

Iron Deficiency Anemia and the Risk of Febrile Seizures in Children: A Clinical Evaluation

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Abstract: Febrile seizures (FS) are one of the most frequently seen and significant paediatric neurological emergencies and mainly affect children between 6 months and 5 years. In this age group, iron-deficiency anemia (IDA) is very common, can result in impaired central nervous system metabolism, and decreases seizure threshold during febrile illnesses. This study aimed to establish IDA as a serious risk factor for pediatric febrile seizures. Additionally, 120 children who have febrile seizures versus 132 febrile children who had no seizures (controls) participated in a cross-sectional study. Serum ferritin levels and full blood count indices were assessed to measure iron status. All the data were gathered from different hospitals in Iraq during the period from March 2025 to March 2026. The statistical analysis results were made and analyzed by SPSS Version 26.0. Children in the FS group had significantly lower levels of hemoglobin (9.04 ± 1.49 vs. 10.58 ± 1.65 g/dL) and lower levels of serum ferritin (11.72 ± 9.71 vs. 74.81 ± 53.62 ng/mL) than controls according to patients' clinical outcomes. There was significantly higher IDA prevalence in the FS cases (89.2%) compared with controls (53.0%). Subgroup analysis for IDA-positive cases showed significantly lower hemoglobin, MCV, and ferritin levels compared to non-IDA cases in the FS cohort. Moreover, iron supplementation history was significantly lower in the FS group (9.2% vs. 38.6%). In summary, it is strongly suspected that IDA is a risk factor for febrile seizures in young children. Cases had significant hemoglobin and ferritin deficiency, suggesting that iron deficiency might be involved in neurological hyperexcitability during febrile episodes.

Keywords: Children, Febrile Seizures, Hemoglobin (g/dL), and Ferritin.

INTRODUCTION

The most common neurological emergency of childhood was febrile seizure, which occurred in two to five percent of children ages 6 months to 5 years old [Johnston, M. V. 2007; Jones, T., & Jacobsen, S. J. 2007; Flury, T., & Aebi, C. 2001]. These convulsions are always related to a very rapid rise in temperature, usually due to a common viral or bacterial infection, and are not associated with CNS infection or metabolic disturbance [Gourie-Devi, M. *et al.*, 2004]. Most febrile seizures are harmless in the long term, but in almost one-third of patients, the seizures come back [Leela K. P. *et al.*, 2012].

At the same time, it is estimated that iron deficiency anemia is the most common dietary deficiency among children worldwide, especially under 5 years of age. Iron is a cofactor for many neurodevelopmental processes, such as myelin synthesis, mitochondrial oxidative phosphorylation, and regulation of monoaminergic neurotransmitters. Iron deficiency may affect the stability of neurons, gamma-aminobutyric acid (GABA) inhibitory pathways, and thermoregulatory pathways in the brain [Vestergaard, M. *et al.*, 2006; Vaswani, R. K. *et*

al., 2010; Bidabadi, E., & Mashouf, M. 2009]. Moreover, some iron-dependent enzymes, like tyrosine hydroxylase, are directly engaged in the synthesis of neurotransmitters, and their dysfunction during critical developmental periods may increase the excitability of the cortex [Amirsalari, S. *et al.*, 2010]. The neurophysiological changes offer a strong biological basis for exploring the possibility that iron-deficiency states may make young children more vulnerable to febrile convulsions [Miri-Aliabad, G. *et al.*, 2013].

A few studies have reported significantly higher prevalence of iron-deficiency in children with febrile seizures [Petry, N. *et al.*, 2016; World Health Organization, 2015; Mikati M. A. *et al.*, 2019; Kwak, B. O. *et al.*, 2017], while some studies have not shown any association when controlling for socioeconomic factors, developmental status, and age. To try to fill this void. This study will evaluate the results of iron deficiency anemia by itself as a risk factor for febrile seizures in children.

