VITAMIN D LEVELS IN CHILDREN WITH EPILEPSY ON ANTI-SEIZURE MEDICATIONS(ASM)

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Abstract

Aim: To asses effect of Anti-seizure medication (ASM) on vitamin D3(25- hydroxy vitamin D) levels and calcium profile in children with new onset epilepsy

Materials and methods: This study was a prospective observational study.Children fulfilling inclusion criteria were enrolled in the study after getting informed consent from the parents in the language they understood. Children age group 1-15 years of both genders attending pediatric Opd/Pediatric neurology opd/admitted in ward diagnosed with new onset epilepsy as per ILAE -2017 definition who were going to be started on Anti seizure medication (ASM).

Results: The study determined the effect of Vitamin D levels in children with epilepsy on Anti seizure medications(ASM) . The Mean vitamin D level, post Treatment (18.489 ± 5.2) as compared to preTreatment (24.670 ± 4.1) were significantly lower ($p < 0.001$). Vitamin D insufficiency was detected in two thirds of the children after 6 months of anti-seizure medication usage. The study found that, all 9 children (100%) on oxcarbazepine monotherapy and 2 children on sodium valproate monotherapy had Vitamin D3 insufficiency while all 10 (100%) children on Levetiracetam monotherapy had normal vitamin D levels. The mean levels of calcium and phosphorus decreased while the mean levels of ALP increased following ASM, both of which were statistically significant ($p < 0.001$).

Conclusion: Current study revealed that there is significant decrease in vitamin D3 levels after 6 months of initiation of anti-seizure medication. we found a significant association between type of anti seizure medication and vitamin D levels as well. Oxcarbazepine, which is an enzyme inducer was strongly associated with low vitamin D3 levels .Sodium valproate, which is an enzyme inhibiting effect, has also found to be strongly associated with low vitamin D3 levels

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1. Introduction

An extremely important mineral, vitamin D aims in keeping the body's calcium and phosphorus levels in balance. [1] In addition to being essential for calcium and bone metabolism, vitamin D is required for boosting intestinal absorption of calcium and phosphorus and preventing the release of parathyroid hormones. [2] The main source of vitamin D is exposure to sunlight. Epilepsy is defined as a condition in which recurring seizures are susceptible to develop, when at least two unprovoked seizures take place more than 24 hours apart.[5] The most common childhood neurological illness is seizure disorder, which is occurring in 4-6 per 1000 children.[6] Anti-seizure medication (ASM) used for seizure prevention include carbamazepine, sodium valproate, phenytoin, and phenobarbitone.[4] Numerous studies have found that patients taking enzyme-inducing anti-seizure medications have significantly less bone mineral density and a higher risk of fracture. Antiseizure medications that induce CYP450 are thought to up regulate the enzymes involved in vitamin D metabolism. This is thought to have the effect of turning 25(OH)vitamin D into inactive metabolites, which then reduces calcium absorption and causes secondary hyperparathyroidism. Majority of anti-seizure medications stimulate hepatic CYP450 metabolism. [4]. These anti-seizure medications stimulates the hepatic metabolism of vitamin D, which leads to lowering the levels of vitamin D3. However, some non-enzyme inducing antiepileptic drugs, like valproic acid, have also been linked to low vitamin levels, which may damage bone health. Antiepileptic medications that stimulate the liver's cytochrome P450 enzymes, such phenytoin and carbamazepine, promote the catabolism of vitamin D and its derivatives. As a result of these decreased vitamin D3 levels, hypocalcemia and secondary hyperparathyroidism develop, which ultimately cause a decline in bone mineral density.[2]

Anti-epileptic drugs were grouped under anti-seizure medications.Henceforth ASM will be used in place of anti-epileptic drugs.

