas epilepsy as defined by International League Against Epilepsy(ILEA), is at least two unprovoked seizures occurring greater than 24 hours apart.

A number of medications are used in the treatment of seizure disorder. The association between vitamin D, anti epileptic drugs and bone health has been recognised for more than 30 years.[3] Anti epileptic drugs (AEDs) are exert deleterious effect on vitamin D metabolism.[4] The side-effects involve changes in homocysteine, lipoproteins and vitamin D metabolism.[5] vitamin D is known to have anti epileptogenic activity and hence its deficiency in children with seizure disorder is associated with difficulty in seizure control and risk for mechanical injury, including fractures; and the poor bone health.

A limited number of studies on association of vitamin D levels in children with antiepileptic therapy is reported and hence the controversy of this association in paediatric age group still remains unsolved.

This study was done to estimate the levels of vitamin D and the associated risk factors in children between 1-12 years of age on Antiepileptic drugs.

## MATERIALS AND METHODS

It was a Hospital based cross sectional study from 1st January 2018 to 31st December 2018 on Children aged between 1 to 12 years with seizure disorder on antiepileptics attending the paediatric outpatient department, Karnataka Institute Of Medical Sciences Hubli were the study population.

**INCLUSION CRITERIA:** Children aged between 1 to 12 years with seizure disorder on antiepileptics for at least more than 1 year .

**EXCLUSION CRITERIA:**

- Children with known metabolic bone disease.
- Children on irregular treatment of antiepileptics.
- Children on vitamin D supplements.
- Children with significant renal, hepatic impairment and endocrine disorders.

**METHODOLOGY:** Ethical clearance was obtained from the Institutional Ethics Committee. Children who fulfil the inclusion/exclusion criteria for the study were selected.Informed and written consent was obtained from the parents. Detailed demographic data, clinical history including indication of antiepileptic treatment, age at initiation of antiepileptic therapy, number and type of antiepileptic drugs used, duration of seizure free period, developmental history and general physical examination including anthropomentary including of all the enrolled cases were recorded on a structured proforma. Details of previous investigation like EEG and neuroimaging was also noted. All enrolled children were subjected for assessment of vitamin D, calcium, phosphorous and ALP levels. 4ml of peripheral venous blood was collected in plain bulb, sample was sent for estimation of vitamin D, calcium (Ca), phosphorus (P), alkaline phosphatase (ALP). **Estimation of 25 OH Vitamin D levels** was done by fully automated chemiluminescent immunoassay technology, vitamin D total test is analyzed on ADVIA centaur, standardised against ID-LC/MS/MS, as per Vitamin D Standardization Program(VDSP).

Data analysis was done by using SPSS 20 VERSION software.

Percentage, mean, standard deviation, chi-square and p values were calculated using this software. **chi-square test** was used as test of significance for qualitative data **Karl-Pearson correlation** was done to find the correlation between two quantitative variables. p value of **<0.05** was taken to denote statistically significant relationship.

## RESULTS

A total of 100 children in the age group between 1-12 years on antiepileptic drugs were studied those befitting the inclusion and exclusion criteria.

In this study 56 (56%) of children were on AED from 1-3years, 38 (38%) of children on AED from 4-6years and 6( 6%) of children were taking AED for>7 years, the mean duration of AED treatment was found to be 3.52 ± 1.94.

**Table No. 1: Duration of AEDS (years) wise distribution in study population.**

| Duration of AEDS | Number | Percent |
|---|---|---|
| 1-3yrs | 56 | 56.00 |
| 4-6yrs | 38 | 38.00 |
| >7yrs | 6 | 6.00 |
| Total | 100 | 100.00 |
| Mean | 3.52 | |
| SD | 1.94 | |

