Low Serum Ferritin Level: A Risk Factor of Simple Febrile Seizures– A Hospital-Based Case-Control Study

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Abstract:

Background: Febrile seizure (FS) is the single most common seizure type in children younger than 5 years. The age for peak incidence of febrile seizure is 14 to 18 months, which overlaps with that of iron deficiency anemia.

Objectives: The purpose of this study was to explore the association of serum ferritin and iron deficiency anaemia with simple febrile seizures.

Methods: In this case-control study 50 patients with febrile seizure were evaluated for iron deficiency anaemia by estimation of Hemoglobin%, MCV, MCH, RDW, and serum ferritin. The control group consisted of 50 febrile children of the same age group without convulsion. Data were recorded in case record form and all the outcomes were recorded.

Results: In this study, the mean age of the patients was 20.48 ± 13.79 (range: 6-60) months. In the case group, the mean (± SD) Serum Ferritin level was 52.54 ± 52.64 µg/L and in the control group, the mean (± SD) S. Ferritin level was 87.40 ± 75.74 µg/L. In the case group, 46% of patients had low ferritin level and in the control group, 24% of patients had low ferritin level. Iron Deficiency Anaemia (IDA) was found among 26% of children in the case group and 14% in the control group. A statistically significant difference was found regarding mean S. Ferritin level and ferritin status between the case and control group. (Odds ratio 0.002 and 2.698) But, in the case of IDA, there was no statistically significant difference observed between the groups.

Conclusion: A low ferritin level was associated with an increased risk of febrile seizures. Therefore, in children with febrile seizures, clinicians should be concerned about ferritin status even at normal hemoglobin levels.

Keywords: Febrile seizure, Serum ferritin level, Iron deficiency anaemia, Risk factor

Introduction:

A febrile seizure is defined as 'seizures that occur between the age of 6 and 60 months with a temperature of 38-degree centigrade or higher, that are not the result of central nervous system infection or any metabolic imbalance and that occur in the absence of a history of prior afebrile seizures'.[1]

Although febrile seizure is benign and almost never causes brain damage, it is one of the leading causes of doctor consultation on an emergency basis and hospital admission of children. It accounts for about 2% of children's hospital emergency department visits.[2] Patients and families may have very frightening experiences and high levels of anxiety during the event.

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It has a risk of epilepsy in 1% of cases and has a recurrence rate of 30 - 40%.[3] It is therefore important to find out its modifiable risk factors. To establish an association between febrile seizures and one of the most prevalent micronutrient deficiency - IDA, several international[1,4,5-10] and a few local researches[11,12] were done. Furthermore, the age for peak incidence of febrile seizure is 14 to 18 months which overlaps with that of iron deficiency anaemia which is from 6 to 24 months.[13] Despite these facts, the results of the studies are completely conflicting. While most studies have suggested iron insufficiency as a predisposing factor for febrile seizures, some have even described iron deficiency anaemia (IDA) to be less frequent in children with febrile seizures. Concerning the high prevalence of both febrile seizure and IDA in children and because IDA is a probable modifiable risk factor for its occurrence, as well as controversy in previous studies on this subject, we thought to evaluate whether iron deficiency anemia would be a risk factor for patients of febrile seizures admitted in a tertiary care Hospital.

Methodology:

This was a case-control study. The study was conducted in Chittagong Medical College Hospital (CMCH) in the Department of Pediatrics from September 2022 to February 2023. Patients aged 6 months to 5 years presenting with or without convulsion admitted during that period were enrolled in the study. Children with simple febrile seizures enrolled as cases and children with acute febrile illness without seizures were labelled as control. A detailed history was taken and clinical examination were done. Convenient sampling method was followed. Children with a history of afebrile seizure, having hematologic problems like hemolytic anemia, bleeding or coagulation disorder, hematologic malignancy, hypoglycemia, children who were on iron supplementation and very sick children were excluded from the study. Iron deficiency anemia was defined as hemoglobin <11g /dL, MCV <70 fl, MCH <27 pg, red cell distribution width (RDW) of >15% and serum ferritin <12 µg/L.[14] In the presence of fever, a higher cut-off value of serum ferritin 30 µg/L was considered.[15] Ethical clearance was taken from the ethical review committee of Chittagong Medical College.

