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Role of Vitamin D Deficiency in Pediatric Febrile Seizures

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ABSTRACT

The primary objective was to study Vitamin-D level in children presenting with Febrile Seizure (FS) from 6 months to 5 years of age and to correlate it with the risk for occurrence of FS a well as for recurrence. Second objective was to correlate Vitamin-D levels and FS with demographic factors. This Cross-sectional study was conducted at a tertiary referral hospital. 100 consecutive cases of FS satisfying inclusion criteria were taken up for the study after getting informed consent from the parents. Detailed proforma were collected and data entered in MS Excel and analyzed using SPSS. Statistical tests used were Chi square test, Odds ratio, Pearson Correlation coefficient etc. Out of the 100 children, majority were from age group between 1-3 years (53%). From the total cases, 71% of children were found to have insufficient level while 13% of children were having deficient level. Deficiency was more in children from 6 months to 1 year of age (16.7 %) group while insufficiency was more in the 1-3 year age group (86.8%). Vitamin-D insufficiency and deficiency correlated with the risk for simple FS and risk of recurrence of FS. Majority of children were having insufficient level of Vitamin-D. It is seen that Vitamin-D deficiency is an independent risk factor for FS as well as its recurrence risk. Hence it is suggested that further prospective trials on the effects of adequate Vitamin-D supplementation on children at risk for FS be carried out to elucidate the protective role of Vitamin-D.

OPEN ACCESS

Key Words

Febrile seizure (FS), vitamin-D level, vitamin-D insufficiency (VDI), vitamin-D deficiency (VDD)

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INTRODUCTION

Febrile seizures (FS) are the most common seizures in children affecting 2-5% of paediatric population[1,2]. Median age of occurrence is 18-22 months[3,4]. There exists a group of risk factors for the occurrence of FS, their recurrence and future risk of epilepsy[5-7]. Genetic components also play significant role in susceptibility to FS like mutation in voltage gated sodium channels[8,9]. There is increasing concern that vitamin-D deficiency may be a risk factor for FS. Vitamin-D deficiency is a major health problem in children and its worldwide prevalence has been estimated at about 1 billion. It prevails in 50-90% among children in India[10-12]. Iron deficiency is associated with increased risk of FS[13]. Sodium and Zinc are other factors[14,15]. Similarly the factor which is currently under study is Vitamin-D[12,16].Prevalence of hypovitaminosis-D ranges from 44.3-66.7% among infants and 60-80% among children[11,16].

Mechanisms of Anti Epileptic Action of Vitamin D: Epidemiological data as well as a variety of case studies also point to a connection between Vitamin-D and epilepsy and support the use of Vitamin-D as a potential therapy for human epilepsy, both in its own right and in conjunction with existing AEDs[17-19]. Vitamin-D is also involved in neuro protection[20-22], brain cell proliferation, differentiation and brain development[23-25]. A neurological role of Vitamin-D is further supported by the presence of Vitamin-D specific receptors and enzymes in neurons and glial cells throughout the brain, in the spinal cord and in the peripheral nervous system[26-29]. Vitamin-D through its genomicmechanisms down regulates the expression of Pro Convulsant cytokines[30] in the brain like Interleukin-1 Beta and TNF-Alpha. This leads to decreased activation and stabilization of NMDA receptors, reduced release probability and increased reuptake of Glutamate-an excitatory neuro transmitter and increased inhibitory GABA chloride flux[31-35]. Vitamin-D reduces the recruitment of AMPA receptors into the neuronal cell membrane and internalization of GABA-A receptors away from the cell membrane by inhibiting TNF[36,37]. Vitamin-D increases the expression of Neuronal growth factors like GDNF and NT3 which in turn reduces synaptic transmission[38-40]. Vitamin-D receptor activation leads to increased expression of Calcium binding proteins like Calbindin and Parvalbumin in presynaptic terminals which also reduces synaptic transmission by binding calcium[41,42]. The purpose of this study is to study the Vitamin-D level in children presenting with febrile seizure (FS) and to find out Correlation between Vitamin-D level and risk of FS and its recurrence.

