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Original Research Article

Association of serum vitamin D levels and simple febrile seizures in children

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ABSTRACT

Background: Febrile seizure is one of the commonest childhood neurologic diseases. There is an increasing concern that vitamin D deficiency may play an etiological role. This study was conducted to find out the association between vitamin D levels and febrile seizure. Objective were to determine the association of vitamin D levels in children with simple febrile seizure.
Methods: This case control study was conducted in institute of child and mother health, Dhaka from July 2019 to June 2020. Children aged six to sixty months with simple febrile seizure were 'cases' and those having fever without seizure were controls. Detailed history regarding breastfeeding, intake of calcium and vitamin D rich diet, sunlight exposure, family history of seizure was taken and physical examinations were done. Data collection was done through a pretested structured questionnaire. Serum vitamin D level was measured.
Results: There were 44 cases of simple febrile seizure and 50 controls. Mean age of the study participants was 16.5±8.9 and 14.4±7.1 months in case group and control group respectively, with a majority in the age group 6-12 months. 34.1% of cases and 22% of controls had deficient vitamin D while 50% of cases and 34% of controls had insufficient vitamin D, respectively. Reduced vitamin D level was more common in case group. Mean vitamin D level was also significantly lower in case group.
Conclusions: Decreased vitamin D level was found to be significantly associated with simple febrile seizure.

Keywords: Vitamin D status, Simple febrile seizure, Neurological disorder

INTRODUCTION

Febrile seizure is a common childhood neurological disorder that involves almost 2%-5% of children globally.[1] The American academy of pediatrics (AAP) has defined FS as a seizure accompanied by fever (temperature ≥100°F or 38°C by any method), without central nervous system infection, that occurs in infants and children 6 through 60 months of age.[2]

The exact pathogenesis of FS is unknown, but different genetic, metabolic, environmental and other factors play role in the incidence of febrile seizure. One of the electrolyte disturbances that can cause seizure episodes is hypocalcemia, and in infancy it usually occurs due to

vitamin D deficiency.[3] The exact mechanism by which vitamin D exerts its beneficial effect in averting febrile seizures is still to be explored. Vitamin D receptors and the 1-alpha-hydroxylase, the enzyme that produces 1, 25-hydroxy vitamin D, the active form of vitamin D, are distributed widely in the brain. It is recognized that the effect of vitamin D in the central nervous system is propitiated by both calcemic and non-calcemic actions.[1] The latter include variations in gene expression in response to the binding of 1,25(OH)D to the nuclear vitamin D receptor thus contribute to the attack of febrile seizure.[1] It is an increasing concern that vitamin D deficiency may also play an etiological role in febrile seizures in children.[4]

Therefore, this study was conducted in a tertiary care hospital to find out the association between serum vitamin D level and the first attack of febrile seizure.

METHODS

This case control study was carried out at department of pediatrics, ICMH, Dhaka from July 2019 to June 2020. Children of age group 6 months to 5 years presenting with simple febrile seizure were enrolled as cases and children of age group 6 months to 5 years presenting with fever without seizure were controls. Children presenting with recurrent attacks of a febrile seizures, complex febrile seizure, prior episodes of afebrile seizure, those having any signs of CNS infections, neurodevelopmental delay, clinical features of rickets, liver, renal or endocrinal disorders were excluded from the study.

To determine the sample size the following formula was followed

$$n = \frac{P1(100-P1)+P2(100-P2)}{(P_1-P_2)^2} \times (Z_\alpha + Z_\beta)^2$$

Proportion of insufficient vitamin D in children with febrile seizure, P1=59.5%.[5]

Proportion of insufficient vitamin D in children without febrile seizure P2=39.1%.[5]

Zα=1.96,

Zβ=0.84.

So, n=90.90=91. Estimated sample size was 182 (91 children in each group, so 91+91=182). But due to time constraint and resource limitation, we took 94 children as study sample (44 cases and 50 controls).

After enrollment detailed history regarding breastfeeding, intake of calcium and vitamin D rich diet, sunlight exposure, family history of febrile seizure or epilepsy etc. and physical examination were done. Five ml sample of venous blood was collected in labeled sterile test tube from each child using disposable syringe. After centrifugation, the supernatant serum was taken for assays of vitamin D and calcium level. Serum vitamin D was measured using the 25-hydroxy vitamin D EIA kit, by Immunoassay Analyzer. In order to categorize various degrees of vitamin D deficiency criteria, sufficient are defined as levels >30 ng/ml, insufficient as 21-29 ng/ml and deficient as levels <20 ng/ml.[6] Sun exposure of minimum 30 minutes per week was taken as adequate duration.[7]

Statistical analysis was performed with statistical package for social science (SPSS) version 20. Chi-square (x^2) statistical test was done to determine the association between categorical variables. Unpaired student t test done to determine difference between continuous variables. A $p<0.05$ was considered as statistically significant.