Procedure of data collection:

In this case-control study, 50 children with a diagnosis of simple febrile seizure were assessed as case. The control group consisted of 50 febrile children of the same age group without convulsion. Patients with fever were selected according to inclusion and exclusion criteria. After getting written informed consent from the parents' information regarding demographic data, seizure details, nature of the febrile illness, family history of epilepsy/ febrile seizures, and nutritional status were recorded. Estimation of Hemoglobin level, RBC indices, and plasma ferritin were done from both cases and control. With all aseptic precautions, 6 ml of venous blood was collected from each participant using an evacuated tube system. A 3 ml blood sample was taken in red colored top vacutainer without any anticoagulant for estimation of serum ferritin and the rest 3 ml into EDTA containing lavender colored top vacutainer for estimation of complete blood count including RBC indices. The samples of red top vacutainer were allowed to clot completely and centrifugation was done. After centrifugation samples had to be observed for any hemolysis or fibrin thread due to incomplete clot. Then the samples were placed into an Eppendorf tube and preserved at 2-8 degrees for storage. The other lavender one had to be tested as early as possible. The samples were analyzed in a well-equipped biochemistry laboratory. Hemoglobin, MCV, and MCH were estimated as part of a complete blood count in an autoanalyzer (Sysmax-XN 1000). Serum ferritin level was measured by using the immunonephelometry method in the Atellica NEPH 630 system. All relevant data were noted in the pretested data sheet. All data were checked and rechecked to avoid errors.

Data analysis:

Data were collected from patients by interview, physical, and laboratory examination using a structured questionnaire containing all the variables of interest and were entered in Google form for organizing the data. Later the data set was downloaded and analyzed through SPSS (Statistical Package for the Social Sciences) version 25 and MS Excel to generate a master sheet. The chi-square test and Student t-test were applied to compare two or more populations and two means respectively. Univariate and multivariate logistic regression analyses are applied to assess the independent predictors of febrile seizures, with the results expressed as an odds ratio (OR) with a 95% confidence interval (CI). A p-value of <0.05 was regarded as significant.

Results:

A total of 100 children were included in the study. Both case and control groups were evaluated for iron deficiency anaemia by estimation of hemoglobin%, MCV, MCH, RDW, and serum Ferritin and data were compared.

The mean (± SD) age of the patients was 20.48 ± 13.79 (range: 6-60) months and two-thirds of them were male. There was no statistically significant difference between case and control groups regarding socio-demographic characteristics and nutritional status (Table I). On

univariate analysis, the mean (± SD) S. Ferritin level was lower in the case group (52.54 ± 52.64 µg/L) in comparison to the control group and the difference was statistically significant. Though S. Ferritin status was significantly lower in patients of the case group than in the control group (46% vs 24%), the majority of patients of both groups had no iron deficiency anaemia (74% vs 86%) according to the operational definition (Table II). According to multivariate logistic regression analysis, low S. Ferritin level and low ferritin status significantly increased the risk of febrile seizure (Table III).

Table I

Socio-demographic characteristics and Nutritional status of the studied population (n=100)

Characteristics	Case	Control	Total	P value
Age (months)				
Mean ± SD	22.82 ± 13.57	18.14 ± 13.75	20.48 ± 13.79	0.090
Range	8-60	6-60	6-60	
Gender	n (%)	n (%)	n (%)	
Male	33 (66%)	30 (60%)	63 (63%)	0.534
Female	17 (34%)	20 (40%)	37 (37%)	
Residence				
Rural	29 (58%)	29 (58%)	58 (58%)	1.00
Urban	21 (42%)	21 (42%)	42 (42%)	
Nutritional status				
No malnutrition	17 (34%)	18 (36%)	35 (35%)	0.966
Grade I malnutrition	20 (40%)	20 (40%)	40 (40%)	
Grade II malnutrition	13 (26%)	12 (24%)	25 (25%)	

Table II

Laboratory profile of the patients (n=100)

Variables		Case	Control	Total	P value
Hb% (g/dl)	Mean ± SD	10.25 ± 1.33	10.41 ± 1.42	10.33 ± 1.37	0.557
	Range	7.1-14.2	6.8-13.7	6.8-14.2	
RBC (´10^{12}/L)	Mean ± SD	4.635 ± 0.43	4.557 ± 0.50	4.596 ± 0.47	0.414
	Range	3.69-5.7	3.48-5.82	3.48-5.82	
MCV (fl)	Mean ± SD	68.60 ± 7.45	71.09 ± 8.75	69.85 ± 8.18	0.129
	Range	53.1-84.0	50.0-93.7	50.0-93.7	
MCH (pg)	Mean ± SD	22.20 ± 2.98	23.17 ± 3.96	22.68 ± 3.52	0.171
	Range	16.0-29.0	14.3-32.2	14.3-32.2	
RDW (%)	Mean ± SD	16.68 ± 3.52	16.67 ± 4.18	16.68 ± 3.85	0.992
	Range	12.1-31.6	11.8-33.7	11.8-33.7	
S. Ferritin (µg/L)	Mean ±SD	52.54 ± 52.64	87.40 ± 75.74	69.97 ± 8.18	0.009
	Range	4.53-280	5.0 - 294	4.53-294	
Ferritin status	Low	23 (46%)	12 (24%)	35 (35%)	0.021
	Normal	27 (54%)	38 (76%)	65 (65%)	
IDA	Yes	13 (26%)	7 (14%)	20 (20%)	0.134
	No	37 (74%)	43 (86%)	80 (80%)	

