

Relationship between Iron Deficiency Anemia and Febrile Seizures: A Case–Control Study

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Abstract

Introduction: Febrile seizure (FS) is a common convulsive disorder of childhood, which affects approximately 2%–5% of children aged 3–60 months. The etiology of FSs is not clear. Different etiological factors have been considered previously that include familial (genetic) factors, prenatal factors, acute illness, the degree of fever, and finally, anemia. Relationship between iron deficiency anemia (IDA) and febrile convulsions in children has been seen in various studies. Our study has also reported that IDA could be a risk factor for FS and can be considered as one of the modifiable risk factors that predisposes to FSs in children. **Methods:** It was a case–control study. A total of 150 (75 cases and 75 controls) were included between 6 months and 6 years who presented with febrile convulsion. The controls included 75 children between the age group of 6 months and 6 years who presented with short duration of fever (<3 days) but without seizures. Diagnostic criteria for FSs were based on the AAP clinical practice guidelines. Complete blood count and serum ferritin were evaluated for all subjects. Iron deficiency was diagnosed as per the WHO criteria (hemoglobin [Hb] value <11 g%, red cell distribution width of >15%, serum ferritin value <12 ng/ml, and red blood cell indices). **Results:** The mean age of the study group was 27.16 ± 16.65 months, and in control group, it was 27.82 ± 15.33 months. Mean Hb was 9.64 ± 1.54 in study group and 10.05 ± 1.45 in control group, mean corpuscular volume was 72.52 ± 4.94 in cases and 75.06 ± 3.94 in control. Mean corpuscular Hb (MCH) was 25.36 in cases and 27.08 ± 1.90 in control group, MCH concentration 32.73 in cases and 34.63 in control. Mean serum ferritin in Group A was 39.54 ± 24.55 and 51.29 ± 20.26 in control group which was found to be statistically significant ($P < 0.01$). **Conclusion:** In the present study, we found high incidence of IDA in patients with FSs (48%) as compared to controls (22%). Serum ferritin level was also significantly lower in study group as compared to control group suggesting that children who had FS were more iron deficient than the controls.

Keywords: Febrile seizure, ferritin level, iron deficiency anemia

INTRODUCTION

Febrile seizure (FS) is one of the most common causes of seizure in childhood. These are usually benign type of seizures which do not cause central nervous system (CNS) damage in most of the cases, but a minor cognitive imbalance can occur.^[1] FSs occur approximately 2%–5% of children more common in the age group of 6 months–5 years but can occur as early as from 1 month of age. Only 6% of total cases of FSs occur below 6 months of age and 4% above 3 years of age.^[2] Males have a slightly higher incidence of FSs compared to females. FS is defined as a seizure occurring in the childhood age group of 6–60 months with temperature 38° or higher that are not result of CNS infection or any metabolic imbalance and that occurs in the absence of a history of prior an FS.^[3,4] FS is classified as simple and complex FSs. Simple FSs are

defined as primary generalized seizures occur during fever, lasting for <15 min and do not recur within 24 h. Complex FSs are defined as focal, prolonged (more than 15 min) and/or recurrence within 24 h.^[5] Simple FS reflects a genetic predisposition to convulsion manifesting with abrupt elevation of body temperature.^[6] The pathophysiology of FS is unknown, and it remains to be accurately described; different studies have reported various risk factors, including iron deficiency.^[7] Iron deficiency anemia (IDA) is one of the most common nutritional deficiencies leading to anemia in infants and children. Studies

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Submitted: 12-02-2020 Accepted: 29-02-2020 Published Online: 17-06-2020

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How to cite this article: Khanna A, Kumar A, Hota D, Sharma A, Swami M. Relationship between iron deficiency anemia and febrile seizures: A case–control study. *Med J Babylon* 2020;17:144–7.

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DOI:
10.4103/MJBL.MJBL_7_20

show that 46%–66% of children <4 years of age are anemic and 50% of them have IDA in developing countries.^[8] Neurological symptoms like irritability, short attention span, breath holding spells, learning deficits, sleep disturbance, weak memory, papilledema, pseudotumor cerebri, 6th nerve palsy, and behavioral disturbances caused by iron deficiency are well known.^[9] Iron perform key role for the transport of oxygen to various tissues such as the brain and also has importance in the metabolism of neurotransmitters and various enzymes such as aldehyde oxides and monoamine oxidase.^[10] It is thought that iron deficiency may alter the child's seizure threshold. Hence, iron deficiency is postulated as one of the possible risk factors among children with FSs.^[7] Apart from contradictory results regarding the association of FSs with IDA, most of the studies have shown that IDA was associated with FSs. Considering the fact that IDA is a risk factor for FS, as well as lack of adequate information from past studies^[11–13] the present study is carried out to determine the association of IDA in children presenting with febrile convulsion.