MATERIALS AND METHODS

This study was designed as a hospital based Cross sectional study. The study setting was the General Pediatrics Wards, Pediatric ICU and Casualty of our institution which is one of the biggest public sector Medical colleges in the state and tertiary referral centre. The study period was for 1 year, from January 2019 to January 2020, after getting Institutional Research Committee clearance and Human Ethics Committee clearance. The study subjects were children in the age group 6 months to 5 years who presented with FS to our hospital. Consecutive sampling method was employed. All consecutive patients who fulfilled the eligibility criteria were enrolled into the study.

Inclusion Criteria: Included all children in the age group 6 months-5 years who presented to the hospital with either simple or complex FS during the study period.

Exclusion Criteria: Had known cases of Epilepsy, Neuro developmental delay, children on Vitamin-D supplementation or treatment and children of parents who refused to give consent. Also proven cases of meningitis or encephalitis presenting with FS were excluded.

Sample Size: Was calculated based on a previous study of " Exploring Vitamin-D in children with febrile seizure" by Ghazal Shariatpanahi[46]. It was found that in children with FS, Vitamin D level below sufficient range was found to be 80% in that study. This was used and sample size was calculated as 100. All collected data were entered into a semi structured proforma. In order to categorised various degrees of vitamin-D deficiency, authors used criteria that was mentioned in Indian Academy of Pediatrics 2017 guidelines on vitamin-D deficiency[16]. Based on these criteria, sufficient are defined as levels >20ng/ml, insufficient (VDI) as 12-20ng/ml and deficient(VDD) as levels as < 12ng/ml. After getting informed consent from the parents, we obtained demographic details from all the study subjects in a detailed performa. Vitamin-D assay was done from venous blood samples of the patients using standard techniques.

Data Analysis: Data was entered in MS Excel and completeness of the data collected was checked. Data was analyzed using statistical software-SPSS. Quantitative variables have been summarized as mean (=SD) and categorical variables as proportion and 95% CI was taken for significance. Statistical tests used were Chi square test, Odds ratio, Pearson Correlation coefficient etc. Significance was set at a p value of <0.05.

RESULTS AND DISCUSSIONS

In our present study majority of children were in the age group 1-3 yrs (53%) .There is a high proportion of VDI (71%) while VDD was seen in 13% .Children from 1-3 years age group had more VDI (86.8%) when

Table-I. Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Age Groups

	Vitamin D level										
Age in years	Deficient		Insufficient		Sufficient		Total				
	n	%	N	%	n	%	n	%	χ2	df	p
6 months-1 year	3	16.7	12	66.7	3	16.7	18	100	23.3	4	<0.00
1-3 year	6	11.3	46	86.8	1	1.9	53	100			
3-5 year	4	13.8	13	44.8	12	41.4	29	100			
Total	13	13	71	71	16	16	100	100			

Table II: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Family History

F/H/O	Deficient		Insufficient		Sufficient		Total				
Febrile Seizure	n	%	N	%	n	%	N	%	χ2	df	p
Yes	3	6.7	30	66.7	12	26.7	45	100	8.559	2	0.014
No	10	18.2	41	74.5	4	7.3	55	100			
Total	13	13	71	71	16	16	100	100			

Table III: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Sunlight Exposure

Sunlight	Deficient		Insufficient		Sufficient		Total				
Exposure	n	%	n	%	n	%	N	%	χ2	df	p
<1 Per week	1	1.6	53	85.5	8	12.9	62	100	23.29	4	<0.001
2-3 times per week	8	36.4	10	45.5	4	18.2	22	100			
>3 times per week	4	25	8	50	4	25	16	100			
Total	13	13	71	71	16	16	100	100			

Table IV: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Seizure Type

Seizure	Deficient		Insufficient		Sufficient		Total				
Type	n	%	N	%	n	%	n	%	χ2	df	p
Simple	9	14.8	48	78.7	4	6.6	61	100	10.39	2	0.006
Complex	4	10.3	23	59	12	30.8	39	100			
Total	13	13	71	71	16	16	100	100			

Table V: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Seizure Episode

Seizure	Deficient		Insufficient		Sufficient		Total				
Episode	n	%	N	%	n	%	n	%	χ2	df	p
1st episode	3	9.4	16	50	13	40.6	32	100	21.23	2	<0.001
≥2 episode	10	14.7	55	80.9	3	4.4	68	100			
Total	13	13	71	71	16	16	100	100			