2. Materials and methods

This was a prospective observational study conducted at a tertiary care teaching institute from Western Maharashtra, India. Our institute is a tertiary care referral centre having an established Pediatric ward/ Pediatric neurology unit. This study was conducted from October 2020 to September 2022, after approval from the ethics committee. Children age group 1-15 years of both genders attending paediatric Opd/ Pediatric neurology Opd/ admitted in ward diagnosed with new onset epilepsy as per ILAE -2017 definition who were going to be started on Anti seizure medication(ASM) were included in this study . Children with epilepsy on anti-seizure medications(SAM) who have received VitaminD supplements in last 6 months period and Children who are already on anti seizure medication (ASM) therapy were excluded from this study, Children with metabolic bone diseases or Rickets or Renal diseases or hepatic disorder or endocrine disorder also excluded. Serum vitamin D3, Serum calcium, Phosphorus, Alkaline phosphatase levels were done. Subjects with lower Vitamin D3 levels were treated as per standard guidelines and excluded from this study. Children fulfilling inclusion criteria were enrolled in the study after getting informed consent from the parents in the language they understood.Clinical details of patients including socio-demographic profile, age of onset of seizure, type of seizure number of anti seizure medication(ASM) taken, developmental history, clinical examination details were documented in a structured proforma .Lab investigations were done in NABH Accredited lab of our hospital.vitamin D3, serum calcium and Alkaline phosphatase was done by ARCHITECT CI 8200 (ABBOTT -brand name) and Phosphorus was done by DIMENSION EXL200 (Simen). 39 newly diagnosed patients with epilepsy were enrolled and screened , out of them, 9 were excluded due to lower vitaminD levels prior to the treatment.The diagnosis was based on the detailed history, neurological examination and Lab investigations. The following investigations serum vitamin D3, serum calcium, serum phosphorus and serum alkaline phosphatase were done before starting anti-seizure medication (ASM) and repeated after 6 months of anti epileptic treatment.

Sample Size

Assuming Incidence of 1% at 95% Confidence Level, Sample size is calculated to be 30 including 10% dropouts. $Z1-\alpha/2$ = Critical value and a standard value for the corresponding level of confidence. (At 95% CI or 5% level of significance = 1.96).

P = Expected prevalence or based on previous research q = 1-p

d = Margin of error or precision

Statistical analysis

The study statistics had been presented in the form of numbers and percentage % for qualitative data and quantitative data. Mean and standard deviation (SD) was used. Data was entered in MS Excel using Epidata and google forms. Analysis will be done using SPSS 23.0. Appropriate test of statistical significance such as chi square, t test and logistic regression were performed.

3. Result

The current study included children who attended the Paediatrics OPD and Ward of DY Patil Medical College and were enrolled and screened for newly diagnosed epilepsy. A total of 39 children were screened in this study, out of them 9 were excluded due to low vitamin D levels (5 insufficiency and 4 deficiency). these 9 children were treated with vitamin D as per 2021 IAP guideline.[31]

Demographic data of children with epilepsy on ASM

Age groups (years)	**Total (n)**	**(%)**
1 to 3 years	17	56.7
4 to 7 years	9	30.0
8 to 11 years	4	13.3
Gender Male : female	17:13	56:44

Area of residence	**(n)**	**(%)**
Urban	26	86.7
Rural	4	13.3

Socioeconomic status (BG Prasad Classification)	**(n)**	**(%)**
Class III (middle class)	13	43.3
Class IV (lower middle)	11	36.7
Class II (upper middle)	5	16.7
Class I (upper class)	1	3.3

BMI	**(n)**	**(%)**
Normal range	22	73.3
Underweight	5	16.7
Overweight	2	6.7
Severely underweight	1	3.3

Developmental delay	**(n)**	**(%)**
Delayed	12	40.0
Normal	18	60.0

Distribution of study subjects based on the Type of seizures

Sl. no	**Type of onset**	**(n)**	**(%)**
1.	Generalized onset seizures	13	43.3
2.	Focal onset Seizures	9	30.0
3.	Focal progressing as secondary to generalized seizure	3	10.0
4.	Unknown onset	5	16.7

Distribution of the study on the basis of etiological profile

Sl no.	**Etiological profile**	**(n)**	**(%)**
1.	Structural Perinatal Causes	15	50.0
2.	Structural post infectious	3	10.0
3.	Structural congenital malformation of brain	2	6.7
4.	Possible Genetic Epilepsy	3	10.0