Table III

Multivariate logistic regression analysis of factors associated with febrile seizures

Variables	OR	95% CI		P value
		Lower	Upper	
Age	-0.007	-0.014	0.000	0.054
Male	1.294	0.573	2.921	0.534
Hb	-0.049	-0.195	0.097	0.504
S. Ferritin	0.002	0.000	0.004	0.046
Low ferritin status	2.698	1.148	6.341	0.021
IDA	2.158	0.779	5.977	0.134

OR: Odds Ratio; CI: Confidence Interval

Discussion:

Febrile seizure, a common seizure disorder in children, can lead to increased morbidity and mortality because of the risk of aspiration and hypoxia during the event. There are many risk factors associated with febrile seizures.[16] In this study, patients of both case and control groups were evaluated for iron deficiency anaemia by estimation of hemoglobin%, MCV, MCH, RDW, and serum ferritin. Our study found that among 50 patients with febrile seizures, most of the patients (78%) developed seizures within 24 hours of fever and all the patients had a single seizure.

In this study, the mean (± SD) age was 22.82 ± 13.57 months in case groups and 18.14 ± 13.75 months in the control group which was not statistically significant. This finding is consistent with other studies.[6,12,18] Alom et al found the mean age of the cases and controls were 18.55±6.60 and 18.70±8.73 months respectively.[12] Sex distribution in the current study has a seizure predilection towards male children with 66% and 34% in females (p-value>0.05). Male predominance was also found in the study by Alom et al [12], Aziz et al[18].

The nutritional status of the children can influence iron deficiency. In the present case series, grade I and grade II malnutrition were found among 40% and 25% of children respectively; 35% of children had no malnutrition. There was no significant difference observed between the two groups of patients according to the p-value for residence and nutritional status.

Alam et al.[12] observed that in children with febrile seizure, 28(35%) had no PEM, 32(40%) had mild malnutrition and 20(25%) had moderate malnutrition.

Whereas, within controls, 32(40%) had no PEM, 24(30%) had mild malnutrition and 24(30%) had moderate malnutrition. There was no significant difference in nutritional status between the cases and controls (p>0.05), that is cases and controls were nutritionally matched. This finding is consistent with our study. Therefore, it appears that iron deficiency found significantly higher in simple febrile seizure was not due to nutritional influence among the two groups.

The mean (± SD) Hb of the cases and controls were 10.25 and 10.41g/dl respectively. No statistically significant difference was found when comparing Hb%, MCV, MCH, and RDW between the two groups. This finding is similar to few other studies.[6,7] Daoud et al. found that mean Hb, MCV, and MCH were lower in the case group than the control but it was not statistically significant, they also found a significantly lower value of mean ferritin in the case group which matches with our study result.[7] But Alam et al. found in their study, the mean Hb level of cases and controls were 9.86±1.30 and 10.94±0.94(gm/dl) respectively (p<0.001), the mean MCH of cases and controls were 20.50±3.36 and 23.24±2.76 (pg) respectively (p<0.001) and the mean RDW % of cases and controls were 17.52±2.15 and 16.10±1.79 (%) respectively (p<0.001). The level of MCV was also found lower among cases than controls and the differences were statistically significant (p<0.001).[12]

Among all indices that we measured to establish IDA according to operational definition, only mean S. ferritin level and S. ferritin status were significantly lower in studied cases compared to control. Ferritin is a storage form of iron and provides a sensitive and specific

indicator for determining iron deficiency at an early stage. Differences in Hb, MCV, and MCH reflect chronic iron status and they are not influenced by acute stress conditions. Febrile seizures usually occur early in the illness, before hemoglobin concentration has a chance to drop as a result of infection.

