The association between serum ferritin and febrile seizure in children



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ABSTRACT

Background: Between the ages of 6 and 60 months, febrile seizures can happen when a child's temperature is 38°C or higher, there is no infection in the central nervous system, and there is no metabolic imbalance. These seizures can happen in 2-5% of neurologically healthy infants and children. Iron deficiency has been postulated to reduce neurotransmitter function, thereby decreasing seizure threshold in children. Most studies conclude that iron deficiency anemia is common in febrile seizure patients, although some have found no significant association. Aims and Objectives: Investigate the association between serum ferritin levels and the occurrence of febrile seizures in children aged 6-60 months. Materials and Methods: The study population included 180 patients, 90 of whom had febrile seizures, and 90 controls without seizures. Hematological parameters, including complete blood count, mean corpuscular volume, mean hemoglobin concentration, red cell distribution width, serum iron, plasma ferritin, and total iron binding capacity, were performed, along with a peripheral smear. Statistical analysis of laboratory results was performed using the Statistical Package for the Social Sciences version 24. Significance levels were denoted as P≤0.05. Results: Simple febrile seizures were the most common type in children. The serum ferritin levels were significantly lower in cases compared to controls $(41.13 \pm 22.12 \text{ vs. } 70.06 \pm 36.47 \text{ ng}), P = 0.0003.$ Children with febrile seizures had a higher proportion of microcytic hypochromic anemia (39/90), in contrast to controls (25/90); P=0.029. Conclusion: Plasma ferritin levels were significantly lower in cases compared to controls, suggesting that iron-deficient children are more prone to febrile seizures. Hence, children with febrile seizures should be investigated and treated for iron deficiency anemia.

Key words: Febrile seizures; Serum ferritin; Children; Hematological parameters

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INTRODUCTION

A febrile seizure is any type of seizure (most often a generalized tonic-clonic seizure) occurring with fever (at least 38°C but in the absence of central nervous system infection, severe metabolic disturbance, or other alternative precipitant in children between the ages of 3 months and 6 years. Simple febrile seizures (SFS) are generalized attacks with a fever lasting 15 min or less and often tonic-clonic. Complex febrile seizures (CFS) are

longer, focal, and recurrent within 24 h.² Febrile status epilepticus (FSE) is longer than 30 min. SFS, being the most prevalent, generally has a good prognosis, whereas CFS and FES require more attention due to their complexity and potential risks. Most patients with SFS return to normal behaviors within minutes. Genetics contribute to the disorder, with genes such as SCN1A, SCN1B, SCN9A, and CPA6 associated. There is also a link to the dysregulation of pro-inflammatory and anti-inflammatory cytokines.² Risk factors for recurrent febrile seizures include

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genetic predispositions, age, gender, fever characteristics, family history, multiple seizures, perinatal exposure to antiretroviral drugs, and maternal behavior.³⁻⁵

Iron deficiency is a prevalent nutritional issue in developing countries, particularly in infants aged 6-24 months. It is linked to febrile seizures and is a vital micronutrient for neurotransmitter production, hormones, DNA replication, myelin formation, and brain energy metabolism.6 Low iron status reduces aldehyde oxidase and monoamine oxidase activity.^{7,8} Iron deficiency in children can lead to anemia, abnormal growth, cognitive deficits, and immune dysfunction. 9,10 It increases dopamine and norepinephrine levels, alters metabolism and neurotransmission in brain structures, and impairs myelination.¹¹ Infants aged 6–24 months with iron deficiency anemia are at risk.¹² Iron deficiency is linked to neurological disorders such as irritability, restless leg syndrome, and attention deficit hyperactivity disorder. Low serum ferritin levels can lower seizure thresholds, potentially triggering seizures in children. Fever can exacerbate these effects. 13 The morphological evidence supports the diagnosis of irondeficiency anemia and shows how important it is to look at peripheral blood smears when diagnosing children who are having febrile seizures. In addition, further investigation into the patients' dietary habits and nutritional status may provide insight into the prevalence of iron deficiency in this population. Addressing these deficiencies could play a vital role in managing febrile seizures and improving overall health outcomes for affected children.

Iron deficiency refers to reduced body iron stores, leading to anemia. Serum ferritin levels indicate iron stores, with levels below 12 µg/L indicating deficiency. ¹⁴ Elevated levels may occur in infection and inflammation. This research investigates the potential relationship between iron deficiency anemia and febrile seizures in children, considering iron's role in neurotransmitter metabolism. Despite conflicting results, most studies suggest IDA is common in febrile seizure patients. The aim is to determine the association between serum ferritin levels and febrile seizures.