5.	Unknown Causes	7	23.3

Distribution of study subjects on the basis of Anti-seizure medications (SAM)used

Sl no	**Generic drug name**	**(n)**	**(%)**
1.	Levetiracetam monotherapy	10	33.3
2.	Oxcarbazepine monotherapy	9	30.0
3.	Sodium valproate monotherapy	2	6.7
4.	*Levetiracetam + Sodium valproate Combination therapy*	7	23.3
5.	*Oxcarbazepine + Clobazam Combination therapy*	2	6.7
Sl no	**Number of ASM used**	**(n)**	**(%)**
1.	One	21	70
2.	Two	09	30

Vitamin D levels(Pre-Treatment and Post-Treatment)

Sl no.	**Table 1: Vitamin D levels**	**Pre-Treatment (%)**	**Post-Treatment at 6months n (%)**	Fischer's exact test
1.	**<12 ng/mL (<30 nmol/L) – Deficiency**	0 (0.0)	3 (10.0)	***p value <0.001***
2.	**12-20 ng/mL (30-50 nmol/L) – Insufficiency**	0 (0.0)	17 (56.7)	
3.	**>20 ng/mL (50 nmol/L) – Sufficient**	30 (100)	10 (33.3)	
	Mean Vitamin D levels ng/mL (Mean ± SD)	24.670 ± 4.1	18.489 ± 5.2	***Wilcoxon test - p value <0.001***

The above table shows that the Mean vitamin D level, post Treatment (18.489 ± 5.2) as compared to pre-Treatment (24.670 ± 4.1) were significantly lower (p <0.001).

impact of type of ASM on Vitamin D level

Comparison of Vitamin D levels at 6 months andAED use		**Vitamin D levels at 6 months post AED**			**Statistical test**
		<12 ng/mL (Deficiency)	**12-20 ng/mL (Insufficiency)**	**>20 ng/mL (Sufficient)**	
Sl no.	**AED**	**n (%)**	**n (%)**	**n (%)**	**Fischer's exact test**
1.	**Levetiracetam + sodium valproate**	1 (14.3%)	6 (85.7%)	0	
2.	**Oxcarbazepine + Clobazam**	2 (100%)	0	0	
3.	**Oxcarbazepine monotherapy**	0	9(100%)	0	0.344
4.	**Sodium valproate monotherapy**	0	2 (100%)	0	
5.	**Levetiram monotherapy**	0	0	10(100%)	

4. Discussion

This study was a prospective observational study which was conducted among children age between 1 to 15 years and who were diagnosed with new onset epilepsy attending Paediatric opd/ Paediatrics neurology OPD / Paediatric ward of DR.D.Y.Patil Medical College Pimpri, Pune, Maharashtra .In total 39 children were enrolled and screened for this study of which 9 were excluded due to low vitamin D3(25(OH)D) levels (5 insufficiency and 4 deficiency), These 9 children were treated with vitamin D as per guideline issued by IAP 2021[31].The majority of the children in the current study, of both genders, were aged between the ranges of 1 and 3 .Males had a mean age of 5.3+/- 3.2 years and females of 2.7+/- 1.4 years. As per the previous study conducted by W.Allen Hauser [77]found that highest incidence of epilepsy was seen in 1st year of life. In contrast, a study conducted by Fathy Z. Pohan et al [60] showed that the mean age was 9.1 years (SD: 1.8).In contrast to other research, the age of onset in the current study was lower, ranging between 1 and 3 years .This difference might be caused by the fact that our study only included cases of newly onset epilepsy. In present study ,17 cases out of 30(56.7%) were males and remaining cases 13/30 (43.3%) were females. Males preponderance was observed in this study .The male to female ratio was 1.3:1. The majority of the patients in this study were in Class III (43.3%), followed by Class IV (36.7%), Class II (16.5%), and Class I (3.3%), according to socioeconomic status data on BG Prasad's classification . 86.7% of participants in the study resided in urban areas, based on the study