PATIENTS & METHOD

The study was a cross-sectional study aimed as a case-control comparative study that was carried out among 252 children who aged between 6 months to 5 years, where included children cases with febrile convulsions (FC cases) were included, while the control group was with fever but no convulsions. They were recruited into the study according to a predetermined inclusion criteria and divided into (febrile convulsions group with 120 patients) and (controls group with 132 patients, who with fever but no convulsion where gathered in a structured format. Children among the ages of six months and five years who presented with febrile convulsions for cases and a control group of the same age who had fever but no convulsions, along with both first and following episodes of FC, were included in the inclusion criteria. Diagnosed organic causes of convulsions, delayed milestones, neurological anomalies, infections of the central nervous system (meningitis, encephalitis), anemia from other causes (hemolysis, hemorrhage), and refusal of consent were the exclusion criteria. Also, we collected all data from different hospitals in Iraq from March 2025 to March 2026, including demographic information consisted of age, sex, weight, and background information such as parental consanguinity and a family history of febrile convulsions or epilepsy. Clinical data was used to record the nature of the fever and the recorded cause of fever, which was major infectious sources.

Nutritional history was determined based on the report of caregivers in terms of the feeding type, such as breastfeeding, bottle feeding, mixed feeding, same family diet, and complementary diet. In FC cases, clinical classification related to seizures was noted where possible (e.g., proportion with simple versus complex febrile convulsions). Hematological indices and iron status were determined by analyzing venous blood samples. As a marker of iron stores, serum ferritin (ng/mL)

was determined. The status of iron deficiency anaemia (IDA) was established through laboratory criteria, which was based on the hemoglobin and ferritin values, and the participants were grouped as IDA and non-IDA in the FC cases. The research compared the hematological parameters between FC and controls, and even compared hematological parameters in FC children stratified by IDA. Continuous variables (weight, hemoglobin, ferritin, and other indices) were compared via proper tests of the difference of means, whereas categorical variables (age-group distribution, categories of feeding types, categories of causes of fever, and prevalence of IDA) were compared with the help of chi-square testing. All patients' information were settled by SPSS, version 26.0.

RESULTS

In comparison of demographic characteristics between febrile convection (FC) cases (n=120) and controls (n=132), there was no significant difference between the two groups for most baseline measurements. There were no statistically significant differences in mean age (21.85 ± 14.30 vs. 20.23 ± 16.52 months) or sex distribution (males: 62.5% vs. 59.1%). The mean body temperature at the onset of the febrile episode was also similar in both groups (39.15 ± 1.00 vs. $38.98 \pm 0.94^\circ\text{C}$), as was the occurrence of consanguineous marriage among the parents (54.2% vs. 49.2%). But the difference in the mean weight was significant, where the mean weight of the FC cases were greater than that of the controls (11.94 ± 3.46 kg vs. 10.19 ± 3.53 kg). Notably, there is a difference in the history of iron therapy between the FC cases and controls (9.2% vs. 38.6%), which is suggesting a possible protective association. The family history of febrile seizures in FC cases was 56.7%, and that of epilepsy, 15.8%, with the majority (80.8%) having simple febrile seizures.

Table 1: Outline the basic features of patients who participated in the study.

Variable	FC Cases (n=120)	Controls (n=132)	P-value
Age (months), Mean \pm SD	21.85 ± 14.30	20.23 ± 16.52	0.407
Sex, Male n (%)	75 (62.5%)	78 (59.1%)	0.671
Sex, Female n (%)	45 (37.5%)	54 (40.9%)	
Weight (kg), Mean \pm SD	11.94 ± 3.46	10.19 ± 3.53	<0.001
Temperature ($^\circ\text{C}$), Mean \pm SD	39.15 ± 1.00	38.98 ± 0.94	0.168
Parental Consanguinity, Yes n (%)	65 (54.2%)	65 (49.2%)	0.513
Family History of FC, Yes n (%)	68 (56.7%)	N/A	—
Family History of Epilepsy, Yes n (%)	19 (15.8%)	N/A	—
Type of FC: Simple n (%)	97 (80.8%)	N/A	—

Type of FC: Complex n (%)	23 (19.2%)	N/A	—
History of Iron Therapy, Yes n (%)	11 (9.2%)	51 (38.6%)	<0.001

The age distribution analysis showed a clear age distribution for febrile seizures. The 13–24 month age group had the highest number of FC cases with 42.5%, and the fewest number of controls, only 10.5%. In contrast, the youngest age group (6-12 months) were overrepresented in the controls (54.1%) compared to the cases (30.0%). There was a slight increase in the number of cases in the middle age group compared to controls (15.0% > 10.5%), and the highest age group (37–60 months) had a higher proportion of controls (21.1% > 12.5%). Based on these results, the age group of 13-24 months had the highest risk of febrile convulsions in this population.