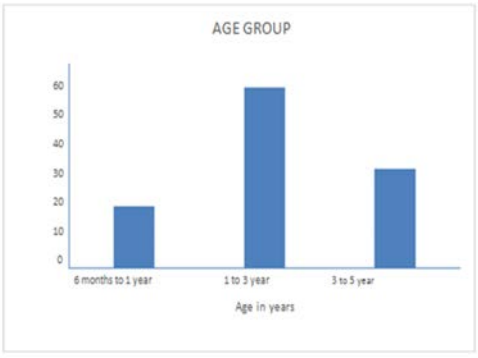

Fig. 1: Distribution of Febrile Seizure with Respect to Age Groups

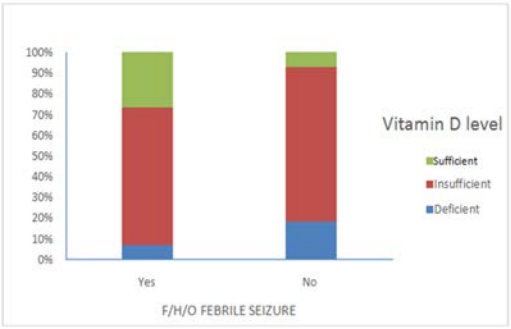

Fig. 3: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Family History

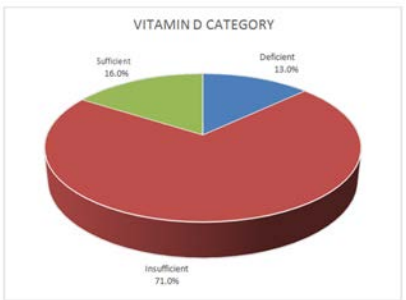

Fig. 2: Distribution of Febrile Seizure with Respect to Vitamin D Level

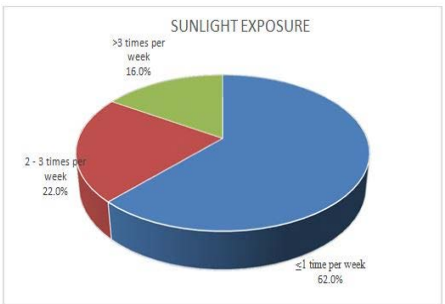

Fig. 4: Distribution of Febrile Seizure with Respect to Sunlight Exposure

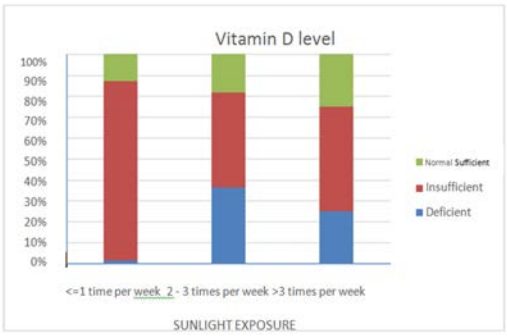

Fig. 5: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Sunlight Exposure

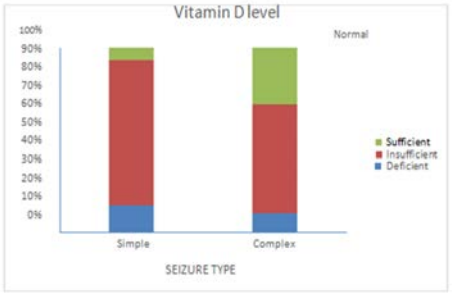

Fig. 6: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Seizure Type

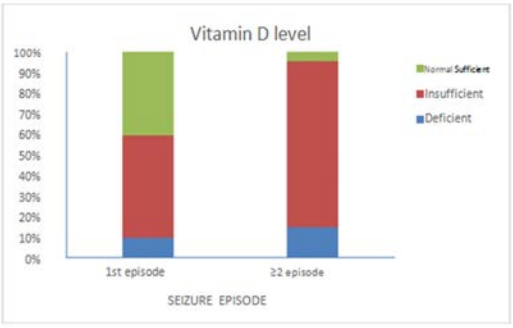

Fig. 7: Distribution of Vitamin D in Children with Febrile Seizure Depending Upon Seizure Episode