Ethical clearance certificate was obtained from institutional review board. Informed written consent was taken from each parent of the study subject.

RESULTS

The highest percentage of patients belonged to 6-12 months (45.5% in case group and 50% in control group) (Table I). Mean age was 16.5±8.9 (SD) months in case group and 14.4±7.2 (SD) months in control group. Male respondents were predominant in both groups (54.5% and 58% in respectively) (Figure 1). Urban respondents were predominant in both groups (52% and 64% respectively) (Figure 2).

Statistical difference was found in breast feeding in first 6 months, sun exposure, diet containing vitamin D sources and family H/O febrile seizure between two groups ($p<0.05$) (Table 2), but no significant difference found in family H/O epilepsy and consanguineous parents ($p>0.05$). Among the respondents (6.8% and 36% respectively) had history of exclusive breast feeding ($p<0.001$), 16% and 54% respectively had adequate sun exposure-minimum 30 min/week ($p<0.001$), 20% and 56% respectively was on diet containing vitamin D sources ($p<0.001$), 39% and 4% respectively had family H/O febrile seizure ($p<0.001$). Among the respondents 2.3% and 4% respectively had family H/O epilepsy ($p=0.635$), 9% and 10% respectively had consanguineous parents ($p=0.881$).

Among the case group children upper respiratory tract infection was present in 56.8%, viral croup in 4.5%, urinary tract infection in 2.3%, acute otitis media in 2.3%, pneumonia was in 2.3%, acute gastroenteritis in 4.5% and no associated disease was found in 29.5% (Figure 4). There was no statistical difference was found in serum calcium level between two groups ($p=0.626$). But statistical difference was found in vitamin D level between two groups ($p=0.042$). The serum calcium level was 9.89±0.7 (SD) mg/dL in case and 9.23±0.5 (SD) mg/dl in control (Table 3). The level of vitamin D was 23.1±8.3 ng/ml in case group and 26.4±7.7 ng/ml in

control group. Significant statistical difference in vitamin D level was found between two groups (p<0.05). Among cases, 34.1% had deficient vitamin D levels. 50% had vitamin D levels in insufficient category and in 15.9% levels were normal (Table 4). Similarly, in controls, levels of vitamin D were deficient in 22%, insufficient in 34% and normal levels found in 44% children.

Table 1: Age group distribution of the study children, (n=94).

Age group (months)	Case, (n=44) (%)	Control, (n=50) (%)	P value
6-12	20 (45.5)	25 (50)	0.436
13-24	19 (43.2)	21 (42)	
25-36	2 (4.5)	4 (8)	
37-48	2 (4.5)	0 (0)	
49-59	1 (2.3)	0 (0)	
Mean ± SD	16.5±8.9	14.4±7.2	0.412

Data expressed as frequency and percentage and mean ± SD.

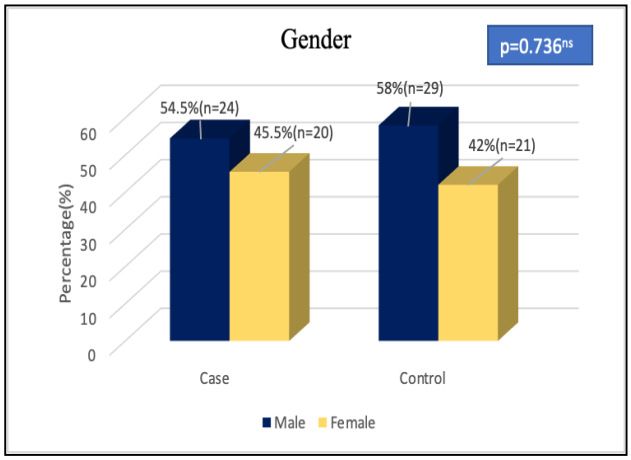

Figure 1: Gender distribution among the cases (n=44) and controls, (n=50).

