Open Access

Original Article

Paediatric Patients-Based Case-Control Analysis: The Association Between Serum Vitamin D Levels And Febrile Seizures

Shaheen Masood, Riffat Farrukh, Amber Naseer, Farhina Nasir*, Ibrahim Shakoor, Syed Arif Iqbal

Department of Paediatrics, Abbasi Shaheed Hospital, Karachi Medical and Dental College (KMDC) Pakistan, *Department of Pathology, Karachi Medical and Dental College, Pakistan

ABSTRACT

Objective: To determine the association between serum vitamin D levels and febrile seizures in the paediatric patients.
Study Design: Case-Control Study.
Place and Duration of Study: Abbasi Shaheed Hospital, Karachi Pakistan, from Mar 2020 to Mar 2021.
Methodology: The study included all pyrexia paediatric patients, both with and without febrile seizures, as cases and controls. Children aged below six months or older than 60 months, with a previous history of afebrile seizures, diagnosed with central nervous system infection, dehydration, or electrolyte disturbance, were excluded from the study. Serum vitamin D levels and other demographic data were documented.
Results: The study included 86 cases and controls. The mean age of cases was 28.07±16.47, and the controls were 26.38±15.72 months. The rate of vitamin D insufficiency was three times more likely in cases compared to controls, i.e. [OR, 95% CI: 3.95 (2.084—7.489)] with p=0.0001.
Conclusion: Vitamin D deficiency is substantially more likely in the case than in the control group. As a result, children with febrile seizures should have their serum vitamin D levels tested.

Keywords: Febrile seizures, Hypovitaminosis, Paediatric population, Vitamin D.

How to Cite This Article: *Masood S, Farrukh R, Naseer A, Nasir F, Shakoor I, Iqbal SA. Paediatric Patients-Based Case-Control Analysis: The Association Between Serum Vitamin D Levels And Febrile Seizures. Pak Armed Forces Med J 2024; 74(2): 335-338.*
DOI: https://doi.org/10.51253/pafmj.v74i2.6801

INTRODUCTION

The leading cause of seizures associated with a febrile illness in children accounts for 2-5% of the children admitted to the Emergency Department.[1] Febrile seizures are more common in the first one and a half years of life.[2] However, febrile seizures occurring within six months after birth raise suspicion of an underlying central nervous system infection.[3]

Certain intrinsic pyrogens, like interleukin beta 1, have been reported to contribute to increased neuronal excitability and stimulation, leading to an increased risk of febrile seizures.[4] A typical seizure is described as a generalised tonic-clonic episode of fits, persisting for at least fifteen minutes.[5] There are certain risk factors associated with febrile seizures, including maternal intake of alcohol and smoking during gestation, age, male gender, family history, genetic predisposition, perinatal exposure to antiretroviral drugs and certain vitamin deficiencies.[6]

Recently, low vitamin D levels were found to be linked to an increased risk of febrile seizures. Vitamin D deficiency is fairly common in the paediatric population, with a known global prevalence of 12.1%.[7] Seizures are common in children with febrile illnesses associated with low vitamin D levels.[8] sIn several international studies, the insufficiency or deficiency of serum vitamin D levels has been linked to febrile seizures in infants and young children. There is a relationship between brain maturation and serum vitamin D levels.[7-9]

There are only limited studies from Pakistan that have reported socio-demographic parameters of children presenting with febrile seizures; however, no study thoroughly evaluated the relationship between vitamin deficiency in children and febrile seizures in our study population.[9-10] Thus, in the present study, we evaluated the association between vitamin D levels and increased frequency of febrile seizures in the paediatric population at our setup.

METHODOLOGY

The case-control study was conducted at Abbasi Shaheed Hospital Karachi, Pakistan from March 2020 to March 2021 after the Institutional Ethical Committee approval (Number 2020-PM/012923/ASH). Sample size was calculated using WHO sample size calculator for health studies based

Correspondence: Dr Shaheen Masood, Department of Paediatrics, Abbasi Shaheed Hospital, Karachi Medical and Dental College Pakistan
Received: 28 May 2021; revision received: 02 Dec 2021; accepted: 17 Dec 2021

on the prevalence of vitamin D deficiency in cases v/s control as (73% v/s 45.9%).[10]

Inclusion Criteria: Children of either gender, aged six months to five years old with pyrexia (defined by a body temperature greater than 38.3°C on a Mercury thermometer documented on two consecutive occasions 4 hours apart) were included.

