



## IRON DEFICIENCY ANEMIA AS A RISK FACTOR FOR FEBRILE SEIZURES

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**ABSTRACT** **Background:** Febrile seizures (FS) are one of the common concerns for hospital visit and major source of parent's anxiety and distress. Incidence of febrile seizures in neurologically normal infants and children is 2-5%. Febrile seizures occur between the ages of 6 month to 5 years of age (peak 12-18 months). Iron deficiency anemia (IDA) is possible risk factor for febrile seizures and it is easily preventable and treatable. **Methods:** An observational case control study was conducted among 80 cases of febrile seizures and 80 controls of acute febrile illness in SMS medical college, Jaipur, between July 2021 to December 2022. Blood investigations including hemoglobin, MCV, serum iron, serum ferritin and TIBC were done to diagnose IDA in both groups. Association of iron deficiency anemia between febrile seizure and acute febrile illness children was compared by Chi-square test. Results: The mean values of hemoglobin (8.60 g/dL, p=0.001), MCV (69.67 fL, p=0.001), serum iron (42.15 mcg/dL, p=0.001), TIBC (432.40 mcg/dL, P=0.001) and serum ferritin (27.12 ng/mL, p=0.001) among case group were significant as compared to the control group. Hence iron deficiency anemia was significantly associated with febrile seizures. **Conclusion:** Iron deficiency anemia is a significant risk factor for febrile seizures in children. Early detection and treatment of iron deficiency may aid in the prevention of febrile seizures in children of this age group.

**KEYWORDS :** Iron deficiency anemia, Febrile seizures

### INTRODUCTION

Febrile seizures are seizures that occurs between the age of 6 month to 5 years of age (peak 12-18 months) with temperature of 38°C (100.4°F) or higher, that are not the result of CNS infection or metabolic imbalance, and that occur in the absence of history of prior afebrile seizures.<sup>1</sup>

Febrile seizures are one of the common concerns for hospital visit and major source of parent's anxiety, though febrile seizures are usually benign.

A simple febrile seizure is a primary generalized, usually tonic-clonic, attack associated with fever, lasting for a maximum of 15 minutes and not recurrent within a 24 hour period. A complex febrile seizure is more prolonged (>15 min), and/or is focal, and/or recurs within 24 hours. Incidence of simple febrile seizure in neurologically normal infants and children is 2-5%.<sup>1</sup> In children between the ages of 6 months and 5 years old in the United States and Western Europe, febrile seizures are the most prevalent neurologic condition, with a peak incidence between the ages of 12 and 18 months.<sup>2-4</sup> All ethnic groups experience febrile seizures, however Asian children are more likely to experience them (5-10% of Indian children and 6-9% of Japanese children).<sup>5</sup> In Guam, the incidence might reach 14 percent.<sup>6</sup> The ratio of men to women is roughly 1.6 to 1.<sup>3,7,8</sup>

The risk of later epilepsy after a simple febrile seizure is 1% and the risk of developing epilepsy after complex febrile seizure is about 6%. Recurrence of febrile seizures.<sup>1</sup>

Recurrence of febrile seizures varies between 25-100% based on the number of risk factors involved.<sup>13</sup> Both recurrent FS and Epilepsy are apparent life threatening events and carry a burden on the child's growth and development and impose extra health expenditure on the family.<sup>9</sup>

Multiple factors contribute to febrile seizures causes. According to widespread consensus febrile seizures are caused by the growing CNS susceptibility to the effects of fever, as well as underlying genetic predispositions and environmental variables. A febrile seizure is the immature brain's age-dependent response to a fever. The development of brain results in an increase in neuronal excitability, which puts the youngster at risk for febrile seizures. As a result, febrile seizures mostly affect young children under the age of three since their seizure threshold is low.<sup>10</sup>