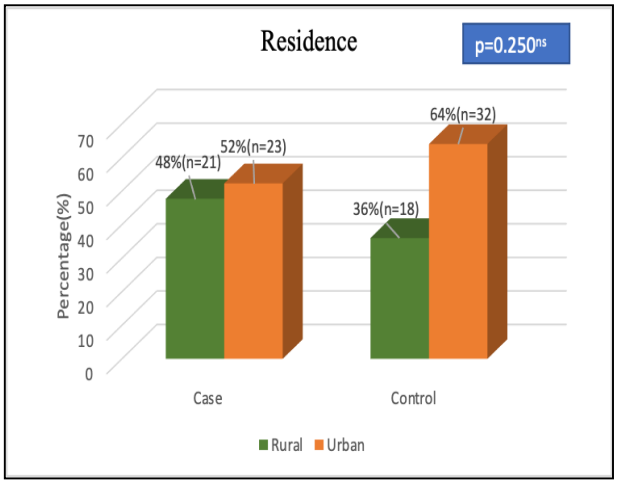

Figure 2: Distribution of cases and controls by residence, (n=94).

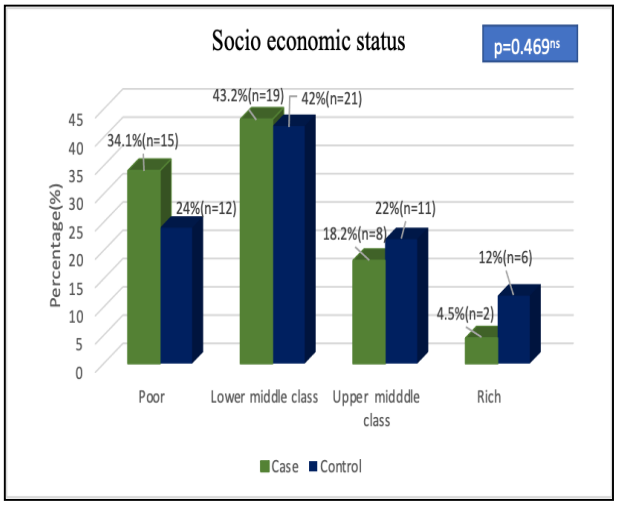

Figure 3: Socio economic status among cases and controls, (n=94).

Table 2: Risk factors associated with febrile seizure (cases) and controls, (n=94).

Risk factors		Case, (n=44) (%)	Control, (n=50) (%)	P value
Breast feeding in first 6 months	**EBF**	3 (6.8)	18 (36)	<0.001
	PBF	12 (27.3)	21 (42)	
	Mixed feeding	27 (61.4)	6 (12)	
	Extended EBF	2 (4.5)	5 (10)	
Sun exposure	**Adequate minimum 30 min/week**	7 (16)	27 (54)	<0.001
	Inadequate less than 30 min/week	37 (84)	23 (46)	
Diet containing vitamin D sources	**Present**	9 (20)	28 (56)	<0.001^{s}
	Absent	35 (80)	22 (44)	
Family H/O febrile seizure	**Present**	17 (39)	2 (4)	<0.001^{s}
	Absent	27 (61)	48 (96)	
Family H/O epilepsy	**Present**	1 (2.3)	2 (4)	0.635
	Absent	43 (97.7)	48 (96)	
Consanguinity	**Present**	4 (9)	5 (10)	0.881
	Absent	40 (91)	45 (95)	

*EBF=Exclusive breast feeding, PBF=Partial breast feeding.

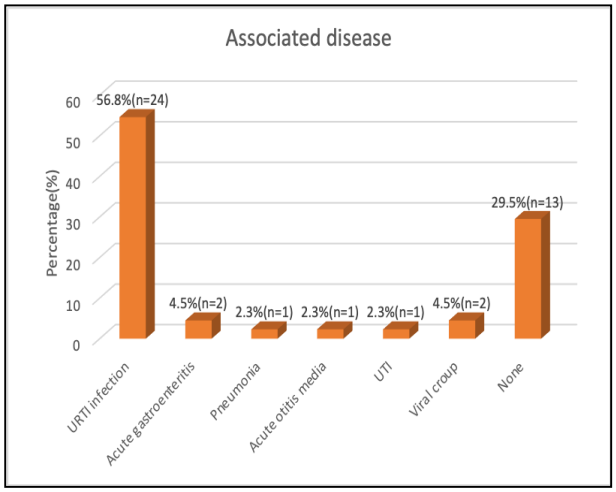

Figure 4: Associated disease among cases, (n=44).

Table 3: Serum calcium and vitamin D level among the cases and controls, (n=94).

