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Vitamin D Levels In Patients With Epilepsy

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Introduction:

The current burden of epilepsy is very high in India with nearly 12 million people suffering from epilepsy at a mean prevalence of 1 percent .[1]Low levels of Vitamin D levels are seen in patients with epilepsy Antiepileptic drugs used for seizure control have also been known to cause Vitamin D deficiency especially as they are used over prolonged periods of time.[3]
Plasma levels of 25 hydroxy cholecalciferol are significantly lower in patients on antiepileptic drugs as compared to normal adults and adolescents with no difference in dietary intake or exposure to sunlight.[2,3]
Hypovitaminosis of Vitamin D is linked to several brain disorders including cognitive decline, epilepsy, affective disorders and schizophrenia.[4] Vitamin D has alsobeen reported to potentiate the anticonvulsant activity of conventional antiepileptic drugs.[5]
Moreover, Vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 80%–90 % of the general population.[6] currently there is a dearth of studies in this area hence current study was done.

Objective:

To estimate the vitamin D levels in patients with interictal psychopathology and compare them with patients having epilepsy but no psychopathology and those not having epilepsy

Materials and method:

The present study is a hospital based cross sectional study.

Source of data:

Patients attending psychiatry OPD having a clinical diagnosis of epilepsy were recruited for the study

Method of data collection:

Consecutive patients who met the inclusion criteria and did not get excluded were recruited to the study by purposive sampling.

Inclusion criteria:
Patients aged between 18- 55 years. Patients having generalised tonic-clonic seizures - primary or secondary and complex partial seizures. Epilepsy duration of 1 year or longer.

Exclusion criteria:
Patients having other illnesses known to cause Vitamin D deficiency History of a seizure within a week before the evaluation.

Mental retardation
1) Patients who are having psychiatric Illness preceding the onset of epilepsy.

Sample size: Vitamin D levels were assessed in 31 patients with epilepsy and interictal psychopathology, 26 patients with epilepsy but no interictal psychopathology and 30 healthy controls

Assessment tools

1) Informed Consent form
2) Self-designed proforma to elicit socio-demographic data
3) Self-designed proforma to obtain details of epilepsy and its treatment
4) General health questionnaire 12 item version (GHQ-12) by Goldberg to screen for psychopathology

Method of data collection:

Consecutive patients attending psychiatric the treatment of epilepsy who met the inclusion criterion and did not get excluded were recruited into the study. A total of 195 patients were screened.
All patients who gave written informed consent for participation in the study were screened for psychopathology using GHQ 12 item version.
Psychopathology in the comparator groups was ruled out by clinical interview and administering the 12 item version of General Health Questionnaire.
Vitamin D levels in blood were assessed in 31 patients having epilepsy& interictal psychopathology, 26 patients having epilepsy but no interictal psychopathology and 30 controls recruited into the study. Using the Siemens ADVIA Centaur, standardised against ID-LC/MS/MS as per the Vitamin D standardisation Programme which uses Chemiluminescent with Advanced Acridinium Ester Technology, i.e., C.L.I.A.
Vitamin D levels were considered to be deficient if below 20ng/dl, insufficient between 20 and 30 ng/dl and normal if between 30ng/dl to 100ng/dl.[256]

Statistical Analysis

- Statistical analysis was done using SPSS version 22
- Sociodemographic data were compared using descriptive statistics and chi-square test
- ANOVA was used to compare means of serum Vitamin D levels among three groups
- Kruskal-Wallis test was used to compare self-reported duration of average time spent in sunlight per day as it failed to meet the test of normal distribution
- Chi-square test was used to compare sociodemographic variables
- Unpaired t test to compare continuous variables
- P values were taken significant at 0.05 level and highly significant at 0.01 level

Results:

The three groups did not differ in the various sociodemographic details including age, gender distribution, religion, occupation, the area of residence and maritalstatus.They, however, differed in distribution across Socioeconomic status and type of family. (Table 1)

