

## Assessment of the Relationship between Iron Deficiency and Febrile Convulsion: A Case-Control Study

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Conflict of interest: Nil

### Abstract:

**Introduction:** Although the exact origin of FC is unknown, a number of environmental and genetic variables have been suggested. The greatest age at which FC occurs is 14–18 months, which coincides with the age at which anaemia due to iron deficiency (IDA) is most prevalent. Iron is necessary for the synthesis of myelin, which is needed for nerve cells and can alter the amplitude and sensitivity of a neuron's excitation, as well as for the metabolic processes of the brain and neurotransmitters.

**Aims/ Objective:** To compare the incidence of IDA and haematological parameters in children with febrile convulsion (FC) versus patients with febrile illness without convulsion (control).

**Materials and Method:** In this observational study, 50 patients with FC and 50 patients without FC were evaluated for haematological parameters. Children's anaemia was classified by the Ministry of Health and Family Welfare Guidelines as Hb < 11g/dl. For children under one year old, the normal amount of iron levels was defined as Fe greater than 40 µg/dl, and for those over one year old, Fe greater than 50 µg/dl. The TIBC normal range was defined as 210–430 µg/dl. Transferrin saturation greater than 15% was defined as normal.

**Results:** There were significantly greater cases with family history of febrile convulsion in FC group ( $p < 0.05$ ). Patients with febrile convulsions had significantly lower serum iron and transferrin saturation as compared to patients with febrile illness without convulsion ( $p < 0.05$ ). There were significantly more cases of iron deficiency anaemia (46%) in febrile convulsion group as compared to 22% in control group ( $p < 0.05$ ).

**Conclusion:** The results indicate that low serum iron and iron-deficiency anaemia affect a significant portion of children with febrile convulsion essentially, this suggests that anaemia and low blood iron levels can reinforce febrile seizures in children.

**Keywords:** Iron Deficiency Anaemia, Febrile Convulsion, Serum Iron, Transferrin Saturation.

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### Introduction

When a child experiences febrile convulsions (FC), it means that they have not experienced any previous afebrile seizures and that their body temperature is 38°C or above. These convulsions do not come from a disorder of the CNS (central nervous system) and any metabolic imbalance. Two to five percent of paediatric patients who are considered neurologically healthy have this problem. [1] Although the exact origin of FC is unknown, a number of environmental and genetic variables have been suggested. [2] The greatest age at which FC occurs is 14–18 months, which coincides with the age at which anaemia due to iron deficiency (IDA) is most prevalent. [3]

High fevers, head traumas, smoker or drink alcohol, and a family history of convulsions or FC are risk factors for this disease. [4-6] Since the likelihood that IDA will progress to convulsion or epilepsy is a risk factor, numerous researches have

been conducted to find modifiable risk variables that can lower the prevalence of FC and, consequently, epilepsy and convulsion. [7,8] The most prevalent nutritional deficiency worldwide is IDA. A vital micronutrient, iron is utilized by almost all of the body's cells. It is commonly known that iron functions as an enzyme cofactor for a number of bodily enzymes and plays a part in the synthesis and action of neurotransmitters, hormone production, and DNA duplication. [9]

Iron is necessary for the synthesis of myelin, which is needed for nerve cells and can alter the amplitude and sensitivity of a neuron's excitation, as well as for the metabolic processes of the brain and neurotransmitters. [10] Lack of iron enhances neuronal function, which raises the possibility of convulsions. [3,11] Both restless leg syndrome (RLS) as well as "attention deficit hyperactivity disorder (ADHD)" are associated with similar

circumstances. 12 Research on animals have demonstrated the etiology of this defect. It is uncertain how IDA and FC are related. Although some research has linked IDA to the emergence of FC, other studies have not supported this association. [13–17] However, very few reports have suggested that IDA could be able to prevent FC development. [2,18,19]

Since the exact cause of febrile seizures and iron shortage is unknown, it is possible that chance or other unidentified factors play a role. 20 Given the aforementioned findings and the lack of research on the association in India, this study aimed to compare the incidence of IDA and haematological parameters in children with febrile convulsion (FC) versus patients with febrile illness without convulsion (control).

### Materials & Methods

This was an observational and prospective study conducted on patients with febrile convulsion (case) and without febrile convulsion (control) in Department of General Medicine in a tertiary care hospital of India from January 2018 to June 2018. Informed consent was taken from children with and without FC as per recommendation of Declaration of Helsinki and Good Clinical Practice.