Parameters	Case, (n=44) mean ± SD	Control, (n=50) mean ± SD	P value
Vitamin D Level (ng/mL)	23.1±8.3	26.4±7.7	0.042
Serum calcium level (mg/dL)	9.89±0.7	9.23±0.5	0.626

Table 4: Categories of vitamin D level among the cases and controls, (n=94).

Vitamin D level	Case, (n=44) (%)	Control, (n=50) (%)	P value
Deficient	15 (34.1)	11 (22)	0.001[s]
Insufficient	22 (50)	17 (34)	
Sufficient	7 (15.9)	22 (44)	
Total	44 (100)	50 (100)	

*Chi square test was done.

DISCUSSION

Febrile seizures are the most common type of seizure in children causing emergency visits in hospital. There is growing evidence that vitamin D can affect gene expression and modulate various cell metabolisms, thus contribute to the attack of febrile seizure. In Bangladesh, no study was done to find out the association of vitamin D with simple febrile seizure till date.

There was no significant difference between the two groups of children regarding age group (p=0.436) and mean age (p=0.412). The highest percentage of patients belonged to 6-12 months (45.5%) in the case group and 50% in the control group. Mean age was 16.5±8.9 (SD) months in the case group and 14.4±7.2 (SD) months in the control group. In the study by Nahar et al they also found that the mean±SD age of onset of 1st attack of febrile seizures was 18.3±11.4 (SD) months and which corresponds with the current study.[8]

In this study, no statistical difference was found in gender between the two groups (p=0.736). Male respondents were predominant in both groups (54.5% and 58% in respectively). In Esmaili et al study, 124 cases with febrile seizure were boys (57.9%) and remainder were girls (42.1%).[9] These results are similar to the findings of a study conducted by Mahyar et al in Iran; he found that the male gender (p=0.01) had a greater risk of febrile seizure.[10]

According to the study, no statistical difference was found in the residence and the socio-economic status between the two groups (p=0.250). Urban respondents were predominant in both groups (52% and 64% in respectively). Moreover, the lower middle-income group were predominant in both groups (43.2% and 42% in respectively). In Aydin et al study, they also found that most of the children with febrile seizures belonged to the urban area and from the lower middle class, which corresponds with this study findings.[11] They also found that febrile convulsion was relatively higher in the population of developing countries.[11]

In our study, statistical difference was found in breast-feeding in the first six months, sun exposure, diet containing vitamin D sources, and family H/O febrile seizure between two groups (p<0.05). No significant difference was found in family H/O epilepsy and consanguineous parents (p>0.05). Among the respondents (6.8% and 36% respectively) had a history of exclusive breast-feeding (p<0.001), 16% and 54% respectively had adequate sun exposure-minimum 30min/week (p<0.001), 20% and 56% respectively were on a diet containing vitamin D sources (p<0.001), 39% and 4% respectively had family H/O febrile seizure (p<0.001). Among the respondents, 2.3% and 4% respectively had family H/O epilepsy (p=0.635), 9% and 10% respectively had consanguineous parents (p=0.881).

Shariatpanahi et al also found that in patients with febrile seizures, the diet containing vitamin D, history of sun exposure was insufficient.[12] They also found that 60% had a positive family history of febrile seizure, which corresponds with the current study.[12] Tosun et al reported that 57% of children with febrile seizures had a positive family history.[13] In Mahyar et al study, breast-feeding duration was lower among the children who developed febrile seizures.[10] The mean was 15.38±6.88 months in the case and 19±5.35 months in the control group and the difference between two groups found statistically significant (p<0.05), which corresponds with the current study.[10]

According to the study, among the case group children who had febrile seizure, upper respiratory tract infection was present in 56.8%, viral croup in 4.5%, urinary tract

infection in 2.3%, acute otitis media in 2.3%, pneumonia was in 2.3%, acute gastroenteritis in 4.5%. In Shrestha et al study, upper respiratory tract infections were the most common cause of fever in children with a febrile seizure, which was seen in 56.3% of children, which corresponds with this study.[14]

In current study, no statistical difference was found in serum calcium level between two groups ($p>0.05$), but statistical difference was found in vitamin D level between two groups ($p<0.05$). The serum calcium level was 9.89±0.7 (SD) mg/dl in case and 9.23±0.5 (SD) mg/dL in control. The level of vitamin D was 23.1±8.3 ng/mL in the case group and 26.4±7.7 ng/ml in the control group. In Shariatpanahi et al study, the mean vitamin D level was 24.41±11.21 ng/ml that was in insufficient range in children with a febrile seizure, which corresponds with this study.[12]