Exclusion Criteria: Children with a previous history of afebrile seizures, diagnosed with central nervous system infection, dehydration, or electrolyte disturbance, were excluded.

Data collection was initiated after informed verbal consent from the parents and the child's guardian. The non-probability consecutive sampling technique was applied to recruit patients for the study.

The sample of 86 children with febrile seizures and 86 without febrile seizures were included in the study as cases and controls, respectively. One hundred seventy-two children were enrolled.

A febrile seizure was characterised as a seizure with a generalised pattern without focal activity persisting for less than 15-20 minutes in concomitance with a febrile illness.[11] Blood samples of all the patients included were taken. The serum levels of vitamin D, haemoglobin (Hb), blood sugar (BS), creatinine (Cr), blood urea nitrogen (BUN), calcium (Ca), potassium (K), sodium (Na), alkaline phosphatase (ALP), phosphorus (P), and platelet and white blood cells (WBC) counts were measured. The immunochemical method was used for analysis for the biochemical assessment of vitamin D. Vitamin D status was classified into three categories based on serum 25-hydroxy vitamin D (25(OH)D) ≥ 30 ng/ml for normal, 21-29 ng/ml for insufficient, and ≤20 ng/ml was taken as the cut-off for the vitamin D deficiency. Venous blood samples were collected into plain tubes, and serum was separated and stored at -700C until analysis.

The Statistical Package for Social Sciences (SPSS) version 26 was used for data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. For statistical difference, Chi-square and independent sample t-tests, as appropriate, were used. The odds ratio were calculated to measure the association of vitamin D levels with febrile seizures. Odds ratio >1 with p ≤0.05 considered as statistically significant.

RESULTS

One hundred seventy-two children were enrolled in the study (86 in the Case Group and 86 in the Control Group). The mean age of the patients was 27.23±16.07 months. Both groups' average vitamin D levels were 29.69±10.19 ng/ml, shown in Table-I.

Table-I: Baseline Characteristics of Study Group (n=172)

Variables	Groups		95% Confidence Interval	*p*-value
	Cases (n=86)	Controls (n=86)		
Age (Months) Mean±SD	28.07±16.47	26.38±15.72	-3.16 to 6.53	0.493
Vitamin D(ng/mL) Mean ±SD	24.44±7.60	34.94±9.76	-13.13 to 7.86	0.001*

Vitamin D deficiency was noted in 65(75.6%) patients in cases while 29 (33.9%) were in control, with a highly significant difference (p=0.001), mentioned in Table-II.

Table-II: Demographic and Clinical Parameters of Study Groups (n=172)

Variables	Groups		*p*-value
	Case	Control	
Gender			
Male	54(62.8%)	50(58.1%)	0.533
Female	32(37.2%)	36(41.9%)	
Vitamin D Status			
Normal	21(24.4%)	57(66.3%)	0.001*
Deficient	13 (15.1%)	5(5.8%)	
Insufficient	52(60.5%)	24(27.9%)	

The Laboratory investigation of the study groups are shown in Table-III.

Deficient status of vitamin D was noted in 13(72.2%) cases and 5(27.8%) in controls. The odds of being deficient in vitamin D status were 2.8 times more likely in cases as compared to control, i.e. [OR, 95% CI: 2.885 (0.98--8.48)] with p< 0.05. While insufficient vitamin D was noted in 52(68.4%) cases and 24(31.6%) in controls, the odds of having insufficient vitamin D status were 3.9 times more likely in cases as compared to control, i.e. [OR, 95% CI: 3.951 (2.08—7.48)] with p< 0.05, shown in Table-IV.