Table-1: Socio-demographic variables across the three groups

Socio-demographic factors		Epilepsy with Psycho-pathology	Epilepsy	Control	Statistical tests
MEAN AGE		33.35± 10.837	34.31± 10.402	33.87± 10.075	F=0.059, P=0.943
AGE	< 20	2	1	3	X^2= 4.31 P= 0.828
	20-29	11	8	9	
	30-39	11	8	7	
	40-49	3	6	8	
	50-55	4	3	3	
GENDER	MALE	15	12	15	X2= 0.08 P= 0.959
	FEMALE	16	14	15	
RELIGION	HINDU	25	18	17	X2= 4.09 P= 0.129
	MUSLIM	6	8	13	
EDUCATION	UPTO 9th	16	8	5	X^2= 15.8 P= 0.104
	SSLC Pass	7	5	10	
	PUC Pass	3	5	7	
	DEGREE	3	7	7	

	PG DEGREE	2	0	0	
. OCCUPATION	UNEMPLOYED	2	0	0	X^2= 17.3 P= 0.361
	HOUSEWIFE	11	9	10	
	AGRICULTURE	5	3	6	
	COOLIE	3	4	2	
	GOVT JOB	0	1	0	
	PVT JOB	0	3	2	
	BUSINESS	3	0	0	
	STUDENT	3	3	4	
	OTHERS	4	3	6	
AREA OF RESIDENCE	RURAL	15	15	13	X^2= 1.17 P= 0.557
	URBAN	16	11	17	
SES	CLASS I	5	5	1	X^2= 31.69 P= 0.00
	CLASS II	7	8	2	
	CLASS III	8	9	1	
	CLASS IV	8	2	16	
	CLASS V	3	2	10	
TYPE OF FAMILY	NUCLEAR	16	23	19	X^2= 9.21 P= 0.05
	JOINT	13	3	10	
	EXTENDED	2	0	1	
MARTIAL STATUS	MARRIED	24	20	23	X^2= 0.005 P= 0.997
	UNMARRIED	7	6	7	

People with epilepsy had significantly lower values of serum Vitamin D levels when compared with healthy controls. (Table 2)

Table-2: Comparison of Vitamin D levels between patients having epilepsy and healthy controls

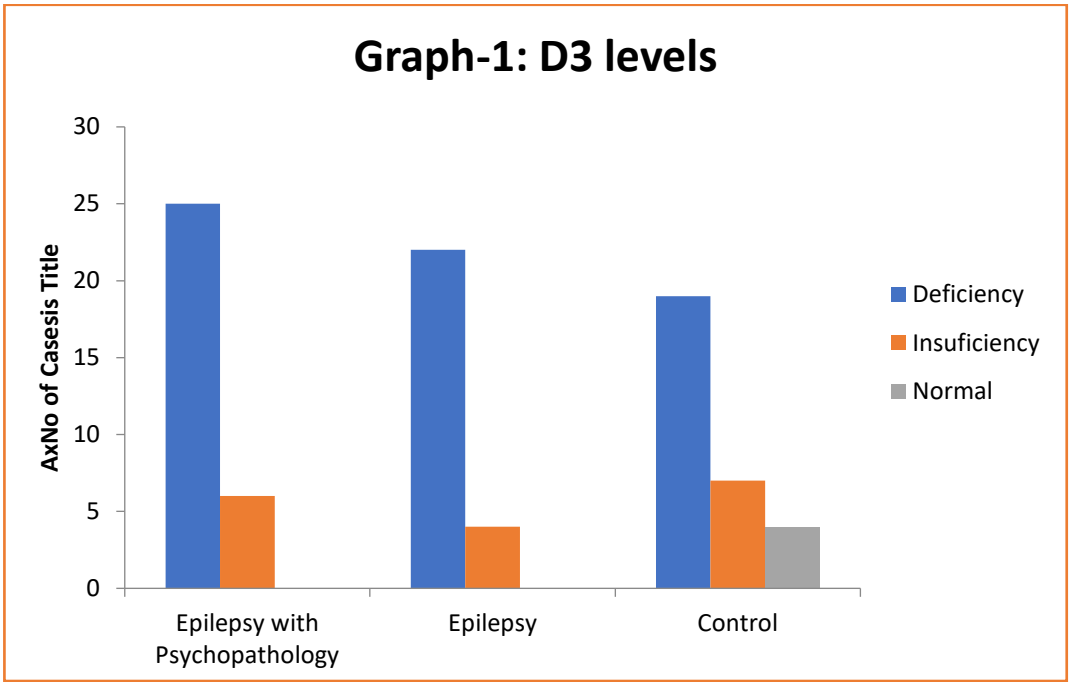
Group	Vitamin D levels	
Healthy controls	19.11±7.49	T= 3.210 P=0.02
Ppl with epilepsy	14.37±6.01	