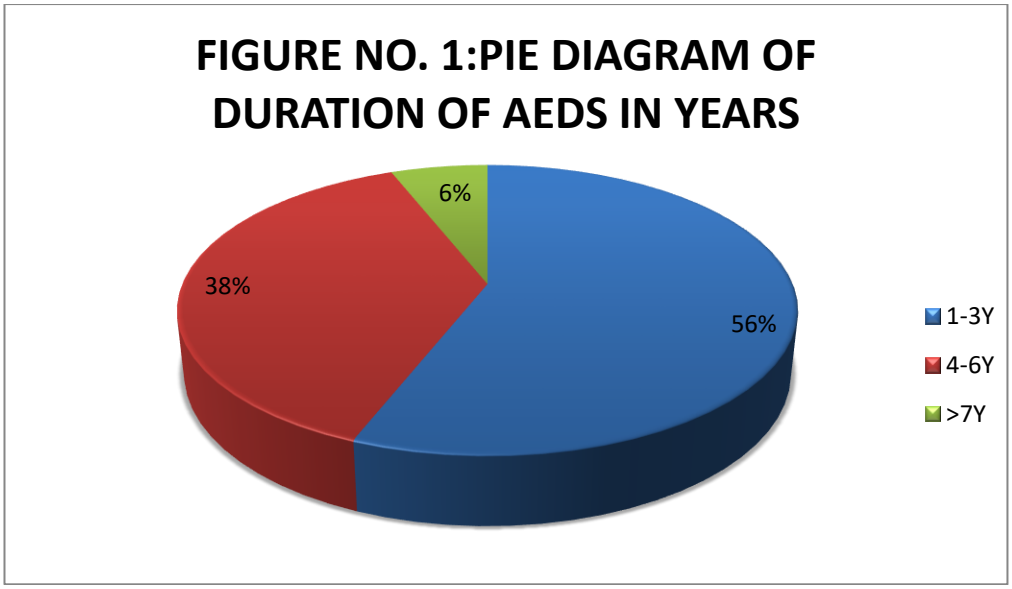



Figure No . 1: PIE DIAGRAM OF DURATION OF AEDS IN YEARS

In our study, it was found that sodium valproate is the commonly used drug, 73 cases were on valproate ,the next commonly used drugs were phenobarbitone and phenytoin. 15 cases were on phenobarbitone, 15 were on phenytoin, 8 cases on clobazam,5 on carbamazepine and the least commonly used drug was found to be levitacetam, out of 100 cases only 3 cases were on levitracetam.

**Table No.2: Type of AED wise distribution in study population**

| Type of AED | Number | Percent |
|---|---|---|
| SODIUM VALPROATE | 73 | 73.00 |
| PHENOBARBITONE | 15 | 15.00 |
| PHENYTOIN | 15 | 15.00 |
| CARBAMAZEPINE | 5 | 5.00 |
| LEVITRACETAM | 3 | 3.00 |
| CLOBAZAM | 8 | 8.00 |

