

ASSOCIATION OF IRON STATUS WITH FEBRILE SEIZURES

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ABSTRACT

Objective: to investigate the relationship of iron status and febrile seizures (FS).

Methodology: This case control study was conducted at Military Hospital Rawalpindi, from January 2006 to January 2007. Indicators of iron deficiency including hemoglobin, Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), and plasma ferritin levels (FL) were prospectively studied in 60 children with first febrile seizures compared with 60 controls with febrile illness without convulsions.

Results: In the FS group, the mean hemoglobin was 8.96 ± 1.6 gm/dL, the mean MCV was 64.9 ± 8.39 fL, mean MCH was 21.36 ± 3.65 pg and mean FL were 4.4 ± 2.44 ng/dL. In the control group the mean hemoglobin was 10.9 ± 1.79 gm/dL, the mean MCV was 74.98 ± 8.49 fL, MCH was 26.55 ± 4.59 pg and mean FL were 14.87 ± 6.47 ng/dL ($p=0.005$). In the FS group, 48 (80%) children had low hemoglobin <10 gm/dL, 45 (75%) had a low MCV <70 fL, 47 (78.3%) had a low MCH <24 pg and 48 (80%) had a low FL <10 ng/dL. In the control group, 18 (30%) children had low hemoglobin <10 gm/dL, 17 (28.3%) had a low MCV <70 fL, 18 (30.3%) had a low MCH <24 pg and 19 (31.7%) had a low FL of <10 ng/dL ($p < 0.005$).

Mean peak temperature was 38.35 ± 0.40 C° & 38.12 ± 0.41 C° in FS group and controls respectively ($p < 0.005$).

Conclusion: Hemoglobin, MCV, MCH, and plasma FL were significantly lower in children with febrile seizures than in control group suggesting a possible role for iron deficiency in febrile seizures.

Key words: iron deficiency anemia; febrile seizures; plasma ferritin

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INTRODUCTION

Febrile seizures (FS) are the most common type of seizures that occur in 3-4% of all children between 5 months and 5 years.¹ A family history of convulsion, maternal smoking and alcohol intake during pregnancy has been associated with febrile seizures, but the risk factors remain largely unknown.² Because of their association with epilepsy later in life, it is important to identify the risk factors associated with their recurrence.³

Iron deficiency anemia is a common disorder worldwide in pediatric age group.⁴ In Pakistan about two third of children below 5 years of age have iron deficiency anemia.⁵ Iron is required in the metabolism of various neurotransmitters including dopamine, serotonin, and GABA (gamma-amino butyric acid). Aldehyde and monoamine oxidases are reduced in iron deficiency anemia, which is common during the second and third year of life and

has been associated with behavioral and developmental disturbances.⁶

Fever can worsen the negative effects of iron deficiency anemia on brain and seizures can occur as a consequence. Alternatively anemia can be associated with severity of febrile illness, and severe cases could be more likely to get seizures.⁷

Results of recent studies showed that plasma ferritin level was significantly lower in cases of febrile illness with seizures as compared to controls suggesting that iron deficient children are more prone to febrile seizures.⁸ One such study conducted at Karachi⁹ showed that plasma ferritin level was significantly lower in children with first febrile seizure than in reference group, suggesting a possible role for iron deficiency in first febrile seizure.

In Military Hospital Rawalpindi we receive large number of patients with febrile seizures because of the hot and humid atmosphere and the prevalence of upper respiratory tract infections and gastroenteritis. Keeping in mind the results of recent studies this study was planned to investigate the association between iron deficiency anemia and febrile seizures. The result of the study can be utilized for future reference in the prevention of febrile seizures with iron supplements.

METHODOLOGY

This case control study was conducted at pediatric

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department of Military hospital Rawalpindi from January 2006 to January 2007. During this one year period 120 patients from 5 months to 6 years of age presenting with febrile illness were selected by convenience sampling technique. Study was conducted after getting approval from hospital ethical committee. Informed consent was taken from parents. Patients were divided into two equal groups matched for age and gender; Group A included cases that presented with febrile convulsions at the time of admission (seizure that occurred while the child had a rectal temperature of 38.3 °F or an axillary temperature of at least 37.8°C documented either in emergency department or in the history but without any underlying CNS abnormality). Group B included controls that present with fever but having no seizures. Detailed history and physical examination were carried out.

Blood samples were drawn for complete blood counts including hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin. These tests were done on Cobas Micros Roche. Plasma ferritin level was measured by using the IMx Ferritin assay in a micro-particle enzyme immunoassay (MEIA) for a quantitative determination. Serum electrolytes, calcium, glucose, and lumbar puncture were also performed on group A patients. Seizures chart along with temperature record was maintained. All data was recorded in a specified Proforma.

Data was analyzed using SPSS version 14. Mean and standard deviation were calculated for all quantitative variables like Hemoglobin, MCV, MCH and plasma ferritin. The results were expressed in form of tables, pie chart and bar diagrams. Cases and controls were compared regarding Hb, MCV, MCH, and Plasma Ferritin both as continuous and dichotomous variables. The Chi square test was used to assess the statistical significance of the differences in proportions, whereas the independent samples t-test was used when the data was treated as continuous. To examine the relationship between low serum hemoglobin and low serum ferritin with febrile seizures, relative risk (RR) was estimated.