Vitamin D3 levels were lowest in patients having epilepsy with Interictal psychopathology followed by those having epilepsy and highest in healthy control group. The levels were significantly different amongst the three groups.
Post hoc analysis using Tukey's shows that the mean values of serum vitamin D levels were significantly lower in patients with epilepsy with or without psychopathology when compared with controls but were not different in between the two groups. (Table 3)

Table – 3: Comparison of serum vitamin D levels across the three groups

D3 Values (ng/dl)					
Groups	**N**	**Mean**	**Std Deviation**	**ANOVA**	
Epilepsy with Psychopathology	31	13.93	6.61	5.265	P<0.007
Epilepsy	26	14.90	5.30		
Control	30	19.12	7.49		

Nearly 80 % patients with epilepsy and Interictal psychopathology, 84% patients with epilepsy alone and 63 % of controls lay in the deficiency group i.e. Vitamin D levels less than 20 ng / dl. Only 13 % of controls had vitamin D levels greater than 30 ng/dl. (graph 1)



Lower Vitamin D level was found be significantly correlated with female gender, lesser duration of exposure to sunlight, greater frequency and duration of seizure and presence of side effects

Table – 3 : Correlation of Vitamin D with other factors

Correlation of vitamin D with	
Age	-.122
Sex	.255*
Exposure to sunlight	-.437**
Religion	.083
Frequency of seizures	-.316*
Years of illness	-0.02
Duration of seizure	-.454**
Age of onset	0.028
Duration of treatment with antiepileptics	-0.037
Number of drugs used	-0.185
Side effects	-.325*
DUE	0.017
Comorbid illness	-0.261
Last attack	0.103
Nocturnal attack	-0.107

***** Significant at 0.05 levels,
** Highly Significant at 0.01 levels

Discussion:

The three groups i.e. patients with epilepsy and Interictal psychopathology, patients with epilepsy and no psychopathology and healthy controls were comparable across most sociodemographic details by design. Patients with epilepsy were more likely to have lower socioeconomic status.[7]
Vitamin D deficiency prevails in epidemic proportions all over the Indian subcontinent, with a prevalence of 80-90 %of the general population.[6] the levels of serum Vitamin D were low across all subgroups of participants. Vitamin D 25-OH levels were categorised as deficiency(<20ng/ml), insufficiency (20–29ng/ml), or normal (>30ng/ml).[256]
In the recent retrospective analysis done by Alhaidri et al the prevalence of low Vitamin D levels were seen in nearly 86.6% patients with patients with patients with epilepsy having significantly lower levels in younger age group and Vitamin D supplementation associated with 40 % improvement in seizure control .[2]
In a study by S Nagarjunkonda et al. of the total sample i.e. 87 people who were tested for serum Vitamin D levels 66 i.e. 75 % had deficient Vitamin D levels, 17 i.e. 19.5 % had concentrations in the insufficiency range and four i.e. 4.5 %

had normal levels.[222] Our sample had more proportion of people in the deficiency group as compared to findings in previous studies that showed that 41% of the people sampled were deficient, 49% insufficient and 9% sufficient with vitamin D.