Iron is also important for neurological functioning.<sup>11-13</sup> Such functions include neurotransmitter metabolism,<sup>14-15</sup> myelin formation,<sup>56</sup> and brain energy metabolism.<sup>17</sup> Iron deficiency is strongly associated with neurological problems in children, including growth disturbance, neurodevelopmental delay, stroke, breath-holding spells, pseudo tumor cerebri, and impaired cognitive function which affects brain functioning by multiple mechanism like lack of neuronal iron, hypoxia due to anemia and by changes in neurotransmitter receptors and consequent signal transduction process during the most active period of brain development in young children.<sup>18-19</sup> Iron affects the enzymatic reactions involved in DNA, RNA, and monoamine metabolism, and the production and function of neurotransmitters in the central nervous system, low serum levels of ferritin may reduce the seizure threshold.<sup>20-22</sup> Frequent recurrence could expose the brain to hypoxic damage possibly increasing the chances of future epilepsy.

The relationship between iron deficient state and febrile seizures has been described in several studies with conflicting results. We have conducted a study in Department of Pediatrics, SMS medical college hospital a tertiary care teaching hospital in jaipur, to find the association between the iron status and febrile seizures in children.

### METHODS

This was a hospital based, observational case control study, conducted at the Department of Paediatrics, SPINPH, SMS Medical College, Jaipur, between July 2021 and December 2022. The sample size was calculated as 160 (80 cases and 80 controls) using 95% confidence interval, 80% power, case to control ratio was 1, and percentage of exposure in case was taken 35% and in control was 15% according to previous hospital data.

Cases were children of age group 6 months to 5 years presented with febrile seizures. Controls were children of same age group presented with acute febrile illness but without seizures. A total of 160 children with 80 cases and 80 controls were included in the study.

Children presenting with febrile seizure to pediatrics in-patient department and Casualty/Emergency, were included in the study after obtaining consent from the parents. Iron deficiency anemia will be defined as Hemoglobin <11 g/dL for 6 months to 5 years, MCV <70 fL, s. iron <22 mcg/dL, TIBC >400 mcg/dL and ferritin <12 ng/mL.<sup>23</sup> Since serum ferritin is acute phase reactant and its level is increased in any inflammatory conditions, in presence of fever a higher cut-off value of

serum ferritin less than 30 microgram/dl was considered.<sup>24</sup> Other explanatory variables such as urine routine, stool routine and chest x-ray which can be the potential confounders were also included in the study and considered for analysis. Case and controls were compared with respect to blood indices, serum ferritin, serum iron and TIBC.

Inclusion criteria were children in the age group between 6 months to 5 years with febrile seizure were considered as cases and those in age group between 6 months to 5 years with acute febrile illness were considered as controls.

Children with age <6 months and >5 years, CNS infection, known cases of epileptic syndrome, developmental delay, chronic illness, malignancy, malabsorption or malnutrition and child on iron therapy were excluded from the study.

**Statistical analysis**

Data analysis was done using licensed SPSS software version 21.0 (Chicago, Illinois). Univariate analyses were done initially and the results were presented with the help of tables, text, bar-diagrams and charts. Descriptive statistics were used to calculate frequencies of categorical variables, and measures of central tendencies and dispersion were used to describe continuous variables.

Bi-variate analyses was done using the Chi square test/Fisher's Exact test, to determine the association between categorical variables and for quantitative variable t- test or Mann-Whitney test was used. P value <0.05 was considered as statistically significant.

**RESULTS**

A total of 160 children were included in the study with 80 cases and 80 controls.

Case: Children with febrile illness with febrile seizure  
Control: Children with febrile illness without febrile seizure

**Table 1: Distribution Of Children In The Different Age Groups Amongst The Cases**

Age	Case	
	Count	%
6 months - 1 years	13	16.25%
1-1.5 years	16	20%
1.5-2 years	24	30%
2-3 years	18	22.5%
3-4 years	6	7.5%
4-5 years	3	3.75%
Total	80	100.0%

Maximum children belonged to the age group of 1.5 to 2 years. Least number of children was in the age group above 3 years.

**Table 2: Distribution of gender among cases**

Gender	Case	
	Count	%
Female	30	37.5%
Male	50	62.5%
Total	80	100.0%

Comparing the gender distribution, males were 50 and females were 30 suggesting that incidence of febrile seizure is more common among males (62.5%).