### Inclusion Criteria:

Case:

- Patients of age group 6 months- 5 years
- Patients with normal growth and developmental milestones
- Patients with diagnosis of febrile convulsion
- Control
- Age and gender matched patient with respect to case
- Patient with febrile illness without seizure

### Exclusion Criteria:

- Patients with biochemical or metabolic abnormalities such as hypoglycaemia, electrolyte imbalance, acidosis
- Patients with other neurological disorders
- Patients with history of seizure within 6 months or enrolment
- Patients receiving haematinic or history of blood transfusion within 3 months

**Sample Size:** With reported prevalence of 67.1% IDA in cases and 32.9% in control as reported by Sharif MR et al., 21 minimum sample size required to achieve 90% power with 0.05 alpha value was calculated to be 86 with 43 patients in each group. So, 50 patients were enrolled in each group to adjust with expected attrition rate of 5%.

### Methodology

Parental interview questionnaires were used to obtain personal data about the children, such as age, gender, as well as family history of seizures. The axillary method was used to measure and record the body temperature in FC and non-FC groups. The TIBC, serum iron, and CBC were performed. Children's anaemia was classified by the Ministry of Health and Family Welfare Guidelines as Hb < 11g/dl. [22] For children under one year old, the normal amount of iron levels was defined as Fe greater than 40 µg/dl, and for those over one year old, Fe greater than 50 µg/dl. The TIBC normal range was defined as 210–430 µg/dl. Transferrin saturation greater than 15% was defined as normal. [23]

**Statistical Analysis:** Data from patients with or without febrile convulsion were presented in tabular form using Microsoft Excel 365 and transferred to SPSS version 24 for further statistical analysis. Continuous data such as age, haemoglobin, serum iron, TIBC, and transferrin saturation were expressed as mean ± SD (standard deviation). Statistical significance of difference in continuous data between FC and non-FC group was evaluated by unpaired t-test. Categorical data, including incidence of IDA, gender, type of infection, and history were reported as percentages and frequencies and then compared by chi-square test or fisher's exact test. A p-value of less than 0.05 was taken as cut-off for statistical significance.

### Results

In this observational study, 50 patients with FC and 50 patients without FC were evaluated for haematological parameters. The baseline demographic and clinical characteristic of FC and non-FC group is given in table 1.

**Table 1: Comparison of Baseline Demographic and Clinical Characteristics between FC and non-FC Group**

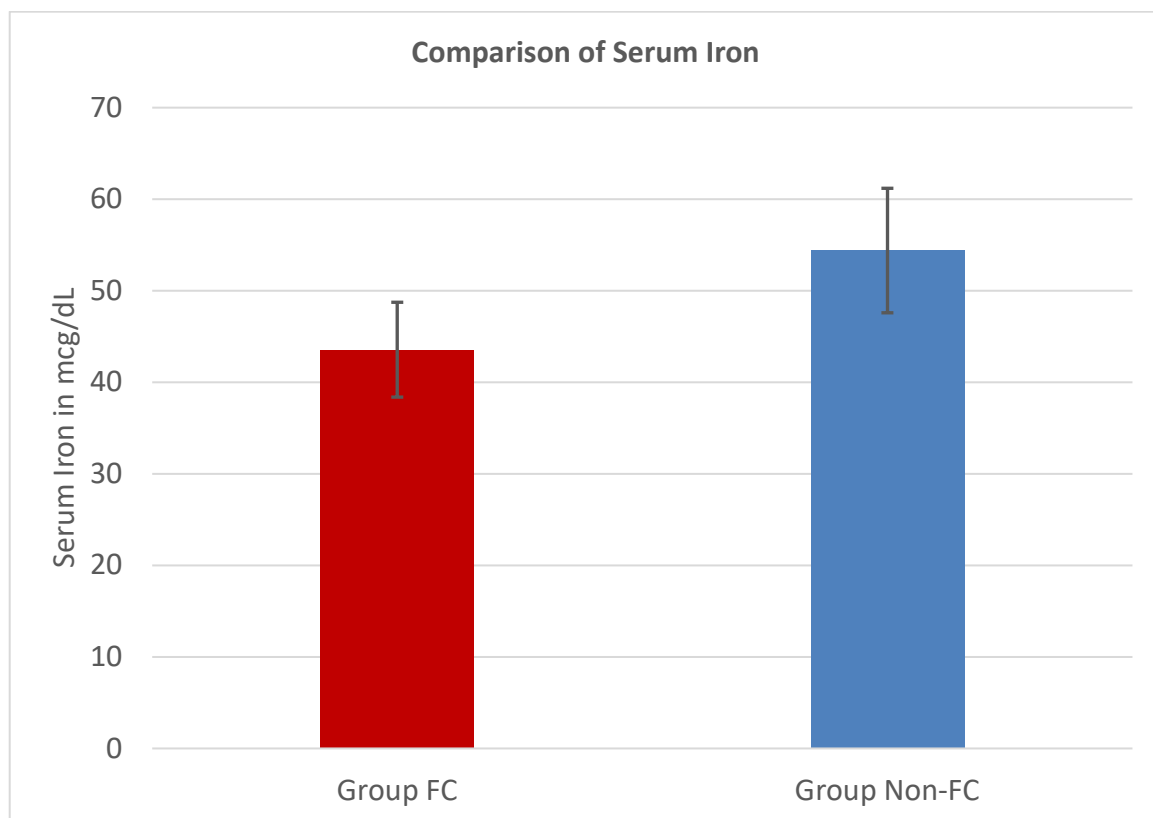
Variables	Category	Group FC	Group Non-FC	P-Value
Age in months (mean ± SD)		26.46 ± 4.67	25.89 ± 3.96	0.51
Gender (n)	Male	31	28	0.68
	Female	19	22	
Type of Infection (n)	Pulmonary Infection	29	28	0.87
	Gastroenteritis	17	19	
	Urinary Tract Infection	4	3	
Family History of Seizure (n)	Yes	14	5	0.04
	No	36	45	