DISCUSSION

Seizures are a common neurological occurrence in children aged six months to 5 years old who are suffering from a febrile illness. It is more frequently associated with Asian ethnicity.[11] The aetiology of febrile seizures is dependent upon multiple factors. The phenomenon is dependent upon age, as febrile seizure is a manifestation occurring in an undeveloped

Table-III: Laboratory Findings of Study Groups (n=172)

Variables	Groups		95% Confidence Interval	*p*-Value
	Cases (n=86) Mean±SD	Controls (n=86) Mean±SD		
Platelet (cells/micr)	260.06±5.94	324.93±15.58	-68.41 to 61.31	0.001
Potassium (mmol/L)	4.08±1.75	5.16±0.73	-1.48 to 0.67	0.001
Sodium (mq/L)	139.23±1.4	141.12±58	-3.15 to 0.63	0.001
Phosphorus (mg/dL)	4.38±0.98	4.61±0.75	-0.49 to 0.03	0.007
Haemoglobin(gram/dL)	10.91±3.15	10.95±2.70	-0.91 to 0.84	0.230
White Blood Cells (cell/micro)	10.46±2.38	11.27±2.31	-1.52 to 0.10	0.510
Blood Sugar (mg/dL)	113.23±5.44	105.84±579	5.69 to 9.07	0.195
Creatinine (mg/dL)	0.47±0.03	0.49±0.01	-0.03 to 0.01	0.001
Blood Urea Nitrogen (mg/dL)	22.05±4.31	26.87±4.69	-6.17 to 3.45	0.771
Calcium (mg/dL)	9.60±2.63	9.79±2.33	-0.93 to 0.56	0.227
Alkaline Phosphatase (ALP) (unit/L)	530.93±8.38	519.36±12.18	8.42 to 14.71	0.001

Table-IV: Association between Vitamin D Status and Febrile Seizures (n=172)

Vitamin D Status	Groups		Odds Ratio	95% CI	*p*-value
	Case	Control			
Deficient	13 (72.2%)	5(27.8%)	2.885	0.981 to 8.485	0.046*
Insufficient	52 (68.4%)	24(31.6 %)	3.951	2.084 to 7.489	0.0001 *

and immature brain in response to pyrexia.[12] Due to increased neuronal excitability, the brain of a child is prone to febrile seizures. Many clinical trials have shown that deficiency or insufficiency of vitamin D, B-complex vitamins, calcium, zinc, and magnesium increases the risk of febrile seizures in the paediatric population.[13-14]

The current study evaluated the connection between our population's vitamin D deficiency and febrile seizures. We reported that children with lower levels of vitamin D were more likely to suffer from febrile seizures. Febrile seizures were significantly more frequently seen in children with low levels of serum vitamin D (p<0.05).

In a study by Bhat and colleagues, the relationship between febrile seizures and 25-hydroxy vitamin D was determined. The authors revealed that out of the 223 children who had febrile seizures, 43.5% had vitamin D insufficiency, and 30.85 per cent had a deficiency. Thus, it was concluded that decreasing vitamin D levels correlated with increasing incidence of febrile seizures.[15] In contrast, Heydarian *et al*. evaluated the plasma level of vitamin D in children with or without febrile seizures; however, they found no significant difference between the two groups (48.41 ± 15.25 versus 41.92 ± 22.42 ug/dl). This could be because of their small sample size and variation in socio-demographic parameters of the study population. However, they noted that children with febrile seizures were significantly younger than those without seizures (p=0.001).[16]

Vitamin D deficiency can cause a wide range of neurological disorders and mental retardation, according to a 2017 study by Di-Somma *et al*. Vitamin D is completely necessary for brain development, and deficiency can contribute to a wide range of neurological disorders and mental retardation.[17] This explains why children with a deficiency of vitamin D are more at risk of developing febrile seizures.[18] More studies are necessary to evaluate the statistical association with a larger sample size and more parameters in multiple study centres in Pakistan to validate the findings of the present study.

ACKNOWLEDGEMENT

The authors want to acknowledge the parents who consented to enrol their children in the study.

CONCLUSION

Vitamin D deficiency is significantly more likely in the case than in the control group. As a result, children with febrile seizures should have their serum vitamin D levels tested.

Conflict of Interest: None.

Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

SM & RF: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

AN & FN: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

IS& SAI: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity

of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Natsume J, Hamano SI, Iyoda K, Kanemura H, Kubota M, Mimaki M, et al. New guidelines for management of febrile seizures in Japan. Brain Dev 2017; 39(1): 2-9. https://doi.org/10.1016/j.braindev.2016.06.003
2. Habib Z, Akram S, Ibrahim S, Hassan B. Febrile seizures: factors affecting risk of recurrence in Pakistani children presenting at The Aga Khan University Hospital. J Pak Med Assoc 2003; 53(1): 11-17.
3. Al Morshedy S, Elsaadany HF, Ibrahim HE, Sherif AM, Farghaly MA, Allah MA, et al. Interleukin-1β and interleukin-1receptor antagonist polymorphisms in Egyptian children with febrile seizures: a case-control study. Medicine 2017; 96(11): 1-6. https://doi.org/10.1097/md.0000000000006370
4. Kumar N, Midha T, Rao YK. Risk factors of recurrence of febrile seizures in children in a tertiary care hospital in Kanpur: a one year follow up study. Ann Indian Acad Neurol 2019; 22(1): 31-36. https://doi.org/10.4103/aian.aian_472_17
5. Renda R, Yüksel D, Gürer YY. Evaluation of patients with febrile seizure: risk factors, reccurence, treatment and prognosis. Pediatr Emerg Care 2020; 36(4): 173-177. https://doi.org/10.1097/pec.0000000000001173
6. Hoecker CC, Kanegaye JT. First place winner: Recurrent febrile seizures: an unusual presentation of nutritional rickets. J Emerg Med 2002; 23(4): 367-370. https://doi.org/10.1016/s0736-4679(02)00570-x
7. Khadilkar A, Khadilkar V, Chinnappa J, Rathi N, Khadgawat R, Balasubramanian S, et al. Prevention and treatment of vitamin D and calcium deficiency in children and adolescents: Indian Academy of Pediatrics (IAP) Guidelines. Indian Pediatr 2017; 54(7): 567-573. https://doi.org/10.1007/s13312-017-1070-x
8. Sujatha B, Narayan K, Nair LDV, Shanmuganathan H. Impact of nutritional status and vitamin D levels in children with febrile seizure from a Suburban Tertiary Hospital in Tamil Nadu, India. J Clin Diagn Res 2020; 14(9): 6-10. http://doi.org/10.7860/JCDR/2020/45324.14015
9. Rabbani A, Alavian S-M, Motlagh ME, Ashtiani MT, Ardalan G, Salavati A, et al. Vitamin D insufficiency among children and adolescents living in Tehran, Iran. J Trop Pediatr 2008; 55(3): 189-191. https://doi.org/10.1093/tropej/fmn078
10. Hussain S, Tarar SH, Sabir MU. Febrile seizures: demographic, clinical and etiological profile of children admitted with febrile seizures in a tertiary care hospital. J Pak Med Assoc 2015; 65(9): 1008-1010.
11. Holló A, Clemens Z, Kamondi A, Lakatos P, Szűcs A. Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. Epilepsy Behav 2012; 24(1): 131-133. https://doi.org/10.1016/j.yebeh.2012.03.011
12. Sharawat IK, Singh J, Dawman L, Singh A. Evaluation of risk factors associated with first episode febrile seizure. J Clin Diagn Res 2016; 10(5): SC10–SC13. https://doi.org/10.7860%2FJCDR%2F2016%2F18635.7853
13. Namakin K, Zardast M, Sharifzadeh G, Bidar T, Zargarian S. Serum Trace elements in febrile seizure: a case-control study. Iran J Child Neurol 2016; 10(3): 57-60.
14. Srinivasa S, Manjunath MN. Serum zinc levels in children with febrile seizures. J Evol Med Dent Sci 2014; 3(12): 2983-2989.
15. 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(1): 6-9. https://doi.org/10.4103%2Fajm.ajm_57_19
16. Heydarian F, Bakhtiari E, Golmakani H, Ghasemi NF, Heidarian M. Serum level of vitamin D and febrile seizure? A clinical study. Iran J Child Neurol 2020; 14 (3): 77-82.
17. Di-Somma C, Scarano E, Barrea L, Zhukouskaya VV, Savastano S, Mele C, et al. Vitamin D and neurological diseases: an endocrine view. Int J Mol Sci 2017; 18 (11): 2482. https://doi.org/10.3390%2Fijms18112482
18. 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 Contemp Pediatr 2019; 6 (2): 365-368. http://doi.org/10.18203/2349-3291.ijcp20190019