According to this study, significant statistical difference was found in vitamin D level between two groups ($p<0.05$). Among cases, 34.1% had deficient vitamin D levels. 50% had vitamin D levels in an insufficient category and in 15.9% levels were normal. Similarly, in controls, vitamin D levels were deficient in 22%, insufficient in 34%, and normal levels in 44% of children. In Aliabad et al study, strong and significant ($p<0.01$) association of Febrile seizures with Vit D levels was observed where persons with insufficient vit D levels had three times (OR=3.03) more risk of having febrile seizures as compared to persons with normal vitamin D status.[15]

This study revealed that 25 hydroxy vitamin D level is significantly low in children with simple febrile seizure in comparison to control group. Since vitamin D deficiency remains a major public health problem in developing countries and its possible role in febrile seizures was evaluated by this study and other similar studies, it seems vitamin D screening in children with simple febrile seizure is important.

Limitations

The present study has some limitations. All samples were collected from a single hospital. History of sunlight exposure and dietary history among the study population was taken from mother's recall. So, there may be chance of recall bias. Serum alkaline phosphatase, serum phosphate, parathyroid hormone, serum electrolytes, CSF study were not done. Further multicentered study, with generalized population should be carried out.

CONCLUSION

Vitamin D deficiency and insufficiency was found in more than three-fourth cases of the febrile seizure. The significant association of low vitamin D level and occurrence of febrile seizure could be recognized as a preventable risk factor in simple febrile seizure.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Bhat J, Bhat T, Sheikh S, Wani Z, 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(1):6.
2. Subcommittee on Febrile Seizures; American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics. 2011;127(2):389-94.
3. Mantadakis E, Deftereos S, Tsouvala E, Thomaidis S, Chatzimichael A. Seizures as initial manifestation of vitamin d-deficiency rickets in a 5-Month-old exclusively breast-fed infant. Pediatr Neonatol. 2012;53(6):384-6.
4. Heydarian F, Bakhtiari E, Golmakani H, Fakhr GN, Heidarian M. Serum Level of Vitamin D and Febrile Seizure? A Clinical Study. Iran J Child Neurol. 2020;14(3):77-82.
5. Singh V, Sharma P, Dewan D. Association of vitamin D levels with simple febrile seizures in under five children: a case control study. Int J Contemporary Pediatr. 2019;6(2):365.
6. Eric Seaborg. Just Right: How Much Vitamin D is Enough? Endocrine news. 2014.
7. Reid IR, Gallagher DJ, Bosworth J. Prophylaxis against vitamin D deficiency in the elderly by regular sunlight exposure. Age Ageing. 1986;15:35-40.
8. Nahar N, Ahmed AM, Bhuiyan T, Tayab AM, Islam A. Clinical aspects of febrile seizures, knowledge, attitude, preactice and impacts in admitted children. IOSR-JDMS. 2015;18(5):17-28.
9. Esmaili Gourabi H, Bidabadi E, Cheraghalipour F, Aarabi Y, Salamat F. Febrile seizure: Demographic features and causative factors. Iran J Child Neurol. 2012;6(4):33-7.
10. Mahyar A, Ayazi P, Fallahi M, Javadi A. Risk Factors of the First Febrile Seizures in Iranian Children. Int J Pediatr. 2010;1-3.
11. Aydin A, Ergor A, Ozkan H. Effects of sociodemographic factors on febrile convulsion prevalence. Pediatr Int. 2010;50(2):216-20.
12. Shariatpanahi G, Paprooschi N, Yaghmaei B, Sayarifard F, Sayarifard A. Exploring Vitamin D in Children with Febrile Seizure: A Preliminary Study. Int J Pediatr Mashhad. 2018;6(9):8233-9.
13. Tosun A, Koturoglu G, Serdaroglu G, Polat M, Kurugol Z, Gokben S et al. Ratios of nine risk factors in children with recurrent febrile seizures. Pediatr neurol. 2010;43(3):177-82.
14. Shrestha D, Dhakal AK, Shakya H, Shakya A, Shah SC, Mehata S. Clinical characteristics of children with febrile seizure. J Nepal Heal Res Council. 2014;12(28):162-6.
15. Aliabad GM, Khajeh A, Fayyazi A, Safdari L.

Clinical, Epidemiological and Laboratory Characteristics of Patients with Febrile Convulsion. J Comprehensive Pediatr. 2013;4(3):134-7.

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