Most of patients in our study belonged to 1-3 years of age group and most of the subjects with febrile illness were males. Pulmonary infection was most common cause of febrile illness. There was no difference between FC and non-FC group with respect to age, gender, and underlying cause ( $p>0.05$ ). However, there were significantly greater cases with family history of febrile convulsion in FC group ( $p<0.05$ ).

**Table 2: Comparison of Haematological Parameters between FC and non-FC Group**

Parameters	Group FC	Group Non-FC	P-Value (Unpaired t-test)
Haemoglobin in g/dL	11.57 $\pm$ 1.42	11.94 $\pm$ 1.53	0.21
Serum Iron in mcg/dL	43.56 $\pm$ 5.18	54.39 $\pm$ 6.80	<0.0001
TIBC in mcg/dL	395.16 $\pm$ 29.73	339.02 $\pm$ 25.94	<0.0001
Transferrin Saturation in %	12.69 $\pm$ 3.38	14.53 $\pm$ 4.58	0.02

Patients with febrile convulsions had significantly lower serum iron and transferrin saturation as compared to patients with febrile illness without convulsion ( $p<0.05$ ).

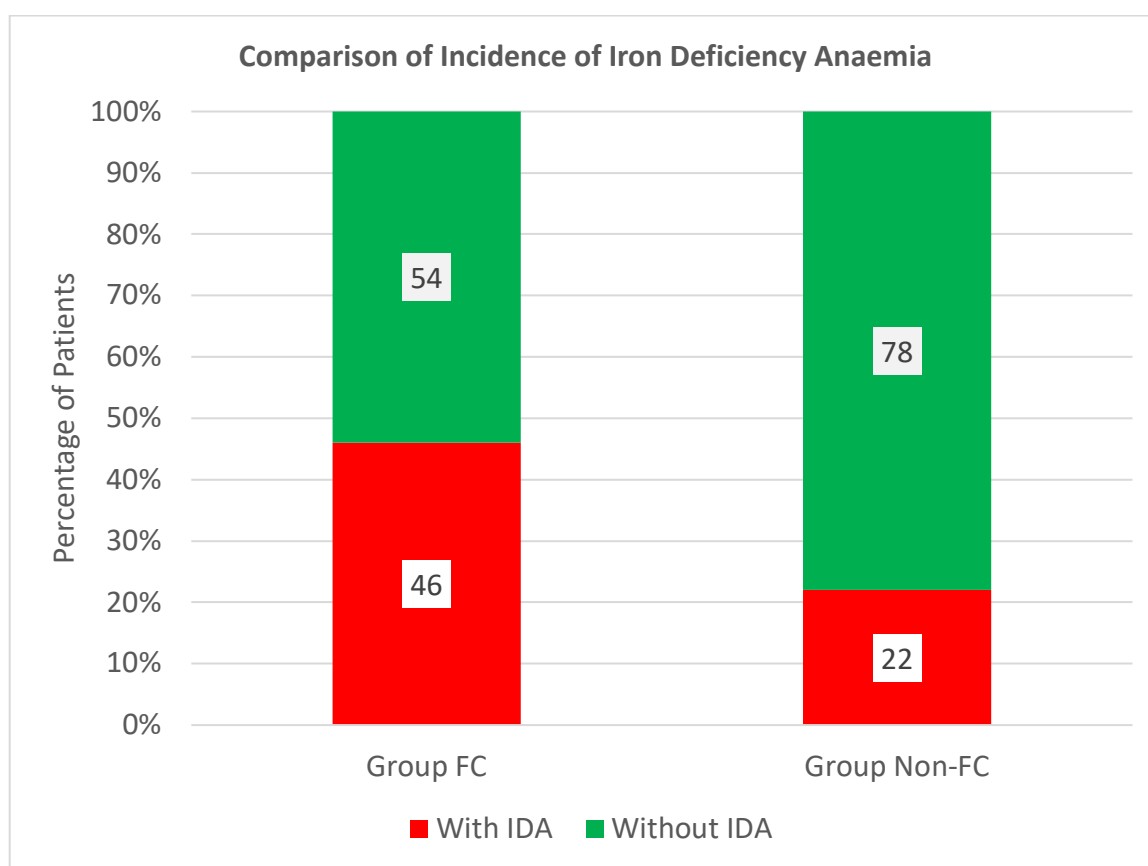


**Figure 1: Comparison of Serum Iron**

**Table 3: Comparison of Incidence of IDA (Iron Deficiency Anaemia) between FC and non-FC Group**

IDA	Group FC	Group Non-FC	P-Value (Fisher's Exact Test)
Yes	23	11	0.02
No	27	39	

There were significantly more cases of iron deficiency anaemia (46%) in febrile convulsion group as compared to 22% in control group ( $p<0.05$ ).



**Figure 2: Comparison of Incidence of Iron Deficiency Anaemia**

### Discussion

The study found that the group experiencing febrile convulsions had a clearly higher prevalence of iron-deficiency anaemia than the control group. Similar to our findings, Pisacane et al.'s investigation revealed that the case group's anaemia (30 percent) was greater than that of the hospital's control group (14 percent) as well as the group with no illness (12%). [24] Additionally, 68% of patients and 30% of controls in the Vaswani et al. research had low iron levels. [25]

Iron deficiency was more prevalent in patients with febrile seizures in the Sadeghzadeh et al. study, despite the fact that anaemia was not prominent among the subjects. In a study conducted by Ur-Rahman and Billoo, iron-deficiency anaemia was found to be considerably more common in the case group compared to the control group in 30 children suffering from febrile convulsions versus 30 children with febrile disorders without convulsion. [26]