METHODS

The present study was a hospital-based study. This study was conducted in the tertiary care hospital in northern India. Seventy-five children between 6 months and 6 years who presented with febrile convulsion (as per the AAP) and attended the department of pediatrics were enrolled as cases. The controls included 75 children between the age group of 6 months and 6 years who presented with a short duration of fever (<3 days) but without seizures. Children who were presented with afebrile seizures or those who had any signs of CNS infection, history of birth asphyxia/developmental delay/epilepsy, on iron supplementation therapy, with family history of epilepsy/mental retardation and those presented with seizures due to abnormal electrolyte balance (Na^+ , k^+ , Ca^{+2} , Mg^{+2}) or decreased glucose levels (blood sugar <50 mg%) were excluded from the study.

Diagnostic criteria for FSs (based on the AAP clinical practice guidelines) included seizures associated with fever, child is otherwise neurologically healthy and without any neurological abnormality before and after the seizures, with the age group between 6 months and 6 years. Cases and controls were selected in 1:1 ratio. The WHO weight for height classification was used to grade protein energy malnutrition. Iron deficiency was diagnosed as per the WHO criteria. After informed written consent, a detailed history was elicited, and physical examination was done to rule out other causes of seizures. At the end of the study, the data were collected and analyzed statistically using Student's *t*-test (unpaired) and Chi-square test. $P < 0.05$ was considered statistically significant.

Ethical approval

All the variable information consents of the patients (and their parents) and control groups were taken after explaining the purpose of the study to the patients, those who refused to participate in the study were excluded. Moreover,

all are approved according to the ethical standards of our institutional research committee.

RESULTS

A total of 150 (75 cases and 75 controls) were included between 6 months and 6 years who presented with febrile convulsion. In our study, maximum number of patients, i.e., 18 in each group were between the age group of 6 and 12 months followed by 17 and 14 patients between 13 and 18 months duration. Overall age range of study and control group was 6–60 months. The mean age of study group was 27.16 ± 16.65 months and in control group, it was 27.82 ± 15.33 months. A total of 61.33% were male in Group A and 58.66% in control group. Similarly, 38.66% were female in Group A and 41.33% in Group B. Socioeconomic status of the study population revealed that maximum number of cases belonged to middle class, i.e., 66.66% in study group and 77.33% in control. With regard to body weight, all the cases in both the groups were between 6.6 kg and 17.9 kg. The mean weight of the study group was 11.37 ± 2.81 kg and 10.97 ± 2.69 kg in the control group. In the present study, we inquired from all the mothers regarding breast feeding to their babies in both the groups. A total of 85.33% cases in Group A and 96% in Group B received breast feeding. On statistical comparison, the difference among the two groups was found to be significant ($P < 0.05$). In this study, hematological parameters, mean hemoglobin (Hb) was 9.64 ± 1.54 in study group and 10.05 ± 1.45 in control group, mean corpuscular volume (MCV) was 72.52 ± 4.94 in cases and 75.06 ± 3.94 in control. MCV values were significant low in cases as compared to control group. Mean corpuscular Hb (MCH) was 25.36 in cases and 27.08 ± 1.90 in control group, MCH concentration (MCHC) 32.73 in cases and 34.63 in control, MCH and MCHC are significantly low in cases than compared to controls. Red cell distribution width (RDW) was 15.46 ± 1.53 in cases and 14.92 ± 1.34 in control. Table 1 shows the distribution of various parameters in case and control groups. Hb was low and RDW was high in study group as compared to control group but not statistically significant. Table 2 shows the distribution of serum ferritin among two groups.

In study group, we observed 4 cases who had <12 ng/ml and none in Group B. Similarly, >12 ng/ml to 30 ng/ml, we found 32 cases in study and 17 in control group. In >30 ng/ml, 39 and 58 cases observed in study and control group, respectively. Mean serum ferritin in Group A was 39.54 ± 24.55 and 51.29 ± 20.26 in control group which was found to be statistically significant ($P < 0.01$).