RESULTS

The total numbers of patients were 120 with 60 children in febrile seizures and 60 children in control group.

The two groups matched with respect to age ($p = 0.728$) and gender distribution ($p = 0.707$) as depicted in table 1.

Mean peak temperature in FS group was 38.35 ± 0.40 and in the controls was 38.12 ± 0.41 ($p < 0.005$). None had a past history of seizures in both groups. However, 11 children had a positive family history for seizures in the FS group and only one child had a positive family history among the control ($p < 0.005$). Commonest cause of fever was respiratory tract infection followed by gastrointestinal infection in both groups as shown in the figure 1.

CSF routine analysis was done in all children of the FS group and was normal in all of them with a negative gram and Zeihl Nelson stain. No patient in the FS group was found to be hypoglycemic, hyponatremic or hypokalemic. However, 8 children had serum calcium level less than 8.5 mg/dl.

Statistically significant difference ($p < .005$) was found between the two groups when the mean hematological parameters were compared as shown in table II.

The frequency of anemia (hemoglobin < 10 mg/dl) with low MCV (< 70 fL), low MCH (< 24 pg) and low ferritin (< 10 ng/ml) was more in the FS group when compared to control group ($p < 0.005$) as shown in figure 2.

The relative risk of febrile seizures was found to be more than 10 times as high among anemic children with low serum ferritin level as among children with normal hemoglobin and normal serum ferritin value (RR: 95% CI= 0.50 –0.267; $p < .005$).

DISCUSSION

Febrile seizures are the most common seizures occurring in 3-4% of children.¹ Because of their association with later epilepsy, recent studies have attempted to identify their risk factors, including family history of febrile convulsions or epilepsy, perinatal factors, features of acute underlying illnesses and the temperature peak. We found that febrile seizures were more common in male gender. This observation is supported by various population based studies.¹⁰ Our study also showed that the peak temperature at time of seizure was significantly high in febrile seizure group as compared to control group. This finding

AGE AND GENDER DISTRIBUTION

Demographic parameters		Febrile seizure group	Control group
Age distribution	Age group	6 months to 5 years	6 months to 5 years
	Mean age (years)	2.14 ± 1.46	2.05 ± 1.43
	Less than 1 year	21 (35%)	24 (40%)
Gender distribution	Boys	36 (60%)	38 (63.3%)
	Girls	24 (40%)	22 (36.7%)

Table I

AGE AND GENDER DISTRIBUTION

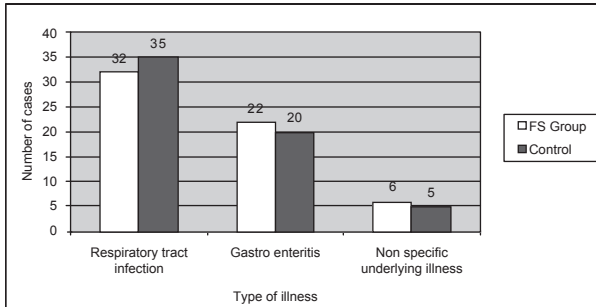


Figure 1

COMPARISON OF HEMATOLOGICAL PARAMETERS

Hematological parameters	Febrile convulsion (FS) group	Control group
Mean Hemoglobin	8.96 \pm 1.6 gm/dL	10.9 \pm 1.79 gm/dL
Mean MCV	64.9 \pm 8.39 fL	74.98 \pm 8.49 fL
Mean MCH	21.36 \pm 3.65 pg	26.55 \pm 4.59 pg
Mean Ferritin level	4.4 \pm 2.44 ng/dL	14.87 \pm 6.47 ng/dL

Table II

HEMATOLOGICAL FINDINGS IN FEBRILE SEIZURES GROUP AND CONTROLS

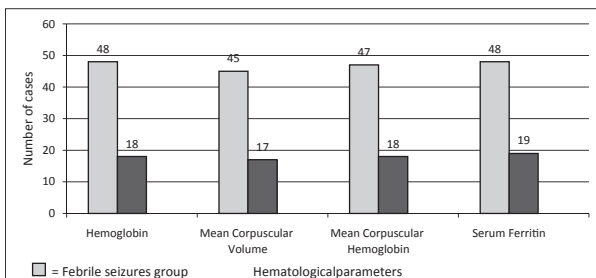


Figure 2

is supported by interventional study conducted by Kim and Connors.¹¹ We found acute respiratory infection is the leading cause of fever in patient with febrile convulsions followed by acute gastroenteritis. It is in accordance with the study conducted in Newyork which found respiratory illness caused by viral infections in winter months, the leading cause for febrile convulsion.¹² Positive family history of Febrile Seizures was more in febrile seizure group as compared to control group which most likely represents a genetic susceptibility to seizures with fever. This finding is in accordance with various national and international studies.^{13,14.}

We found that all the mean hematological parameters (hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin and serum ferritin) were significantly lower in FS group as compared to control group. We also observed that the frequency of anemia with low

MCV, low MCHC and low ferritin was more in FS group as compared to control group. These findings are supported by studies done locally^{8,9} and internationally⁷.