Convulsions may result from a fever that exacerbates the effects of anaemia or an iron deficiency on the brain. Furthermore, the severity of a febrile illness might be linked to anaemia, and individuals with severe manifestations may experience convulsions. However, before haemoglobin is decreased as a result of the infectious disease, febrile convulsion typically

happens in the beginning of a febrile illness. [24] However, additional research has produced results that differ from the study's conclusion. For instance, in Hartfield et al.'s study, children in two groups (one with febrile convulsion and the other without) were found to have iron deficiency at 9% and 5%, respectively; iron-deficiency anaemia was reported to be 6 percent and 4 percent in the FC and non-FC groups, respectively. [27] However, the group experiencing febrile convulsions in the Kobrinsky et al trial experienced reduced iron deficit. They came to the conclusion that a low iron level might prevent febrile convulsions. [27]

The main reasons why the results of their and our research differ could be attributed to a variety of factors, such as the fact that we used different diagnostic criteria for iron deficiency in our study and they did not take age into account when translating the tests for iron deficiency diagnosis. While some of the samples in the majority of the studies cited had previous episodes of febrile convulsions, most of the case group samples in the present study experienced febrile convulsions for the first time. The current study's results indicate that children with fever and convulsions had a greater prevalence of iron deficiency than the group of children without fever and convulsions. The results point to the possibility that anaemia and low blood iron levels may increase the association between febrile convulsions and childhood

anaemia. Therefore, one more risk factor for febrile convulsions is iron deficiency. Undertaking a research to monitor the rate of recurrence of febrile convulsions in patients with iron deficiency suffering from febrile convulsions following treatment would be beneficial.

### Conclusion

The results indicate that low serum iron and iron-deficiency anaemia affect a significant portion of children with febrile convulsion essentially, this suggests that anaemia and low blood iron levels can reinforce febrile seizures in children. As a result, it is advised that children who experience febrile convulsions be closely watched in order to diagnose and treat iron-deficiency anaemia. Additionally, it is best to give iron supplements to patients who have significant and established warning signs for febrile convulsions, like a family history of the condition, earlier and with greater caution.