Feeding-related behaviors were analyzed, and a significant difference between both groups were found. Among the feeding methods, "Same Family Diet" (49.2%) was significantly higher in FC cases than in controls (34.6%). Mixed feeding was also more common amongst cases (25.8% compared with 19.5%). The exclusive feeding of bottles and complementary diet feeding, however, was more prevalent among controls (18.0% and 9.8%, respectively) than among the cases (7.5% and 4.2%). There were relatively low breastfeeding rates that are similar across groups (13.3% vs. 17.3%).

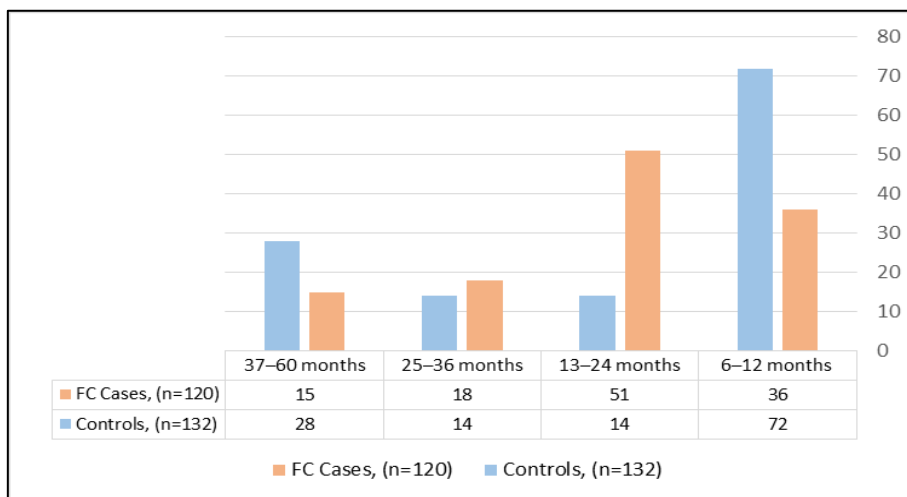


Figure 1: Classification of all patient groups based on age.

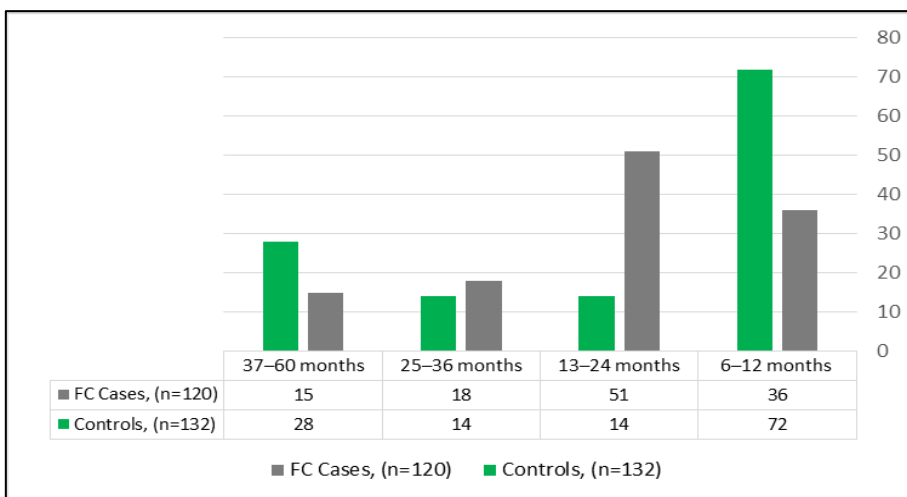


Figure 2: Define feeding types presented in both groups.

Gastroenteritis (GE) was the commonest cause of fever, being the cause of 35.0% of cases and 33.1% controls. The second most common cause was upper respiratory tract infections (URTIs): in 31.7% of cases and 25.6% of controls. There were