The conflicting results underscore the need for further research to clarify the relationship between serum ferritin and febrile seizures in children. Some studies indicating this relationship have been conducted.¹⁵⁻¹⁸ A full understanding of this link could be in the prevention, diagnosis, and treatment of febrile seizures. It could also help facilitate the identification of children who are likely to have seizures early on and give them pre-emptive treatment to lower their risk. Therefore, our aim was to investigate any potential correlation between serum ferritin and febrile seizures in children.

Aims and objectives

- To compare serum ferritin levels between children with febrile seizures and age- and sex- matched control children with febrile illness without seizures.
- To assess whether low serum ferritin levels are a significant risk factor for the development of febrile seizures in children.
- To evaluate the potential clinical implications of serum ferritin measurement in the management and prevention of febrile seizures in pediatric populations.

MATERIALS AND METHODS

This prospective case—control study was performed between August 2022 and January 2024 to investigate any association between serum ferritin and febrile seizures in children aged 6–6 years. The study population consisted of 180 patients aged 6–60 months admitted to the Department of Paediatrics, R.G. Kar Medical College and Hospital. The study included 90 children with febrile seizures and 90 controls with febrile illness without seizures. The parents of all patients provided written informed consent for inclusion in the study. We started this study after receiving approval from the institutional ethical committee of R.G. Kar Medical College and Hospital.

There were 90 people in the febrile seizure group (n=90)who had a seizure along with a fever of 38°C, and the temperature was recorded by parents at home with a thermometer and also in hospital on admission with a digital thermometer in all cases, or higher, and had no infections in the central nervous system or metabolic problems. In accordance with a previous study, 19 the sample size was determined based on the primary objective of the study. The formula employed for calculating the sample size is: $n=([Z]^2 \times P \times [1-p])/d^2$ n=required sample size; Z=The Z-score for the selected confidence level; P=expected proportion; E=margin of error putting the value of Z=1.96 (at 95% Cl), d=0.05 (margin of error 5%), P=0.10[18] $n=([1.96]^2 \times 0.10 \times [1-0.10])/(0.05)^2 n=138.29$. Since the sample size cannot be a fraction, it must be rounded up to the nearest whole number. Therefore, the required sample size is 139. When accounting for a 15% attrition rate, the sample size will be 139 plus 20.85, which equals 159.85. This figure should then be rounded up to the next whole number, resulting in a final sample size of 160, but in our study, we have included 180 subjects. The control group (n=90) was selected randomly from among children admitted for febrile illnesses, such as gastroenteritis, otitis media, or respiratory tract infections. Both cases and controls had fever due to some infection or inflammation, and in both cases, serum ferritin may rise as an acute-phase reactant and marker for inflammation. Hence, this same bias is present in both cases and controls, so it nearly nullifies the bias, as both cases and controls are matched. Moreover, not only ferritin, but also other red cell indices were taken to ascertain anemia. Second, in the case group, despite fever due to infection or inflammation, ferritin was found to be low, which also corroborated with the other red cell parameters of anemia; this eliminates the bias of increased ferritin as an acute phase reactant in both case and control groups, without seizure around the same time as the cases. People who had problems with their central nervous systems, such as developmental delays, motor disabilities, or mental or cognitive defects, were also excluded those subjects from participating in the study because they might not have received enough of certain nutrients, which could alter the results.

We performed routine hematologic investigations on the 1st day of admission. This study examined blood tests and iron levels in two different groups. Iron deficiency was diagnosed based on serum ferritin levels, with a level below 12 µg/L considered deficient. The tests performed were complete blood count, mean corpuscular volume (MCV), mean hemoglobin concentration (mean corpuscular hemoglobin [MCH]), and MCH concentration. We also looked at serum iron, plasma ferritin, total iron binding capacity (TIBC), and transferrin saturation. We entered the patient's demographic details and the investigation report into the master chart and analyzed them using standard statistical tools.

We used the Chi-square test to look at qualitative variables and the independent-samples *t*-test to compare continuous variables between the case and control groups. All the statistical analysis was performed by Statistical Package for the Social Sciences version 24, and P≤0.05 was taken to indicate statistical significance. Subjects with febrile seizures were classified as SFS, CFS, and FSE.

RESULTS

Out of 180 participants, 90 were in the case group, and 90 were in the control group. In the cases group, there were 52 males (57.8%) and 38 females (42.2%), whereas in the control group, there were 50 males (55.5%) and 40 females (44.5%). There is no significant difference found in gender distribution, so gender does not significantly influence the occurrence of febrile seizures. In our study, each group is split into two subgroups: those aged 6–30 months and those aged >30–60 months. There was a significant difference in the age distribution between cases and controls, which suggests that age may play a role in how likely someone is to have febrile seizures. Table 1 provides a summary of clinical parameters.