compared to others-**(Table-I)**. Children from 6mon-1 year age group had more VDD than other groups, their mean Vitamin D value were 14.1±5.97. Pearson correlation coefficient between age and Vitamin D level shows value of 0.137 (r=0.137), it says that there is no correlation between age and Vitamin D level. The Inference is that the higher percentage of VDI in the 1-3 yr age group correlates with the higher proportion of 1-3 yrs with FS and this is statistically significant ($p<0.001$). VDI is more in males when compared to females which is statistically significant. While VDD was more in females when compared with males(12.1%). Overall VDI is more common in children from pucca type of house (75%) while VDD is more common in children from kutcha (33%) type of house: which is statistically significant. These may be accounted for by poor sunlight exposure in both groups with further poor nutrition in children living in Kutcha houses. Out of 45 children with family history of FS, 66.7% belongs to VDI and 26.7% belongs to sufficient range, 6.7% belongs to VDD. Out of 55 children without any family history of FS, 74.5% belongs to VDI, 18.2% had VDD and 7.3% belongs to sufficient category-**(Table-II)**. Children without family history of FS showed more VDI when compared to children with family history. This was statistically significant as it suggests that in children without family history, VDI and VDD acted as an independent risk factor for FS. Children Presenting with FS were also classified depending upon the sunlight exposure and this study shows FS is more among children with ≤1time per week sunlight exposure (62%) followed by children with 2-3 times per week exposure (22%) and it is less when the exposure is >3 times per week(16%).Majority of children were having ≤1 time per week sunlight exposure, out of which 85.5% were having VDI. While children with h/o>3 times per week sunlight exposure were having higher percentage of sufficient level of vitamin D (25%). The inference is that extent of sunlight exposure has a positive correlation with Vitamin D level and negative correlation with FS.Hence strong negative correlation exists between Vitamin D level and Febrile seizure Occurrence-**(Table-III)**. VDI (78.7%) as well as VDD (14.8%) is more prevalent in children with simple FS compared to complex FS. Hence Vitamin D level below sufficient range may be considered as a risk factor for simple FS-**(Table-IV)**. VDI (80.9%) as well as VDD(14.7%) is more prevalent in children presenting with ≥2 episodes while compared to children presenting with 1st episode of FS. Hence Vitamin D level below sufficient range may be considered as a risk factor for recurrent FS just like Iron deficiency **-(Table-V)** . For children presented with ≥2 episodes of febrile seizure, mean value is 15.76 against 20.14 among children with 1st episode of febrile seizure, which indirectly states that lesser the value of Vitamin D, greater is the risk for recurrence of FS that is Negative correlation exists between Vitamin D level and recurrence risk. This cross sectional study looks at the distribution of Serum Vitamin-D levels in Children presenting with Febrile seizures (FS) . It also assesses the association between risk of FS and its Recurrence risk with Vitamin-D levels and a host of other factors like Age, gender. Family history, Sunlight exposure, socioeconomic status etc. As per our study there is high percentage of VDI and a significant percentage of VDD in Children with FS. Also Vitamin-D deficiency was more in Children with no family history of FS suggesting that VDI and VDD may be independent risk factors for FS. Other findings were the association between sunlight exposure, Vitamin-D levels and FS and the association between low Vitamin-D and recurrence risk of FS. Another cross-sectional study by

