ORIGINAL ARTICLE

Status of 25-hydroxy vitamin D level in simple febrile seizures and its correlation with recurrence of seizures

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Access this article online

Website: www.avicennajmed.com

DOI: 10.4103/ajm.ajm_57_19

Quick Response Code:

ABSTRACT

Background: Febrile seizures are associated with a lot of modifiable and nonmodifiable risk factors. Extensive research is currently going on to discover more and more risk factors of febrile seizures, so that they can be modified to decrease their incidence and recurrence. **Aims and Objectives:** The aim of this study was to determine the status of 25-hydroxy vitamin D in children presented with simple febrile seizures and to find its correlation with recurrence of seizures. **Materials and Methods:** This prospective observational study was conducted on 223 children of age group 7–59 months who presented with simple febrile seizures. 25-hydroxy vitamin D were sent to laboratory for quantitative estimation. All data were recorded, status of vitamin D in these children was analyzed, and statistical significance of correlation of vitamin D with the number of recurrent seizure episodes was derived. **Statistical Analysis:** The comparison among groups was carried out by analysis of variance and correlation was conducted by Pearson's correlation analysis. A value of $P < 0.05$ was considered statistically significant. **Results:** 25-hydroxy vitamin D insufficiency was present in 43.5% of the children, deficiency in 30.85 %, and normal level in 25.56% of children who had simple febrile seizures. Majority of the children presented with recurrent episodes of seizures had vitamin D deficiency followed by insufficiency and normal level. Comparison of Vitamin D showed significant negative correlation (As vitamin D level increases frequency of seizure febrile seizure recurrence decreases and vice versa) with recurrence of simple febrile seizures. **Conclusion:** Deficiency of vitamin D is associated significantly with simple febrile seizures and their recurrence is negatively correlated with it.

Key words: Atypical febrile seizure, correlation, simple febrile seizures, 25-hydroxy vitamin D

INTRODUCTION

Febrile seizures are the seizures that are associated with fever of above 38°C (100.4° F), which occur in children older than 6 and younger than 60 months of age, in the absence of any central nervous infections, metabolic disturbances, and any prior afebrile seizures.[1] Febrile seizures can be classified into simple/typical and complex/atypical febrile seizures. Simple febrile seizures are usually generalized tonic clonic type. It lasts ≤ 15 min and does not reoccur within 24 h in children who are neurologically and psychomotorically normal.[2,3] Complex febrile seizures last >15 min. It reoccurs within 24 h and can be focal or generalized with postictal neurological deficit such as Todd's palsy or with prior neurological deficit..[2-4] Etiology of febrile seizure is

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Cite this article as: Bhat JA, Bhat TA, Sheikh SA, Wani ZA, Ara R. Status of 25-hydroxy vitamin D level in simple febrile seizures and its correlation with recurrence of seizures. Avicenna J Med 2020;10:6-9.

multifactorial with a lot of risk factors contributing to its cause. The environmental and genetic factors play a key role in the occurrence of febrile seizures.[5]

At least one episode of simple febrile seizure occurs in 2%–5% of children who are neurologically normal. After the first and second episodes, it reoccurs in 30% and 50% of children, respectively. The risk factors for recurrence of febrile seizures are as follows: age <1 year, duration of fever <24 h, fever 38°C–39°C (100.4–102.2 F), family history of febrile seizures, family history of epilepsy, complex febrile seizure, day care, male gender, and lower serum sodium at the time of presentation.[1]

25-Hydroxy vitamin D is associated with a variety of medical disorders, for example, diabetes, autoimmune disorders, and cardiovascular problems.[6,7] Its role is also well-defined in epileptic patients.[8] However, its role in febrile seizures is under research and few studies are available, which justify its correlation with febrile seizures and their recurrence. The exact mechanism by which vitamin D exerts its beneficial effect in epilepsy is still to be explored. Vitamin D receptors as well as the 1-alpha-hydroxylase, the enzyme that produces 1,25(OH)D (the active form of vitamin D), are distributed widely in the brain.[9] It is suggested that the effect of vitamin D in the central nervous system is mediated by both calcemic and non-calcemic actions.[10] The latter includes changes in gene expression in response to the binding of 1,25(OH)D to the nuclear vitamin D receptor.[11]

In the last decade, a variety of factors such as hypozincemia,[12] low sodium level, and low vitamin B_6[13] were added to the list of risk factors, which increase the incidence and recurrence of simple febrile seizures. Extensive research is currently going on to discover more and more risk factors of febrile seizures, so that they can be modified to decrease their incidence and recurrence. Keeping in view the above discussion, the main objective of our study was hypothesized. The objective was to find the status of 25-hydroxy vitamin D in simple febrile seizures and its correlation with their recurrence.