In our study mean weight of case and controls was 9.6±2.2 and 9.3±2.2 kg respectively. This difference was not found to be statistically significant.

In our study, out of 80 cases maximum 66 were belongs to lower socioeconomic status and out of 80 controls maximum 61 were belongs to lower socioeconomic status according to modified BG Prasad classification. This difference was not found to be statistically significant.

In our study, out of 80 cases, maximum 25 had Acute viral fever followed by 17 had URTI and out of 80 controls, maximum 20 had acute viral fever followed by 20 had URTI. These differences were not found to be statistically significant.

In our study, no statistically significance temperature difference was found between case and controls.

**Table 3: Comparison Of Family History Of Seizure Between Both Groups**

Family history	Case		Controls		p-value
	Count	%	Count	%	
No	73	91.3%	79	98.8%	0.030
Yes	7	8.8%	1	1.3%	
Total	80	100%	80	100%	

A total of 7 had family history of seizure out of 80 cases and 1 had family history of seizure out of 80 controls. This difference was found to be statistically significant.

**Table 4: Comparison Of Iron Indices Between Both Groups**

Group	Case		Controls		p-value
	Mean	SD	Mean	SD	
Hb	8.60	1.11	9.54	1.01	0.001
MCV	69.67	16.19	83.25	13.70	0.001
Sr Ferritin	27.17	26.3	53.89	28.48	0.001
Sr Iron	42.15	16.25	68.21	19.17	0.001
TIBC	432.40	126.54	358.73	103.72	0.001

We found a statistically significant low Hb, MCV, serum ferritin, serum iron and a statistically significant high TIBC in cases compare to controls.

**Table 5: Comparison Of IDA Between Both Groups:**

IDA	Case		Controls		p-value
	Count	%	Count	%	
Yes	52	65.0%	26	32.5%	0.0001
No	28	35.0%	54	67.5%	
Total	80	100.0%	80	100.0%	

We found a statistically significant high prevalence of anemia in cases compare to controls. Out of 80 cases, in 52 (65.0%) IDA was found and out of 80 controls, in 26(32.5%) IDA was found. This difference was found to be statistically significant.

**DISCUSSION**

We conducted a hospital based, observational case control study in the Department of paediatrics, SPINPH, SMS medical college Jaipur. This study aimed to assess iron status in patient of febrile seizure and acute febrile illness. Calculated sample size was 80 in each group. Case group consisting the children with febrile seizures and control group included the children with febrile illness without febrile seizures.

In our study, maximum children belonged to the age group of 1.5 to 2 years. Least number of children was in the age group above 3 years.

Hauser WA found that most febrile seizures occur between 6 months and 3 years of age with the peak incidence at 18 months.<sup>25</sup> Offringa M also found that the median age of febrile seizures was 18 months.<sup>26</sup>

Sharif MR et al also did a similar case control study and revealed that in the febrile convulsion group, most of the members (72%) belonged to the age group of less than two years (18% were less than one year, 36% between 1 and 2 years old, 25% between two and three, and 21% over three years). And 62% were male in case group and 56 were in control group.<sup>27</sup>

In our study, comparing the gender distribution, males were 50 and females were 30 suggesting that incidence of febrile seizure is more common among males (62.5%).

Mahyar et al. in 2010 found that gender is an important factor in febrile seizure; in his study, 66% of the infants with febrile seizure were boys.<sup>28</sup> A study conducted by Habib et al. in Pakistan; he found that the male gender had a 1.3 times greater risk of febrile seizure.<sup>29</sup> This is also supported by a study performed by Abaskhanian et al. in 2010, that quoted a slight predominance of febrile seizure in males.<sup>30</sup> Gender inequality is a major issue in Rajasthan. This may be a contributing factor for high male to female ratio of febrile seizures because female child usually lacks medical care.

In our study mean weight of case and controls was 9.6±2.2 and 9.3±2.2 kg respectively. This difference was not found to be statistically significant.

In our study, out of 80 cases maximum 66 were belongs to lower socioeconomic status and out of 80 controls maximum 61 were

belongs to lower socioeconomic status according to modified BG Prasad classification. This difference was not found to be statistically significant.