Vitamin D levels were found to be low even in the control group. This in concordance with the various epidemiological studies previously done. Diet-based theories proposed in various studies include inadequate intakeand high dietary phytates inhibiting proper absorption. Foods rich in vitamin D-like cod liver oil and egg yolk are sparingly consumed in most strata in the country. [8]

Vitamin D levels were found to be low in patients with epilepsy as whole and were significantly lower than healthy controls (mean levels: 14.37±6.01 vs. 19.11±7.49).This is in concordance with astudy done by Kulak et al. wherein Vitamin D levels in patients with epilepsy were found to be significantly lower than age and sex matchedcontrols.[9]

The study by Shelhauss etal. done in paediatric population found that nearly 75% of the children with epilepsy had Vitamin D levels less than 30 ng/ dl.[10]Teagarden et al. had found lowered Vitamin D levels in patients with epilepsy[3], but these findings are contrary to the conclusions of the study by Nagarjunakonda et al. that found no difference in the Vitamin D levels in patients with epilepsy when compared with those of the control group.[11]

The Vitamin D levels were lower in the subgroup with patients having epilepsy and Interictal psychopathology when compared with patients having epilepsy without psychopathology although the difference was not significant. However, the patients with epilepsy and interictal psychopathology had significantly more exposure to sunlight than patients with epilepsy alone and the control subgroups. There is a probability that if sunlight exposure is controlled for in a study vitamin D levels might be even lower in patients having epilepsy and interictal psychopathology. It is possible that Interictal psychopathology per se may be a causative factor for low Vitamin D levels or vice versa. Low Vitamin D levels havebeen associated with psychiatric illness. Nearly 75 % of the inpatients in the psychiatric ward had Vitamin D levels less than 30ng/ml. Hypovitaminosis has been found to be associated with psychosis, depression and cognitive decline. To our knowledge currently no other study has addressed this subset of patients with epilepsy.

The serum Vitamin, D levels in participants of current study, were found to be associated with the following: -

- Gender:Females had lower levels of Vitamin D as compared to males in all the subgroups. These findings were by a studydone byShellhass et al. in paediatric population wherein girls had lower Vitamin D levels when compared to boys.[10]In an epidemiological survey done by Mithail et al. female sex was significantly associated with lower Vitamin D levels even in the general population.[12]
- Duration of exposure to sunlight: In this study, the Vitamin D levels were significantly correlatedwith the self-reported exposure to sunlight.This is in accordance with studies linking sunlight exposure to Vitamin D levels.[12] Nagarjunakonda. et al.have linked lowered Vitamin D levels in patients with sedentary lifestyle and desk jobs that both will have lower exposure to the sun.[11]Vitamin D levels in the population are observed to be affected by factors that influence exposure to ultraviolet B rays. These factors include pigmentation of the skin, latitude and season.
- The frequency of seizure: Lower Vitamin D levels were seen in patients having more frequent seizure episodes.This is consistent with the studies done by andChristensenClauss etal. in 1977 [13] and Andros hollas et al.[5]in 2014 wherein lower 25 hydroxylcholecalciferol associated with poor seizure control and supplementation of Vitamin D in such patients decreased seizure frequency.However, in the study by Nagarjunkonda et al. there was no difference in Vitamin D levels in patients that had refractoryepilepsy.[11]
- Duration of seizure episode: Lower Vitamin D levels were seen in patients with longer duration of a seizureevent. No previous studies were found, but longer duration probably reflects poor seizure control similar to increased frequency of seizures.
- The presence of side effect: Patients with epilepsy that developed side effects had significantly lower levels of Vitamin D levels when compared to patients who did not develop side effects. Presence of adverse events may represent higher sensitivity of the patient to the AEDs.
- Age: A negative correlation between increasing age and the Vitamin D levels were observed in this study, but this was not significant. This finding is not by previous studies that have shown declining Vitamin D levels with increasing age.Maclaughlin et al. have demonstrateda reduction in the skin's capacity to produce previtamin D3 with increasing age.[14] In our sample, however, the duration of sunlight exposure is relatively more in older age group.
- Duration of AED use: Duration of AED used had a non-significant depletory effect on Vitamin D levels.
  In a study by Bouillon R. et al., the duration of antiepileptic drugs used is inversely related to the 25 alpha hydroxyl levels.[15]However in the study Nagarjunkonda et al. serum Vitamin D levels had no correlation with the duration of treatment.[11]
- The number of drugs used: Though the Vitamin D levels in patients had an inverse relationship with the number of AEDs used, the relationship was not significant.
  Mintzer S. et al. had demonstrated a significantly lower level of serum Vitamin D in patients on both carbamazepine and oxcarbazepine than those on monotherapy.[221]However, our findings are similar to the results by Nagarjunakonda et al. wherein they found no difference in between levels amongst patients on monotherapy vs. those on polytherapy.[11]