Rabbani[44] in Iran was performed to determine the prevalence of VDI in 963 healthy children living in Tehran. The prevalence of VDI as 46.6% and VDD as 7.9% in children younger than 2years in Tehran. The relation between Epilepsy and Vitamin-D was first brought out in a pilot study by Christiansen[17] in 1978 in which there was significant reduction in seizure frequency when Vitamin-D was supplemented to 23 patients with refractory epilepsy who were on multiple anti epileptic drugs. A second study almost 40 yrs later by Andras Holla[18] in 2012 found significant reduction in epilepsy over a 90 day period in 13 patients with pharmacoresistant epilepsy whose vitamin-D levels were Normalise with supplementation. Median seizure reduction was 40%. The conclusion was that the normalization of serum Vitamin-D level has an anti consultant effect over and above AEDs. Another review published in 2018 by Kevin pondo[19] espoused the molecular mechanisms behind the Anti epileptic mechanism of Vitamin-D by reviewing Animal models, human Trials and other Neuroscience research. Our study is based on the hypothesis that if normalizing Vitamin-D level is useful in controlling epilepsy definitely the level will have an impact on Febrile seizures (FS) also. Studies on these associations are quite few. One study by Ghazal Shariatpanahi[43] revealed that there is high proportion (80%) of VDI in children with FS. Our study also found 71% VDI and 14% VDD in the 100 children studied. Another study by Heydarian[45] compared Vitamin D levels in children under 5 yrs who presented with FS versus Children with fever and no seizures. That study found that even though the vitamin-D level in children with FS were lower when compared to controls it was not statistically significant. Interestingly in both groups vitamin-D level was within normal range unlike our study where 71% of children were having VDI. However despite the normal level of vitamin-D in febrile children with and without a seizure, the mean serum vitamin-D level was lower in patients with FS in the Heydarian study. In a Case control study by Singh[46] in India, children under 5 yrs with FS first episode were compared with similar controls with fever and no seizures. Strong and significant ($p<0.01$) association of FS with Vitamin-D levels was observed. Children with VDI (<20ng/ml) had three times (OR=3.03) more risk of having FS as compared to persons with normal vitamin-D status (≥20ng/ml) whereas VDD (<12ng/ml) was associated with highest risk (OR=4). Another study by Zafer Bagchi[47] in Turkey compared Vitamin-D levels in Children with simple FS versus Children with Complex FS. This study kept VDI at a cut off level of 30 ng/ml versus our cut off of 20ng/ml. Children were subdivided into 2 comparison groups 1) Simple FS vs Complex FS and 2) First FS versus Recurrent FS groups. This study showed that vitamin-D levels were not different between simple and Complex FS and among children with first or repetitive FS. But this does not rule out the findings of our study that Vitamin-D deficiency may be an independent risk factor in FS especially simple FS as the Vitamin-D level cut offs were different. Moreover mean values of Vitamin-D in both the Simple Febrile Seizure and Complex febrile seizures groups were in the deficient range in the Zafar study. Another study by Bhat[48] in India studied the correlation between Vitamin-D levels in Simple FS children having recurrent SFS and statistical significance of correlation of Vitamin-D with the number of recurrent seizure episodes was derived, This study revealed that with a decrease in Vitamin-D level the recurrence risk of FS increased. Correlation of Vitamin-D level with recurrence of seizures showed negative correlation with statistically significant correlation coefficient ($r=-0.672$., $P<0.001$).That is as vitamin-D level increases frequency of febrile seizure recurrence decreases and vice versa. This study result strongly supports our own finding that lower vitamin-D levels are associated with higher recurrence risk. They used the same IAP cut offs for Vitamin insufficiency and deficiency as in our study. This could have prophylactic significance as adequate Vitamin-D supplementation in Under 5 children to attain a vitamin-D level above at least 20ng/ml will reduce recurrence risk of febrile seizure. Another research question that needs to be studied is whether higher levels of Vitamin-D in the range 40-60ng/ml[49] which is considered optimal by experts in the field of Vitamin-D research will provide additional benefit. Our study is not without its own share of limitations. This is a cross sectional study carried out over a limited time period in a single centre. We did not study the confounding effect of other possible risk factors. Since our study was not a randomized trial, we could not study any potential protective effect of Vitamin-D supplementation.

CONCLUSION

To conclude there is a high proportion of VDI in children with Febrile seizures in our national setting as well as in our study population . A definite or clear association exists between Vitamin-D levels and risk for FS as well as for the recurrence of FS from our study and from the available studies. Future double blind RCTs to assess the prophylactic protective effect of Vitamin-D supplementation in FS are definitely the need of the hour. If conclusively proved, simple and cost-effective Vitamin-D supplementation can protect thousands of children from developing febrile seizures and its alarming sequella.

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Conflict of Interest: None declared.

Ethical Approval: The study was approved by the Institutional Ethics Committee.

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