In our study, out of 80 cases, maximum 25 had Acute viral fever followed by 17 had URTI and out of 80 controls, maximum 20 had acute viral fever followed by 20 had URTI. These differences were not found to be statistically significant.

In our study, no statistically significance temperature difference was found between case and controls.

A total of 7 had family history of seizure out of 80 cases and 1 had family history of seizure out of 80 controls. This difference was found to be statistically significant.

Tosune (2011) reported that 57% of children with febrile seizure had a positive family history. Other studies have also reported similar results confirming that positive family history increases risk of febrile seizures significantly.<sup>31</sup> Abolfazl and colleagues showed that 55% of patients with febrile seizure had a positive family history.<sup>28</sup> In another study, it was 10-45%.<sup>32</sup> Genes associated with febrile seizures include SCN1A, SCN1B, SCN9A and CPA6.<sup>33-36</sup> Most convincing evidence has emerged from linkage studies with reported linkages on numerous chromosomes (2q,48 5q,49 5,50 8q,51 19p,52 and 19q53), with the strongest linkage on chromosome 2q and specifically, linkage to the genes responsible for sodium channel receptors and specifically a mutation in the alpha ( $\alpha$ ) subunit of the first neuronal sodium channel gene (SCN1A). The linkage on chromosomes 2q and 19q associated with the phenotype of febrile seizures, generalised epilepsy (tonic-clonic, absence, and myoclonic), and a continuation of febrile seizures (>5 years of age) (GEFS+) shows evidence of sodium channel involvement.<sup>37-38</sup>

In our study, a statistically significant low Hb, MCV, serum ferritin, serum iron and a statistically significant high TIBC was found in cases compare to controls.

In our study, a statistically significant high prevalence of IDA was found in cases compare to controls. Out of 80 cases, in 52 (65.0%) IDA was found and out of 80 controls IDA was found in 26 (32.5%). This difference was found to be statistically significant.<sup>39-42</sup>

## SUMMARY

The summary of the findings is as follows:

- Our study revealed that case and control were comparable in term of age, weight and socioeconomic status and no statistically significant difference was in these sociodemographic characters between case and controls.
- In our study, maximum children belonged to the age group of 1.5 to 2 years. Least number of children was in the age group above 3 years.
- In our study, comparing the gender distribution, males were 50 and females were 30 suggesting that incidence of febrile seizure is more common among males (62.5%).
- In our study mean weight of case and controls was 9.6±2.2 and 9.3±2.2 kg respectively. This difference was not found to be statistically significant.
- In our study, out of 80 cases maximum 66 were belongs to lower socioeconomic status and out of 80 controls maximum 61 were belongs to lower socioeconomic status according to modified BG Prasad classification. This difference was not found to be statistically significant.
- In our study, out of 80 cases, maximum 25 had Acute viral fever followed by 17 had URTI and out of 80 controls, maximum 20 had acute viral fever followed by 20 had URTI. These differences were not found to be statistically significant.
- In our study, no statistically significance temperature difference was found between case and controls.
- In our study, out of 80 cases 7 had family history of seizure and out of 80 controls maximum 1 had family history of seizure. This difference was found to be statistically significant.
- In our study, a statistically significant low Hb, MCV, serum ferritin, serum iron and a statistically significant high TIBC was found in cases compare to controls.
- In our study, a statistically significant high prevalence of IDA was found in cases compare to controls. Out of 80 cases, in 52 (65.0%) IDA was found and out of 80 controls IDA was found in 26

(32.5%). This difference was found to be statistically significant.

## CONCLUSION

Our study concluded that iron deficiency anemia was more frequent among children with febrile seizure. There was a significant correlation between various measures of iron deficiency anemia and the prevalence of febrile seizures. The findings imply that IDA may be a risk factor for febrile seizures. We also found that male gender, positive family history and age group of 1.5 to 2 years are additional risk for developing febrile seizures. Children experiencing febrile seizures should be screened for IDA. Early detection and treatment of iron deficiency may aid in the prevention of febrile seizures in children of this age group.

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