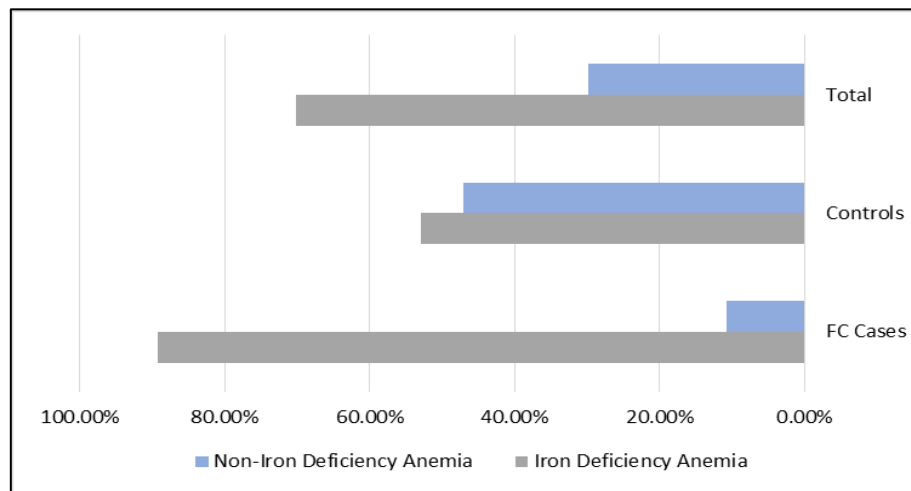
more cases of lower respiratory tract infections (LRTIs) in the FC cases (19.2%) than in the control cases (10.5%). Urinary tract infections (UTI) were less common in cases (10.0%) compared to controls (15.8%).

Table 2: Distribution of the fever causes in all patients.

Cause of Fever	FC Cases n (%)	Controls n (%)	Total
URTI	38 (31.7%)	34 (25.6%)	72
LRTI	23 (19.2%)	14 (10.5%)	37
GE (Gastroenteritis)	42 (35.0%)	44 (33.1%)	86
UTI	12 (10.0%)	21 (15.8%)	33
Vaccine	2 (1.7%)	13 (9.8%)	15
Other	3 (2.5%)	6 (4.5%)	9

Table 3: Hematological clinical outcomes into two groups.

Parameter	FC Cases (Mean \pm SD)	Controls (Mean \pm SD)	P-value
Hemoglobin (g/dL)	9.04 \pm 1.49	10.58 \pm 1.65	<0.001
MCV (fL)	67.43 \pm 8.28	68.81 \pm 11.04	0.267
MCH (pg)	23.37 \pm 2.61	27.11 \pm 19.98	0.043
MCHC (g/dL)	33.85 \pm 27.04	33.66 \pm 27.33	0.956
RBC Count ($\times 10^6/\mu\text{L}$)	4.45 \pm 2.81	4.65 \pm 0.56	0.430
RDW (%)	16.87 \pm 2.85	17.07 \pm 10.36	0.842
Platelet Count ($\times 10^3/\mu\text{L}$)	306.24 \pm 118.00	280.26 \pm 83.30	0.043
Serum Ferritin (ng/mL)	11.72 \pm 9.71	74.81 \pm 53.62	<0.001

**Figure 3:** Determining the extent of iron deficiency anemia in both groups.

Hematological differences were large between cases and controls for FC and suggested an association with iron deficiency. FC cases exhibited significantly lower mean hemoglobin levels (9.04 \pm 1.49 g/dL vs. 10.58 \pm 1.65 g/dL) and markedly reduced serum ferritin concentrations (11.72 \pm 9.71 ng/mL vs. 74.81 \pm 53.62 ng/mL).

Mean corpuscular hemoglobin (MCH) was also significantly lower in cases (23.37 \pm 2.61 pg vs. 27.11 \pm 19.98 pg). Modest, though statistically significant, elevations in platelet count were observed in FC cases (306.24 \pm 118.00 vs. 280.26 \pm 83.30 $\times 10^3/\mu\text{L}$), a finding which is sometimes associated with iron deficiency.

Table 4: Enroll clinical hematological outcomes in febrile convulsions children who suffer from iron deficiency anemia and children without IDA.

Parameter	IDA (n=107) Mean \pm SD	Non-IDA (n=13) Mean \pm SD	t-statistic	P-value
Hemoglobin (g/dL)	8.76 \pm 1.32	11.36 \pm 0.31	-7.072	<0.001
MCV (fL)	66.52 \pm 8.13	74.96 \pm 5.14	-3.648	<0.001
MCH (pg)	23.24 \pm 2.48	24.50 \pm 3.42	-1.659	0.100
MCHC (g/dL)	34.17 \pm 28.62	31.25 \pm 2.96	0.366	0.715
RBC Count ($\times 10^6/\mu\text{L}$)	4.48 \pm 2.96	4.16 \pm 0.74	0.396	0.693
RDW (%)	17.02 \pm 2.83	15.66 \pm 2.84	1.636	0.104
Platelet Count ($\times 10^3/\mu\text{L}$)	307.23 \pm 120.56	298.03 \pm 98.05	0.264	0.792
Serum Ferritin (ng/mL)	10.58 \pm 8.38	21.05 \pm 14.45	-3.882	<0.001