DISCUSSION

It has been seen that association between IDA and FS is inconsistent; some studies indicate there is no association between IDA with febrile convulsions^[14] while some studies suggest higher prevalence of iron deficiency with or without anemia in children with febrile convulsions.^[12,15,16] In the

Table 1: Various hematological/biochemical investigations among two study groups (n=75)

Investigations	Mean±2SD		Statistical significance (P)
	Group A (study)	Group B (control)	
Hb (g/dl)	9.64±1.54	10.05±1.45	0.09
TLC	9276±2264.88	9064±1436.27	0.494
Platelet count (lacs)	2.80±0.92	2.47±0.50	0.007
MCV	72.51±4.94	75.06±3.94	<0.05 (S)
MCH	25.36±1.94	27.08±1.90	<0.05 (S)
MCHC	32.73±3.50	34.05±2.67	0.010
Red cell distribution (%)	15.46±1.53	14.92±1.34	0.06
Serum ferritin (ng/dl)	39.54±24.55	51.29±20.26	0.016

SD: Standard deviation, Hb: Hemoglobin, TLC: Total leukocyte count, MCV: Mean corpuscular volume, MCH: Mean corpuscular Hb, MCHC: MCH Hb concentration, S: Significant

Table 2: Statistical comparison of serum ferritin among two groups (n=75)

Serum ferritin (ng/ml)	Study group	Control group	Statistical significance (P)
<12	4	0	<0.01
>12-30	32	17	
>30	39	58	
Mean±2SD	39.54±24.55	51.29±20.26	

SD: Standard deviation

present study, maximum number of patients were below 24 months of age, and the mean age of children with FS was 27.16 ± 16.6 months. Various studies have reported in which mean age is comparable with this study. A higher prevalence of FSs in young age could be because immaturity of the brain as maximal hippocampus growth is noted to occur before 3 years of age. This is the power of normal brain maturation which is thought to have enhanced neural excitability. In the present study, 61.33% were male (46 out of 75) and 38.66% were female. Ramesh *et al.*^[15] and Sharif *et al.*^[17] reported higher prevalence of FS in male compared to female child. In the present study, all hematological values are lower in cases than control group, but MCV, MCHC, and MCH are significantly lower than control group. Lower Hb and higher RDW, not observed statistically significant value may be due to small sample. In this study, mean serum ferritin in cases was 39.54 ± 24.55 and control 51.29 ± 20.26 ($P = 0.01$) which was statistically significant. Hence, in the present study, we found serum ferritin level in FS group were significantly low as described in many studies.^[10,12,15] In FS group, four children have serum ferritin level below 12 ng/dl. The cutoff point for serum ferritin was arbitrary. Commonly used cutoff point of serum ferritin for IDA is between 10 and 20 ng/dl. Few patients had <20 ng/dl so we use a higher cutoff point of 30 ng/dl. In the present study, in FS group, 36 children out of 75 had ferritin below 30 ng/dl (about 48%). In the control group, only 17 children had serum ferritin level below <30 ng/dl (22.66%).

Daoud *et al.*^[18] observed a significantly lower serum ferritin level in the first FS group than in control group providing that serum ferritin is sensitive specific and reliable measurement for determining iron deficiency at an early stage and it may be best indicator of total body iron status. Low level of serum ferritin may lower the seizure threshold, as iron is important for the function of various enzyme and neurotransmitter part in CNS. Fever may worsen the negative effect of low ferritin level on the brain and therefore seizure can be triggered. It is known that ferritin is acute phase reactant that increases nonspecifically in response to any febrile illness. Fever, however, was present in all patients (both group). Differences in ferritin level in the two groups cannot be explained only by fever.

CONCLUSION

In the present study, we found a high incidence of IDA in patients with FSs (48%) as compared to controls (22%). It was observed that children with FSs were almost twice as likely to have IDA as compared to children with febrile illness without seizures. Serum ferritin level was also significantly lower in study group as compared to the control group suggesting that children who had FS were more iron deficient than the controls. IDA can be regarded as a modifiable risk factor that predisposes to FSs in children between 6 months and 6 years. A strong correlation exists between iron deficiency and FS. We suggest early detection and timely intervention for IDA may help in preventing FSs in children. We also found the risk of FS is lower among exclusive breast-fed infants.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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