Table 1: Clinical and Biochemical parameters				
Parameters	Case	Control	P-value	
Sex (frequency)				
Male	52	50	0.763	
Female	38	40		
Age (frequency)				
6-30 months	66	35	<0.0001	
>30-60	24	55		
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Hemoglobin	10.63±1.54	11.12±1.66	0.043	
(Hb) (g/dL)				
Mean corpuscular	73.55±9.94	76.42±11.24	0.005	
volume (femtoliters)				
Mean corpuscular	25.44±2.34	26.06±2.72	0.022	
hemoglobin				
(picograms)				
Red cell distribution	15.16±1.66	14.62±1.91	0.002	
width (percentage)				
Serum iron (µg/dL)	34.97±19.08	55.77±27.77	0.0001	
Serum ferritin (ng/mL)	41.13±22.12	70.06±36.47	0.0003	
Total iron-binding	491.61±85.19	453.19±86.24	0.048	
capacity (μg/dL)				
C-reactive	5.46±2.86	6.69±2.90	0.005	
protein (mg/L)				
Red blood cells morphology (frequency)				
Microcytic and	39	25	0.029	
hypochromic				
Normocytic and	51	65		
normochromic				

In this study, we find that the mean hemoglobin level was significantly lower in the case population (10.63±1.54 g/dL vs. 11.12±1.66 g/dL, P=0.043), suggesting that lower hemoglobin levels may be associated with an increased risk of febrile seizures. We also discovered that the MCV level was much lower in the case population (73.55±9.94 femtoliters vs. 76.42±11.24 femtoliters, P=0.005). Specifically, febrile seizure patients tend to have lower MCV compared to those without seizures. We discovered that the case population had significantly lower MCH (25.44±2.34 picograms vs. 26.06±2.72 picograms, P=0.022). This suggests that lower MCH may be linked to a higher risk of febrile seizures. We find that red cell distribution width (RDW) was significantly elevated in the case population $(15.16\pm1.66\% \text{ vs. } 14.62\pm1.91\%, P=0.002)$. The case population had significantly lower serum iron levels. This suggests that iron deficiency may make children more likely to have febrile seizures. We discovered that serum ferritin levels were also lower in the case population $(41.13\pm22.12 \text{ ng/mL vs. } 70.06\pm36.47 \text{ ng/mL, } P=0.0003).$ This suggests that iron deficiency, as shown by lower ferritin levels, may be a major risk factor for febrile seizures. TIBC was also significantly elevated in the case population $(491.61\pm85.19 \,\mu\text{g/dL} \,\text{vs.} \,453.19\pm86.24 \,\mu\text{g/dL},$ P=0.048). Elevated TIBC levels are often indicative of iron deficiency, suggesting that children with febrile seizures may have a greater tendency toward iron deficiency. The case population showed a significant decrease in C-reactive

protein (CRP) (5.46±2.86 mg/L vs. 6.69±2.90 mg/L, P=0.005). These results suggest that there might be a link between lower levels of CRP and febrile seizures. However, further research is necessary to fully comprehend the nature of this link and its underlying mechanisms. Cases were more likely to have microcytic and hypochromic red blood cells (RBCs) (39/90), whereas controls predominantly exhibited normocytic and normochromic RBCs (65/90). This difference could potentially be linked to underlying factors such as iron deficiency or other hematological abnormalities associated with febrile seizures.

Table 2 provides a frequency distribution table according to the type of febrile seizure in the case group. The distribution of febrile seizure types among the cases indicates that SFS are the most common form, affecting more than 80% of the children in the study. CFS and FSE are much less common but are clinically significant due to their more severe nature and the potential need for further medical intervention and monitoring. These findings provide a detailed overview of the types of febrile seizures and highlight the need for different clinical approaches based on the seizure type. SFSs, being the most prevalent, generally have a good prognosis, whereas CFS and FSE require more attention due to their complexity and potential risks.