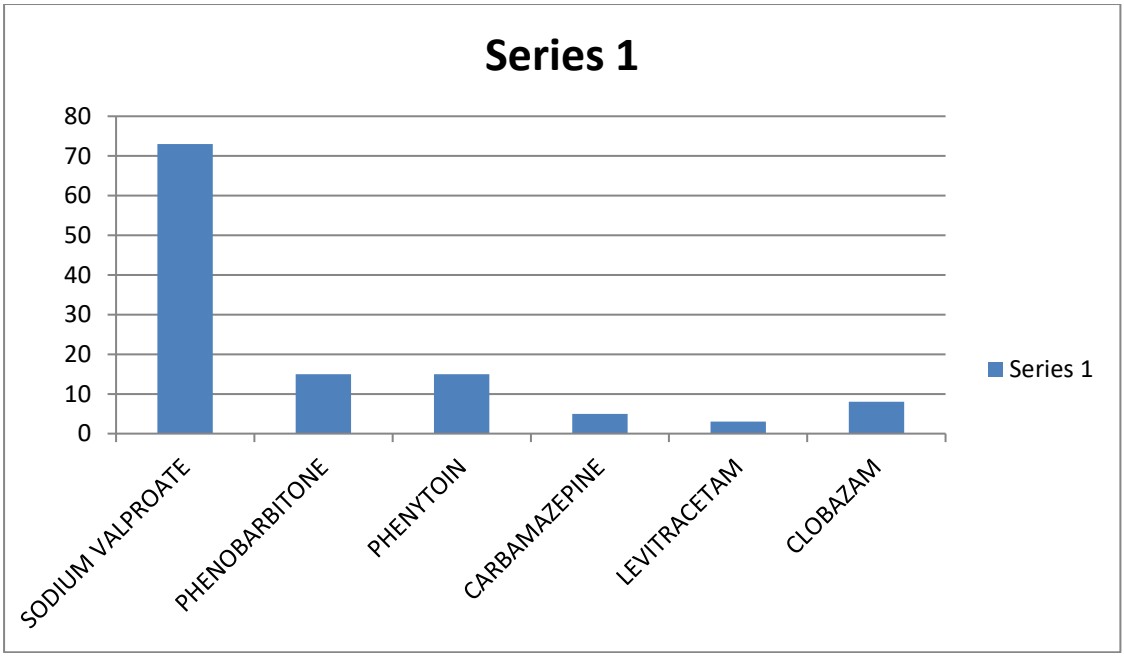



**Figure No.2: Bar Graph Depicting Type of AED wise distribution in study population**

In our study population 2(100%) cases of obese,1(100%)case of each overweight and risk for overweight had vitamin D deficicency. 41(75%) with normal BMI had vitamin D deficiency, 13(59%) cases of wasting and 13(65%) cases of severe wasting had vitamin D deficiency. Obese and overweight cases had100% vitamin D deficiency with p value of 0.0321 indicating BMI is statistically related to vitamin D levels i.e obese individuals are more prone for vitamin D deficiency.

**Table No.3: Comparison between BMI status and vitamin D levels.**

| | VITAMIN D DEFICIENCY | | |
|---|---|---|---|
| **BMI** | 1-5 Y | 6-12Y | TOTAL |
| **OBESITY** | 1(100%) | 1(100%) | 2(100%) |
| **OVERWEIGHT** | | 1(100%) | 1(100%) |
| **RISK OF OVERWEIGHT** | 1(100%) | | 1(100%) |
| **NORMAL** | 11(84%) | 31(75%) | 41(75%) |
| **WASTING** | 6(54%) | 7(50%) | 13(59%) |
| **SEVERE WASTING** | 4(66%) | 9(81%) | 13(65%) |
| Chi-square= 7.2610 | | p=0.0321 | |