population's area of residence. Developmental delay[1] was present in 12 cases(40%) out of 30 cases in our study.where as a previous study by Fathy Z Pohan et al[60] 70% of their cases i.e.86 out of 121children were developmentally delayed. Anthropometry measures for the current study revealed that 22 children (73.3%) had normal BMIs, with the remainder falling into the underweight (16.7%), overweight (6.7%), and severely underweight (3.3%) categories. The types of seizures in our study included generalised onset seizures in 13 patients (43.3%), followed by focal onset seizures in 9 patients (30%) ,unknown onsets in 5 patients (16.7%), and focal onset into generalised onsets seizures in 3 patients (10%). In a similar study, Ameena Taha Abdullah et.al.[49] out of the 50 epileptic cases, 41 (82%) had generalized seizures and 9 (18%) had focal seizures (with 56% having good control and 44% having poor control). 15 (30%) cases of epilepsy were treated with anti-seizure mediacation (ASM) for 6–12 months, 36% for 12–24 months, and 34% for more than 24 months. In this study the etiological profile of epilepsy revealed that structural perenatal causes were observed in 15 patients (50%) and were unknown in 7, infectious causes were found in 3 children and possible genetic epilepsy was present in 3, and structural malformation was present in 2 patients (6.7%). In an Indian study by Gowda.V [81]et al the study was done on 121 children in which 92% cases found ethology in which structural ethology was most common (66%) in which most common causes were found to be perinatal insults with 38% cases and cerebral malformations in 18 cases followed by metabolic with 12% cases and finally infectious with 7% and others were 6% In this present study, levetiracetam monotherapy was most common ASM used in 10 children (33.3%), followed by oxcarbazepine monotherapy in 9 children (23%), sodium valproate monotherapy and clobazam monotherapy in 2 children each.Combination therapy was added in those children whose seizures were not controlled with single ASM. 7 children (23%) received levetiracetam and sodium valproate, whereas 2 children (6.6%) received the Oxcarbazepine and Clobazam combination therapy. But in the earlier study, additional anti-seizure medications (ASM) were also included, such as phenytoin, phenobarbital, and lamotrigine etc. Similarly, Ramelli et al.[63], (2014) used Carbamazepine, oxcarbazepine, phenytoin, phenobarbital; Yaghini et al.[64], 2015 observed them using Carbamazepine, primidone, phenobarbital, valproic acid; Viraraghavan et al.[77], 2019 used Phenytoin, valproic acid, carbamazepine; Durá-Travé et al.[76], 2018 used only Valproic acid and levetiracetam; Sreedharan et al.[75], 2018 used Carbamazepine and valproic acid; Attilakos et al.[74], 2018 used only Levetiracetam; Chaudhuri et al.[73], 2017 used Carbamazepine, clobazam, clonazepam, lamotrigine Before starting anti-seizure medications , all children in the current study had sufficient vitamin D3 levels, as we excluded 9 (23%) children with pre existing vitamin D deficiency and insufficiency .After 6 months of anti-seizure medications ,17 (56.7%) children had vitamin D insufficiency and 3 children developed vitamin D3 deficiency while 10 (33.3%) children had normal vitamin D levels. Pre-ASM mean vitamin D3 levels were 24.670 +/- 4.1, whereas post-ASM mean levels were 18 +/- 5.2, which was statistically significant(P value of <0.001). At the end of six months of anti-seizure medication , it was found that all 10 (100%) children on Levetiracetam monotherapy had normal vitamin D levels, in contrast to oxcarbazepine monotherapy, which found that all 9 children (100%) had insufficiency.Vitamin D3 insufficiency was present in 2 children on sodium valproate monotherapy.All children (7/30) on Levetiracetam and Sodium valproate combination therapy had low vitamin D deficiency after 6 months of ASM,of these, 6 had (85.7%) vitamin D insufficiency while 1(14.3%) child had vitamin D deficiency.whereas Oxcarbazepine and Clobazam, when used in combination therapy, resulted in 100% vitamin D deficiency in both of the children. According to Bindu Menon[42] et al.41, two-thirds of the enrolled subjects had vitamin D insufficiency. At the end of six months, subjects with normal 25(OH)D levels at baseline showed a significant drop in 25(OH)D levels, urine calcium, urinary calcium/kg/BW, and TRACP levels, regardless of the ASM used or the plasma level of ASM. In their study,their community had a high prevalence of pre existing vitamin D deficiency . Subjects with normal 25(OH)D levels experienced 25(OH)D deficit and insufficiency states regardless of the anti-seizure medication type, even at sub-therapeutic serum levels of the medicine. In a study by Fathy Z. Pohan et al.[60], the mean duration of anticonvulsant consumption was 41.9 (SD 20) months. The epileptic group had a mean 25(OH)D level of 41.1 (SD 16) ng/mL, which was higher than that of control group [9.7 (95%CI 1.6 to 17.9) ng/mL]. Compared to the control group, the epileptic group had a greater rate of vitamin D deficiency (12/31 vs. 4/31; P=0.020). The mean levels of calcium and phosphorus decreased while the mean levels of ALP were increased following 6 months of ASM, both of which were statistically significant (p <0.001). The serum levels of calcium, phosphorus, and alkaline phosphate did not statistically alter as a result of the majority of earlier studies using anti-seizure