### References

- Habibian N, Alipour A, Rezaianzadeh A. Association between Iron Deficiency Anaemia and Febrile Convulsion in 3- to 60-Month-Old Children: A Systematic Review and Meta-Analysis. *Iran J Med Sci.* 2014 Nov; 39(6):496-505.
- Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association between iron deficiency anaemia and febrile seizure in children. *Med Glas (Zenica)* 2012; 9:239-42.
- Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The association between iron deficiency and febrile seizures in childhood. *Clin pediatr.* 2009; 48:420-6.
- American Academy of Pediatrics Steering Committee on Quality Improvement and Management. Classifying recommendations for clinical practice guidelines. *Pediatrics.* 2004; 114:874-7.
- Sadleir LG, Scheffer IE. Febrile seizures. *BMJ.* 2007; 334:307-11.
- Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures American Academy of Pediatrics. Febrile seizures: Clinical practice guideline for the long-term management of the child with simple febrile seizures. *Pediatrics.* 2008; 121:1281-6.
- Daoud AS, Batieha A, Abu-Ekteish F, Gharai-beh N, Ajlouni S, Hijazi S. Iron status: A possible risk factor for the first febrile seizure. *Epilepsia.* 2002; 43:740-3.
- Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The association between iron deficiency and febrile seizures in childhood. *Clin Pediatr (Phila)* 2009; 48:420-6.
- Hartfield D. Iron deficiency is a public health problem in Canadian infants and children. *Paediatr Child Health.* 2010; 15:347-50. PubMed PMID: 21731416; PubMed Central PMCID: PMC2921732.
- Beard J. Iron deficiency alters brain development and functioning. *J Nutr.* 2003; 133:1468-72S.
- Heydarian F, Vatankhah H. The role of anaemia in first simple febrile seizure in children aged 6 months to 5 years old. *Neurosciences (Riyadh)* 2012; 17:226-9.
- Johnston MV. Iron deficiency, febrile seizures and brain development. *Indian Pediatr.* 2012; 49:13-4.
- Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. *BMJ.* 1996; 313:343.
- Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anaemia and febrile seizures. *J Coll Physicians Surg Pak.* 2005; 15:338-40. PubMed PMID: 15924837.
- Guzman AR, Castillejos EL, Vicuña GL, Lagui VL, Balarezo ML, Gurreonero RL, et al. La anaemia: un posible factor de riesgo para la primera convulsión febril. *Paediatrica.* 2005; 7:62-5. [Google Scholar]
- Kumari PL, Nair MK, Nair SM, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures--a case control study. *Indian Pediatr.* 2012; 49:17-9.
- Bidabadi E, Mashouf M. Association between iron deficiency anaemia and first febrile convulsion: A case-control study. *Seizure.* 2009; 18:347-51.
- Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does iron deficiency raise the seizure threshold? *J Child Neurol.* 1995; 10:105-9.
- Abaskhanian A, Vahid Shahi K, Parvinnejad N. The association between iron deficiency and the first episode of febrile seizure. *J Babol Univ Med Sci.* 2009; 11:32-6.
- Bidabadi E, Mashouf M. Association between Iron Deficiency Anaemia and First Febrile Convulsion: A Case-control Study. *Seizure.* 2009; 18:347-351.
- Sharif MR, Kheirkhah D, Madani M, Kashani HH. The Relationship between Iron Deficiency and Febrile Convulsion: A Case-Control Study. *Glob J Health Sci.* 2015 Jun 25; 8(2):185-9.
- India. Guidelines - AMB: National Health Mission [Internet]. *Nhm.gov.in.* 2024. Available from: <https://nhm.gov.in/index1.php?lang=1&level=4&sublinkid=1455&lid=804>

23. Kliegman R. M. Nelson Textbook of Pediatrics. 19th ed. W. B. Saunders Co; 2011.
24. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A. Iron Deficiency Anaemia and Febrile Convulsions: Case-control Study in Children under 2 Years. *BMJ*. 1996; 313(7053):343.
25. Vaswani R. K, Dharaskar P. G, Kulkarni S, Ghosh K. Iron Deficiency as a Risk Factor for First Febrile Seizure. *Indian Pediatr*. 2009; 47:437–439.
26. Ur-Rehman N, Billoo A. G. Association between Iron Deficiency Anaemia and Febrile Seizures. *J Coll Physicians Surg Pak*. 2005; 15(6): 338–40.
27. Hartfield D. S, Tan J, Yager J. Y, Rosychuk R. J, Spady D, Haines C, Craig W. R. The Association between Iron Deficiency and Febrile Seizures in Childhood. *Clin Pediatr (Phila)* 2009; 48(4):420–6.