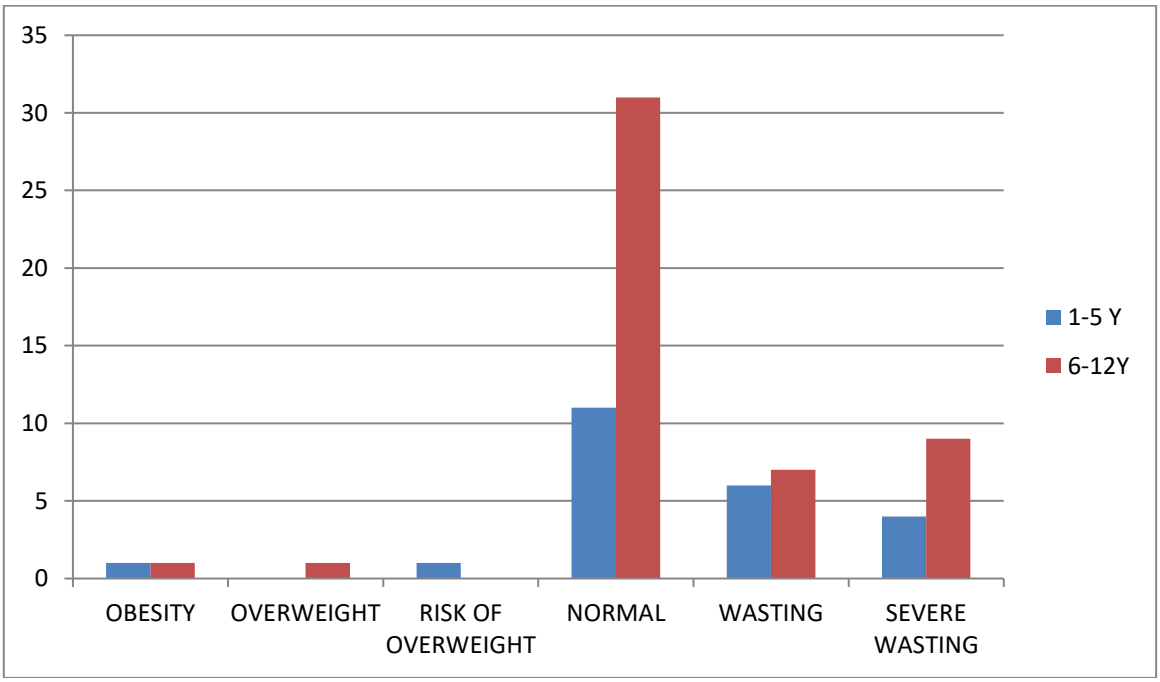
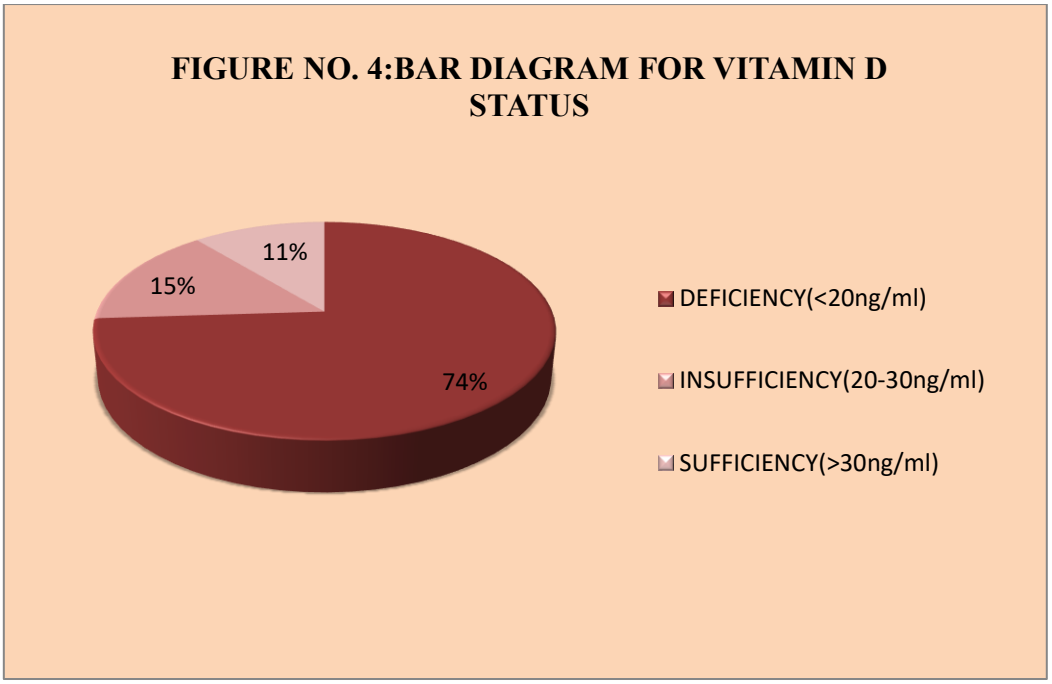



**FIGURE NO. 3: BAR DIAGRAM FOR COMPARISON BETWEEN VITAMIN D LEVELS AND BMI.**

In our study 74(74%) of them had vitamin D deficiency,15 (15%) had insufficiency and 11(11%) of them had sufficiency of vitamin D. None of them had vitamin D toxicity. Mean value of vitamin D in our population was 19.26 ±9.00.

**Table No.4: Status of Vitamin D wise distribution in the study population.**

| Vitamin D | Number | Percent |
|---|---|---|
| Deficiency | 74 | 74.00 |
| Insufficiency | 15 | 15.00 |
| Sufficiency | 11 | 11.00 |
| Total | 100 | 100.00 |




**DISCUSSION**

Vitamin D deficiency in children receiving antiepileptic drugs was first identified in 1979. It is still a poorly studied topic from this region[17]. vitamin D levels in pediatric epilepsy patients is important since these children are at additional risk for bone injury because of their critical period of bone health, seizures, comorbid neuromotor dysfunction, and long term treatment with AEDs that affect the bone health both through vitamin D metabolism and other mechanisms.