MATERIALS AND METHODS

This prospective observational study was conducted in World College of Medical Sciences and Research institute, Jhajjar, Haryana, India for the period of three years from November 2015 to October 2018. A total of 223 children aged 7–59 months who fulfilled predefined inclusion and exclusion criteria were included in this study. Proper ethical and scientific clearance was taken from the concerned hospital department and proper consent was taken from parents of the children.

Inclusion criteria

The inclusion criteria of the study included the following:

- Children in age group of 6–59 months presented with simple febrile seizures.

Exclusion criteria

The exclusion criteria of the study included the following:

- Afebrile seizures.
- Atypical febrile seizures.
- Children on anticonvulsant therapy except midazolam/lorazepam, who were given for seizure control outside or inside our hospital.
- Children with liver, kidney, or other metabolic problem, who had impact on 25-hydroxy vitamin D level

After thorough history and examination and special focus on seizure type and recurrence, routine investigations along with 25-hydroxy vitamin D were sent to laboratory for quantitative estimation. 25-hydroxy vitamin D was estimated by chemiluminescent immunoassays methods.

Vitamin D level of children was classified according to guideline for 25-hydroxy vitamin D deficiency by Indian Academy of Paediatrics. This criterion defined vitamin D deficiency level below 12 ng/mL, insufficiency level at 12–20 ng/mL, and normal level above 20 ng/mL.[14]

STATISTICAL ANALYSIS

All data recorded were tabulated and analyzed by the Statistical Package for the Social Sciences software, IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp.) and MedCalc Software 18.11.3. (Acacialaan 22, 8400 Ostend,Belgium). Mean, standard deviation, frequency, and percentage were used to compare the data. Analysis of variance (ANOVA) was used to analyze the differences in various groups. Correlations among groups were done by Pearson's correlation. A value of $P < 0.05$ was considered statistically significant.

RESULTS AND OBSERVATIONS

Our study comprised total 223 children. Among them, 119 were males and 104 were females. There was no statistical difference when vitamin D levels of male and female cases were compared.

Table 1: Vitamin D level in children who had simple febrile seizures

Vitamin D level	*N* (%)	Mean	Standard deviation	Standard error	95% confidence interval for mean	
					Lower bound	Upper bound
Deficiency	69 (30.9)	10.1159	2.30942	0.27802	9.5612	10.6707
Insufficiency	97 (43.5)	17.8184	1.33728	0.13578	17.5488	18.0879
Normal	57 (25.6)	25.9286	6.29158	0.83334	24.2592	27.5980
Total	223 (100)	17.5081	6.90097	0.46212	16.5974	18.4188

Table 2: Frequency of recurrence of simple febrile seizures in vitamin D deficient, insufficient, and normal children

Vitamin D level		Seizure episodes				Total
		1.00	2.00	3.00	4.00	
Deficiency	Count	6	24	26	13	69
	% of total	2.7%	10.8%	11.7%	5.8%	30.9%
Insufficiency	Count	63	31	3	0	97
	% of total	28.3%	13.9%	1.3%	0.0%	43.5%
Normal	Count	53	4	0	0	57
	% of total	23.8%	1.8%	0.0%	0.0%	25.6%
Total	Count	122	59	29	13	223
	% of total	54.7%	26.5%	13.0%	5.8%	100.0%