medicine (ASM).
It was a prospective observational study for 2 years with strong follow up till 6 months with no loss to follow up.Our study population included all healthy children with new onset epilepsy,with a baseline normal vitamin D3 levels were recruited prior to the start of ASM.We could determine the vitamin D3 levels using same method and tools, pre-treatment and post treatment in the same laboratory of our institute controlling potential bias. The reviewed studies where compared to our present study and is as follows in the table below
.

Table 16: Reviewed studies

Study	Mean age(years)	Prevalence of Vit D def (%)	Treatment time months)	Antiepileptic drugs used
In this present study	4.2	66.7	6	Levetiracetam, sodium valproate& oxcarbazepine
Ramelli et al.[63], 2014	12.2	55	12	Carbamazepine, oxcarbazepine, phenytoin, phenobarbital,
Yaghini et al.[64], 2015	–	53	6	Carbamazepine, primidone, phenobarbital, valproic acid
Baek et al.[65], 2014	11.21	9.1	12	Valproic acid, oxcarbazepine, lamotrigine, phenobarbital
Lee et al.[66], 2015	7.4	61.5	12	Cytochrome P450 inducers andnon-inducers
Vera et al.[67], 2015	6.5	0	–	Valproic acid, carbamazepine, phenobarbital, lamotrigine,
Paticheep et al.[68], 2015	9	23.3	6	Phenobarbital, phenytoin, carbamazepine, oxcarbazepine,
He et al.[69], 2016	7.24	71	2	Cytochrome P450 inducers andnon-inducers
Tosun et al.[70], 2017	–	31.5	24	Valproic acid, oxcarbazepine, carbamazepine, levetiracetam
Fong et al.[71], 2016	12.3	22.5	12	Cytochrome P450 inducers andnon-inducers
Yildiz et al.[72], 2017	9.6	54	12	Valproic acid, carbamazepine, levetiracetam, phenobarbital
Chaudhuri et al.[73], 2017	14	45	12	Carbamazepine, clobazam, clonazepam, lamotrigine,
Attilakos et al.[74], 2018	6.1	40	12	Levetiracetam
Sreedharan et al.[75], 2018	–	16	6	Carbamazepine and valproicacid
Durá-Travé et al.[76], 2018	–	27.2	12	Valproic acid and levetiracetam

5. Conclusion

Current study revealed that there is significant decrease in vitamin D3 levels after 6 months of initiation of anti-seizure medication.we found a significant association between type of anti-seizure medication and vitamin D levels as well. Oxcarbazepine, which is an enzyme inducer was strongly associated with low vitamin D3 levels.Sodium valproate, which is an enzyme inhibiting effect, has also found to be strongly associated with low vitamin D3 levels

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