**Age and Gender distribution:**

Majority of these children were between 9 to 12 years (45 %), 5 to 8 years constituted 28% and 1 to 4 years 27%. Mean age was 7.49 ± 3.31. Mean age in other studies like Yunjin et al is 7.4 ± 4 and Maryam et al is 8.44 ± 2.377 similar to our study[7,16]. In a study conducted by Choong yi et al mean age was more i.e 12±3.85, this could be probably because of age difference in inclusion criteria.[14] Boys constituted 62% of the cases and girls 38%, with male to female ratio of 1.6:1. In the study, there was no significant difference among vitamin D deficiency prevalence when compared between boys and girls, which was similar to studies conducted by Jung hyun et al and Seung ho et al[15,6]. Where as in those conducted by Choong yi et al(p=0.005)) and Shellhaas et a(p=0.0259)l, girls had significantly higher prevalence of vitamin D deficiency than boys for which the probable reasoning mentioned was that most study subjects were adolescents and among them, girls remained more indoor and/or were beauty conscious.[14,2]

**Prevalence of vitamin D deficiency:**

In our study, prevalence of vitamin D deficiency was 74% which was similar to study conducted by Ramya et al, in which 75.5% had vitamin D deficiency.[3] Other studies like Choong yi et al, Shellhaas et al and Jung hyun et al had 22.5%, 25% and 9.1% respectively,where 20ng/ml was the cut off value for vitamin D deficiency.[14,2,15] This difference in their prevalence can be attributed to Indian ethinicity and timing of conduction of their studies, where those done during winter and spring showed lower levels of vitamin D.[15]

**Type and Number of anticonvulsant:** In our study, subjects were on 6 different AEDs with sodium valproate being the most common (73%) similar to other studies and levatiracetam being the least (3%). 93% of the cases on phenobarbitone had vitamin D deficiency compared to those on carbamazepine 80%, valproate 72.6%, phenytoin 60% and levatiracetam 33%.. In a study conducted by jung-Hyun et al enzyme inducing drug had more vitamin D deficiency which was statistically significant .[15] However in our study both enzyme inducing and non enzyme inducing drugs were related with vitamin D deficiency with out any significance difference ,similar to study conducted by Selhaas et al and Yunjin et al.among non enzyme inducing AED valproate was found to be more common similar to other studies.[2,7] Mechanism attributed is valproate inhibits the 25 hydroxylase activity on vitamin D in liver mitochondria ,direct effect on bone cells and inhibition of calcitonin secretion.

In our study 84% of our study subjects were on monotherapy and 16% of them on polytherapy. 73.8% of them on monotherapy had vitamin D deficiency compared to 75% on polytherapy. However it was statistically not significant which was similar to Ramya et al, Jung hyun et al and Seung ho lee et al.[3,15,6] where as in studies conducted by

Sreedharan et al, Marayam et al, Choong yi et al and Yunjin lee et al, there was a significant difference in vitamin D levels between those on polytherapy and monotherapy, where those on polytherapy were more prone for vitamin D deficiency.[7,14, 16,17]

In our study BMI was found to be statistically significant with vitamin D deficiency. Obese children had 100% vitamin D deficiency similar to other studies conducted by Sueng Ho Lee et al,yun jin et al and selhaas et al.[6,7,2] probable reason behind this could be lipid solubility of vitamin D, because of which it gets deposited in body fat compartments of obese individuals.[8-13]

In our study, 63% of cases had hypocalcemia with statistical significant relation to vitamin D levels similar to other studies. [3,15]

## LIMITATIONS OF THE STUDY

The study population was not compared with the healthy population and basal biochemical values before initiation of AEDs was not available.

Factors that could have affected vitamin D levels like diet, daily activities and sunlight exposure was not taken into consideration.

## CONCLUSION

In our study vitamin D deficiency was highly prevalent (74%) among our unselected cohort of children on antiepileptics. we observed that vitamin D deficiency was significantly associated with duration of antiepileptics and seizure free period. However it was not associated with the number of anticonvulsants used.

Recognised risk factors like age, sex, development delay and abnormal neuroimaging did not show any correlation with vitamin D deficiency. Increased BMI was seen to be associated with low vitamin D level, leading to higher prevalence of deficiency of vitamin D in obese children.

Our study highlight the importance of increased attention to be given on the part of treating physicians to vitamin D status among children on antiepileptics. Vitamin D not only has impact on bone health but is also known for reducing the frequency of seizures and overall growth and development of children.

## DECLARATIONS

Funding: Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee
Informed Consent: Written and informed consent was taken from Parents and guardians of all patients for the study and further publication of outcome

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