Children presented with simple febrile seizures had vitamin D deficiency in 69 (30.95%), insufficiency in 97 (43.7%), and normal level in 57 (25.56%) of 25-hydroxy vitamin D [Tables 1 and 2]. Majority of the children (122/54.7%) presented with the first episode of seizure. Of these, 63 (28.3%) had vitamin D insufficiency and 53 (23.8%) had normal level of vitamin D. However, only six (2.7%) children who presented with the first episode of seizure were found to have vitamin D deficiency. A total of 59 (26.5%) children presented with recurrent second episode of seizure. Among them, 31 (13.9%) and 24 (10.8%) had vitamin D insufficiency and deficiency, respectively, whereas only 4 (1.8%) had normal level of 25-hydroxy vitamin D. Only 29 (13%) children presented with recurrent third episode of seizure. Majority of (26 [11.8%]) them had deficiency and only three (1.3%) had insufficiency of vitamin D level. Children who presented with recurrent third episode of simple febrile seizures, none of them had normal vitamin D level. Only 13 (5.8%) children presented with the forth episode of seizure had vitamin D deficiency. None of the children who presented with recurrent forth episode of seizure had insufficiency and normal level of 25-hydroxy vitamin D [Table 2].

Comparison of 25-hydroxy vitamin D levels of normal, insufficient, and deficient children showed statistical significance difference [Table 3].

Our study revealed that with a decrease in vitamin D level the recurrence of febrile seizures increased [Table 2]. Correlation of vitamin D level with recurrence of seizures showed negative correlation with statistically significant correlation coefficient ($r = -0.672$; $P < 0.001$), as shown in Table 4.

DISCUSSION

Our study revealed no gender difference of vitamin D level. Motlaghzadeh *et al.*[15] and Shariatpanahi *et al.*[16] also revealed no gender difference of vitamin D level.

In our study, majority of the children presented with simple febrile seizures had vitamin D insufficiency followed by deficiency and normal level. Motlaghzadeh *et al.*[15] and Singh *et al.*[17] also reported high prevalence of vitamin D insufficiency among children with febrile seizure.

This study revealed significant negative correlation of recurrence of febrile seizures with 25-hydroxy vitamin D. As the number of seizure episodes increased, 25-hydroxy vitamin D level decreased. Maximum number of recurrent seizures episodes, that is, 4 and 3, were seen only in deficiency group. The percentage of children presented with recurrent second episode of seizure was approximately equal in both deficiency and insufficiency groups, and least (1.4%) in normal group. First/single episode of simple febrile seizures was recorded in half (54.7%) of the cases. In these cases (who presented with first/single episode of seizures) only 2.7 % had vitamin D deficiency and rest (97.3%) had either normal (23.8%) or insufficiency (28.3%) of vitamin D levels. After an intensive search, we found only a case presentation of Hoecker *et al.*[18] on recurrent febrile seizure in rachitic child. To our best knowledge there is no study available on correlation of simple febrile seizures with 25-hydroxy vitamin D levels and our study is first one which compared recurrence of simple febrile seizures with 25-hydroxy vitamin D levels. Our study revealed that seizure episode number as compared with various 25-hydroxy vitamin D levels (deficiency, insufficiency, and normal levels) showed statistical significance.

Table 3: Comparison of vitamin D status of normal, deficient, and insufficient children

Vitamin D status		Mean difference	Standard error	Significance (P value)	95% confidence interval	
					Lower bound	Upper bound
Normal	Deficiency	−1.59649	0.11187	0.000	−1.8605	−1.3325
	Insufficiency	−0.31127	0.10431	0.009	−0.5574	−0.0651

Table 4: Correlation of vitamin D level with recurrence of simple febrile seizures

Correlation	*r*	CI for *r*	Significance (*P* value)
Negative	−0.672**	−0.563 to 0.734	<0.001

r = coefficient of correlation, CI = confidence interval

**Correlation is significant at 0.01 level (two tailed)

In conclusion, our research revealed that vitamin D is significantly low in simple febrile patients and it is negatively correlated (negative correlation means: as the level of vitamin D concentration increases recurrence of simple febrile seizures decreases and vice versa) to recurrence of simple febrile seizures. The main drawback of our study could be comparison with controls. However, we overcome this drawback by taking reference vitamin D status values of Indian Academy of Paediatrics, which applies for all the children of our country, and comparison of simple febrile seizures in normal vitamin D level children with deficient and insufficient children.

Recommendations

It will be wise to treat simple febrile seizure and especially recurrent simple febrile seizure patients with vitamin D therapy. However, more studies are needed on this topic and studies must also be conducted on effect of vitamin D therapy on recurrence of simple febrile seizures.

Acknowledgement

We are highly thankful to children and their parents who gave consent to this research. We are highly thankful to our hospital administration, paramedical staff of pediatric department, hospital statistician, and computer operators for helping in conducting this research.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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