- The AED used – In this study, no significant relationship was seen between the AED used and vitamin D levels.This may be because most patients were on enzyme-inducing drugs like phenytoin and phenobarbitone while the percentage of the sample on newer antiepileptics was very less.
  The reports for this have contradictory. Teagarden et al. have shown lowering of Vitamin D levels by both enzyme-inducing AEDs and non-enzyme inducingAEDs[9]. Gough et al. have shown reduced Vitamin D in Patients on enzyme-inducing drugs but not on sodium Valproate which has been considered a non-enzymeinducer.[16] In the study by Shellhaus et al. in paediatricpatients, no differences were found in patients on older enzyme inducing drugs vs. the AEDs that are non-enzyme inducing drugs.[10]
- Type of seizure: No differences were found in Vitamin D levels of patients with generalised seizures vs. those having focal seizure.
- The dosage of AEDs: In this study, no significant correlation was found with a dose of AED.This is contrary to the findings by Davie M. W. J. et al. 198wherein dosage of phenytoin and phenobarbitone is inversely proportional to Vitamin D levels. [17]
- The presence of comorbidity and substance use: Although obesity, hypertension and substance use are independently associated with low levels of Vitamin D in this study they did not significantally contribute to lowering of Vitamin D levels.[18]
- Religion: Vitamin D levels are similar across Hindus and Muslims irrespective of sex.This is contrary to studies where traditional Muslim dress have been associated with lower sun exposure and hence lower Vitamin D levels.[19]

Conclusion:

Overall both patients and controls have low Vitamin D3 levels which may reflect an underlying predisposition to Vitamin D deficiency in Indian Population and may require a revision of norms and /or fortification strategies especially in vulnerable groups .
Depleted Vitamin D levels in patients with epilepsy may be an outcome of AEDs used . Lower levels of Vitamin D were associatedwithpoor seizure control in the form ofincreased frequency and longer duration of seizures and may have implications for seizure control

STRENGTHS

- Very few studies done in Indian population assessing Vitamin D levels in patients having epilepsy. This study focuses on the less researched area of vitamin D levels in patients diagnosed as epilepsy in India.
- Inclusion of control group.
- Focus on the interictal psychopathology group.

LIMITATIONS

- Cross-sectional study design.
- Sequential sampling was employed. Hence possibility of selection bias cannot be ruled out.
- Sample was drawn from restricted population.
- Small sample size.
- Use of non-standardized instruments of assessment.
- Only subjective measure of exposure to sunlight was done.

FUTURE DIRECTION

Future research on this topic can include studies that have follow-up design with a larger sample drawn from multiple centres. These will provide an opportunity to explore the cause and effect relationship between the various factors that influence Vitamin D levels and seizure control in patients with epilepsy
Interventional studies can be planned for establishing association amongst Vitamin D levels, epilepsy and Interictal psychopathology

Conflict of Interest: None

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