IDA was found among 20% of the total patients in our study. Risk factor analysis by adjusted binary logistic regression showed an odds ratio for low ferritin status 2.698 (1.148-6.341) (95% CI) p 0.021 that is low ferritin status is considered a risk factor for developing simple febrile seizure. Though IDA was found comparatively in more cases than in controls and the odds ratio was 2.158 (0.779-5.977) (95% CI) but p-value was 0.134 (ns). So IDA was not considered as a risk factor of simple FS in our study. Some studies also reported similar findings.[6,12,17,18]

Conclusion:

The study finds serum ferritin is significantly low among children with simple febrile seizures compared to febrile children without seizures. Low ferritin status can be regarded as a risk factor for febrile seizure in children. So early detection and timely correction of iron deficiency may be helpful for the prevention of simple febrile seizures in children.

References:

1. Kumari PL, Nair MKC, Nair SM, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures—a case control study. Indian Pediatr 2012;49(1):17–9. Available from: http://dx.doi.org/10.1007/s13312-012-0008-6

2. Biswas R, Munsi AS, Rahman M, Begum N, RC Das. Clinical profile of febrile convulsion among admitted children in a tertiary care hospital at Dhaka city, Bangladesh. Northern International Medical College Journal. July 2015;7(1):101.

3. Saeed T, Haq MZ, Kanwa A, Zulfiqar R, Raja TM. Association of Iron Deficiency Anaemia and Febrile Seizures in Children. Journal of Rawalpindi Medical College (JRMC) 2013;17(2):175-177.

4. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. In dian Pediatr. 2010; 47(5): 437-39.

5. Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anemia and febrile seizures. J Coll Physicians Surg Pak. 2005; 15:338-40. PubMed PMID: 15924837.

6. Jang HN, Yoon HS, Lee EH. Prospective case control study of iron deficiency and the risk of febrile seizures in children in South Korea. BMC Pediatr [Internet]. 2019;19(1):309. Available from: http://dx.doi.org/10.1186/s12887-019-1675-4.

7. Daoud AS, Batieha A, Abu Ekteish F, Gharaibeh N, Ajlouni S. Iron status: a possible risk factor for the first febrile seizure. Epilepsia. 2002; 43(7): 740-43.

8. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P. Iron deficiency anaemia and febrile convulsions: case control study in children under 2 years. Bmj. 1996; 313(7053): 343-47. doi:10.1136/ bmj.313.7053.343. PubMed PMID: 8760744; PubMed Central PMCID: PMC2351736.

9. Heydarian F, Vatankhah H. The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old. Neurosciences (Riyadh). 2012; 17:226-9. PubMed PMID: 22772927.

10. Bharat K,Yadav RK, Kumar D, Yadav A, Sharan R, Chaturvedi V. Association between iron deficiency anemia and febrile seizures. Pediatric Rev: int j pediatrics res 2015; 2(4):41-6. Available from: https://pediatrics.medresearch.in/index.php/ijpr/article/view/28

11. AKM Rashid M, Nasrin T, Rahman L. Iron insufficiency predisposes febrile seizure in children. ES J Pediatr. 2020;1(1).

12. Alam MS, Sultana R, Karim MR, Ulla AKMZ, Nahar K, Khan MA. Iron Deficiency Anemia as A Risk Factor for Febrile Seizure in Children. JCMCTA 2018; 29 (2): 9-15.

13. Habibian N, Alipour A, Rezaianzadeh A. Association between Iron Deficiency Anemia and Febrile Convulsion in 3- to 60-month-old children: A systematic review and meta-analysis. Iran J Med Sci. 2014; 39(6):496–505.

14. World Health Organization. Iron Deficiency Anemia. Assessment, Prevention and Control. A Guide for Program Managers. WHO/NHD/013. Geneva; 2001.

15. Phiri K, Calis J, Siyasiya A, Bates I, Brabin B, Van Hensbrock M. New cut-off values for ferritin and soluble transferring receptor for the assessment of iron deficiency in children in a high infection pressure area. J Clin Path. 2009; 62:110.

16. Waheed N, Butt MA. Iron status: is there a role in febrile seizures? J Ayub Med Coll Abbottabad. 2012;24(3–4):128–30.

17. Bhat JA, Sheikh SA, Bhat SU, Ara R. Association of iron deficiency anemia with simple febrile seizures: a hospital based observational case–control study. Menoufia Medical Journal 2020, 33:882–885.

18. Aziz KT, Ahmed N, Nagi AG. Iron Deficiency Anaemia as Risk Factor for Simple Febrile Seizures: A Case Control Study. J Ayub Med Coll Abbottabad 2017; 29(2):316-319