DISCUSSION

This study explores the link between iron deficiency and febrile seizures, highlighting the risk factor and protective effects of iron deficiency anemia. ²⁰ This prospective case—control study revealed that children with febrile seizures have a higher risk of iron deficiency anemia, a condition linked to low serum iron and plasma ferritin levels. ^{3,21-23}

The study looked at the relationship between serum ferritin levels and febrile seizures in 180 children, with 90 being cases and 90 being controls. It did this by comparing blood tests between children who had febrile seizures and those who did not. The study found significant differences in hematological parameters, suggesting a possible link between iron deficiency and febrile seizures. The age distribution was significant, with younger children being more susceptible, highlighting the need for age-specific strategies and further research to understand the age-related

Table 2: Frequency distribution table according to the type of febrile seizure in the case group

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Type of febrile seizures	Percentage	Frequency	
Simple febrile seizures	83.3	75	
Complex febrile seizure	12.3	11	
Febrile status epilepticus	4.4	4	

dynamics. The previous study²⁴ also supported this work.

This study revealed that 83.3% of febrile seizures in children were SFS, emphasizing the need for early monitoring and educating parents about fever risks, and suggesting early intervention could reduce seizures in these groups. These seizures are the most common type, and their benign nature suggests they do not require extensive medical intervention beyond standard fever management and parental reassurance. The presence of CFS in 12.30% and FSE in 4.40% of the cases underscores the need for careful evaluation of these patients. These children may benefit from further neurological assessment and monitoring for potential developmental issues or epilepsy. Our study found that children with febrile seizures have significantly lower serum ferritin levels compared to controls, indicating iron deficiency. This suggests that iron deficiency in patients may significantly impact their recovery, and further research is needed to understand the correlation between serum ferritin levels and seizure activity. This aligns with national guidelines such as the Anemia Mukt Bharat initiative, which recommends iron supplementation for children to prevent iron deficiency anemia. Therefore, ensuring adequate iron status in all children, especially those with febrile seizures, is crucial.^{25,26} This supports previous studies suggesting that iron deficiency may lower the seizure threshold, making children more susceptible to febrile seizures. The research also found significant differences in the amounts of hemoglobin, MCV, MCH, and RDW. These findings indicate a higher prevalence of iron deficiency anemia in children with febrile seizures compared to febrile controls without seizures. Health-care providers should closely monitor iron levels in children with a history of febrile seizures, as dietary interventions or supplementation could potentially reduce seizure frequency or severity. Previous studies suggest that although anemia was not common among febrile seizure patients, iron deficiency was more frequent in these patients.²⁷

Our research showed that more children (43.33%) who had febrile seizures had microcytic and hypochromic RBCs than kids (26.78%) who did not have febrile fits. The higher frequency of these RBCs could mean that there is an underlying condition, such as iron deficiency anemia, that makes the person more likely to have febrile seizures. One previous study showed that there was an association between the incidence of febrile seizures and the incidence of microcytic hypochromic anemia.² Cases of febrile seizures in children show lower serum iron levels and higher TIBC, indicating iron deficiency anemia, a condition typically associated with increased transferrin production. One of the previous studies shows that TIBC was significantly elevated in febrile seizure cases.²⁸ In this study, we found that children with febrile seizures had

significantly lower mean CRP levels (5.46 mg/L) compared to those without seizures (6.69 mg/L). The study reveals a significant difference in inflammatory response in children with febrile seizures, suggesting that the condition may not necessarily be linked to high systemic inflammation. Previous studies show that CRP was significantly lower in children with febrile seizures compared to children without seizures.³ The study suggests that genetic predisposition or immune system differences may contribute to febrile seizures.

However, it lacks confounding factors and a cross-sectional nature. The study has several limitations. First, the crosssectional nature of the study does not allow for the determination of causality. Second, the selection of the control group from children with febrile illnesses such as gastroenteritis or respiratory tract infections introduces a potential bias, as serum ferritin is an acute-phase reactant and its levels can be elevated in inflammatory conditions, potentially masking true iron deficiency in the control group. Third, the sample size was not based on a formal calculation, which may affect the statistical power of the study. Finally, potential confounding factors such as socioeconomic status and the degree of malnutrition, which could influence both iron status and seizure susceptibility, were not evaluated. Future research should focus on longitudinal studies, intervention studies, and exploring other micronutrients and genetic factors to better understand the etiology of febrile seizures.

Limitations of the study

The limitations of this study include its single-centre design and the restricted duration of the research. Additionally, these factors may affect the generalisability of the findings to larger populations.

CONCLUSION

This study indicates a possible association between lower serum ferritin levels and febrile seizures in children, suggesting iron deficiency may contribute to these seizures. Improving iron levels through diet or supplements could potentially prevent seizures.

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SR- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; NK- Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; PB, KSK- Design of study, statistical analysis and interpretation; DH- Review manuscript; SS- Review manuscript; KSK- Literature survey and preparation of figures; DH- Coordination and manuscript revision.

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