DISCUSSION

In this study, 120 children with febrile convulsions (FC cases) were compared with 132 febrile children who didn't have a seizure (FC controls). This study revealed the paradigm of nutritional status as a modifiable factor in neurological vulnerability in early childhood, specifically iron homeostasis. Additionally, the mean weight of FC cases was significantly higher than that of the seizure group (11.94 ± 3.46 kg versus 10.19 ± 3.53 kg), and there was a significant difference in the prevalence of prior iron therapy obtained by the seizure group (9.2%) as well as the FC cases (38.6%). These findings may suggest that there is a gap in the assessment and treatment of iron deficiency by the seizure groups.

Furthermore, the prevalence of IDA was significantly higher among participants with FC (89.2%) than among those without FC (53.0%), and the unadjusted odds ratio was ~ 7.2 (95% CI: 3.8–13.6), suggesting a strong association between IDA and susceptibility to febrile seizures. Children with febrile seizures and IDA ($n=107$) had significantly lower hemoglobin (8.76 ± 1.32 vs. 11.36 ± 0.31 g/dL) and MCV (66.52 ± 8.13 vs. 74.96 ± 5.14 fL) and much lower ferritin levels (10.58 ± 8.38 vs. 21.05 ± 14.45 ng/mL) than the others, further confirming the role of iron deficiency as a unique pathophysiological group within children with febrile seizures. In a meta-analysis of 17 studies in more than 4,800 children, IDA was significantly associated with febrile seizures (pooled OR: 1.98; 95% CI: 1.26–3.13) when using plasma ferritin to diagnose IDA, and had the strongest association with plasma ferritin levels (OR: 3.78; 95% CI: 1.80–7.94).

The potential association is biologically plausible as iron is essential for neurodevelopment and neuronal function. Iron is a cofactor of enzymes that play a role in myelination, dopamine, serotonin, and GABA biosynthesis, and mitochondrial energy metabolism [Bidabadi, E., & Mashouf, M. 2009; Chaudhary, B. R. et al., 2021; Vaswani, R. K. et al., 2010]. The reduction of the seizure threshold due to iron deficiency has multiple mechanisms, which are impaired GABAergic inhibition, altered dopaminergic signaling, reduction of cerebral oxygen delivery caused by anemia, and increased excitability of neurons that occur as a result of metabolic stress [Ghasemi, F., & Valizadeh, F. 2014]. In addition, in FC cases, elevated platelet counts were observed, which is also identified in other cases of

IDA, confirming the hematological findings of IDA in the studied population. Also, no significant differences were found between groups in MCV or RDW, but functional iron deficiency (low ferritin without microcytosis) may play a role in seizure susceptibility, as recent literature suggests that the outcome of low ferritin before microcytic anemia may be indicative of increased risk of febrile seizures [Bidabadi, E., & Mashouf, M. 2009].

Among cases, we found a peak incidence of febrile seizures during the 13–24 month range, which was related to the brain maturation stage and increased susceptibility to nutritional deficiencies. Controls were more likely to be represented in the 6–12 month age group (54.1% vs. 30.0%), which may be indicative of an earlier engagement with healthcare for fever management in this age group. Additionally, the distribution of etiological factors of fever demonstrated that gastroenteritis (35.0%) and upper respiratory tract infections (31.7%) predominated in FC cases, as in other countries throughout the world [Amouian, S. et al., 2013]. There was no significant difference between the etiology of fever difference among the groups, which indicates that the relationship between IDA and FS is unrelated to the infectious trigger.

CONCLUSION

The present study revealed that Iron deficiency anemia (IDA) is significantly associated with febrile seizures among children, and serum ferritin being the most discriminative biomarker. The very large differences in IDA prevalence between FC cases (89.2%) and controls (53.0%), and the significantly lower ferritin concentrations in the cases. There was a decrease in seizure threshold during febrile illness as a result of iron deficiency. The results support the use of iron status testing as part of the routine evaluation of febrile seizures in children and highlight the need for nutritional interventions as preventative measures in children with febrile seizures.

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