It is known that ferritin is an acute phase reactant that increases nonspecifically in response to febrile illness. Fever however was present in all patients in the two groups. Therefore differences in the ferritin concentration between the two groups cannot be explained by the fever. Differences in Hemoglobin, MCV, and MCH reflect differences in the chronic iron status and are not affected by acute stress reactions. Iron deficiency and convulsions may be seen in children with lead poisoning.¹⁵ There is high incidence of increased lead level in children with iron deficiency anemia especially those living in densely populated cities but its relation to the increased incidence of febrile convulsions has not been investigated.¹⁶

Selection bias as an explanation for the differences in the iron status between the groups is unlikely. Eligible children with and without febrile seizures were matched for age and sex. Both groups belong to the same socio-economic status. A follow-up study of patients found to be iron-deficient at the time of a first febrile seizure and to determine the incidence of subsequent febrile seizures after treatment for iron deficiency would be of great interest.⁹

Our study though conducted on a smaller scale, can provide impetus for further studies on a larger scale, which can prove the association beyond doubt. By correcting anemia in our population we can reduce the incidence of seizures among our children.

CONCLUSION

Hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin and plasma ferritin levels were significantly lower in children with febrile seizures than in control group suggesting a possible role of iron deficiency in febrile seizures. However, a larger study is indicated to confirm these findings.

REFERENCES

1. Paul SP, Blaikley S, Chinthapalli R. Clinical update: febrile convulsion in childhood. *Community Pract* 2012; 85:36-8.
2. Winawer M, Hesdorffer D. Turning on the heat: The search for febrile seizure genes. *Neurology* 2004;63:1770-1.
3. Wo SB, Lee JH, Lee YJ, Sung TJ, Lee KH, Kim SK. Risk of developing epilepsy and epileptiform discharges on EEG in patients with febrile seizures. *Brain Dev Epub* 2012 Aug 11.
4. Bamberg R. Occurrence and detection of iron-deficiency anemia in infants and toddlers. *Clin Lab Sci* 2008;21:225-31.
5. Ikram M, Bai A. Iron deficiency anemia: Evaluation & management in primary care. *Med Today* 2004;2:45-51.

6. De-Regil LM, Jefferds ME, Sylvetsky AC, Dowswell T. Intermittent iron supplementation for improving nutrition and development in children under 12 years of age. *Cochrane Database Syst Rev*. 2011;7:CD009085.
7. Derakhshanfar H, Abaskhanian A, Alimohammadi H, Modanlookordi M. Association between iron deficiency anemia and febrile seizure in children. *Med Glas Ljek Komore Zenicko-Doboj Kantona* 2012;9:239-42.
8. Sherjil A, Saeed Z US, Shehzad S, Amjad R. Iron deficiency anaemia--a risk factor for febrile seizures in children. *J Ayub Med Coll Abbottabad* 2010;22:71-3.
9. Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anemia and febrile seizures. *J Coll Physicians Surg Pak* 2005;15:338-40.
10. Mikati MA, Rahi A: Febrile seizures: From molecular biology to clinical practice. *Neurosciences* 2004;10:14-22.
11. Kim JA, Connors BW. High temperatures alter physiological properties of pyramidal cells and inhibitory interneurons in hippocampus. *Front Cell Neurosci* 2012;6:27.
12. Teran CG, Medows M, Wong SH, Rodriguez L, Varghese R. Febrile seizures: Current role of the laboratory investigation and source of the fever in the diagnostic approach. *Pediatr Emerg Care* 2012;28:493-7.
13. Siddiqui ST. Febrile convulsions in children: Relationship of family history to type of convulsions and age at presentation. *J Ayub Med Coll Abottabad* 2002;14:26-8.
14. Birca A, Guy N, Fortier I, Cossette P, Lortie A, Carmant L. Genetic influence on the clinical characteristics and outcome of febrile seizures--a retrospective study. *Eur J Paediatr Neurol* 2005;9:339-45.
15. Wike WM, Kiser WR. Iron deficiency anemia and febrile convulsion: Possible confounding factor include lead toxicity. *BMJ* 1996; 313: 1205.
16. Rahman MA, Rahman B, Ahmad MS, Blann A, Ahmed N. Blood and hair lead in children with different extents of iron deficiency in Karachi. *Environ Res* 2012;118:94-100.

AUTHOR'S CONTRIBUTION

Following authors have made substantial contributions to the manuscript as under

Am: Conception and design, supervision, Critical Revision and final approval of the version to be published

MAA: Acquisition of data, Final approval of the version to be published

SUM: Data analysis, Drafting the manuscript, Final approval of the version to be published

MTA: Data interpretation, Final approval of the version to be published

CONFLICT OF INTEREST

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