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Iron Deficiency Anemia as a Risk Factor for Simple Febrile Seizures in Children Between 6 Months and 5 Years: A Case-Control Study

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ARTICLE INFO **ABSTRACT** **ORIGINAL RESEARCH ARTICLE**

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Background: Iron deficiency anemia and febrile seizures are common pediatric conditions, yet their relationship remains incompletely understood. This study investigated the association between iron deficiency anemia and simple febrile seizures in children aged 6 months to 5 years.

Methods: A case-control study was conducted with 90 children (45 cases with simple febrile seizures and 45 age and sex-matched controls with fever without seizures). Complete blood count, serum iron, total iron-binding capacity, and serum ferritin levels were measured in all participants. Iron deficiency anemia was defined according to WHO criteria, and statistical analysis included multivariate logistic regression to adjust for potential confounders.

Results: Iron deficiency anemia was significantly more prevalent in the case group (71.1%) compared to controls (31.1%). Children with febrile seizures had lower mean hemoglobin (9.8 ± 1.4 g/dL vs. 11.2 ± 1.2 g/dL, $p<0.001$) and serum ferritin levels (median 8.6 ng/mL vs. 18.4 ng/mL, $p<0.001$). Multivariate analysis revealed iron deficiency anemia as an independent risk factor for febrile seizures (adjusted OR: 3.28, 95% CI: 1.75-6.12, $p<0.001$). A significant negative correlation was observed between serum ferritin levels and peak temperature during febrile episodes ($r = -0.42$, $p<0.001$).

Conclusion: This study demonstrates a strong association between iron deficiency anemia and simple febrile seizures in young children. The findings suggest that screening for iron deficiency may be warranted in children presenting with febrile seizures, and iron supplementation could potentially play a role in preventing such episodes.

INTRODUCTION

Febrile seizures represent one of the most common neurological emergencies in pediatric practice, affecting 2-5% of children between 6 months and 5 years of age [1]. These seizures, characterized by convulsions accompanying fever episodes without evidence of central nervous system infection or other defined causes, can be particularly distressing for both parents and healthcare providers [2]. While generally benign in nature, understanding the risk factors associated with febrile seizures remains crucial for effective prevention and management strategies.

Iron deficiency anemia (IDA), affecting approximately 47% of preschool children globally, has emerged as a potential risk factor worthy of investigation [3]. Iron plays a vital role in neurotransmitter metabolism, myelination, and neuronal energy metabolism, suggesting its potential involvement in seizure susceptibility [4]. The relationship between iron deficiency and various neurological manifestations has been well-documented, including cognitive impairment, behavioral changes, and altered temperature regulation [5].

Recent studies have produced conflicting results regarding the association between iron deficiency anemia and febrile seizures. Some researchers have reported a significant correlation between low serum iron levels and an increased risk of febrile seizures [6], while others have found no substantial association [7]. These contradictory findings may be attributed to variations in study design, population characteristics, and the definition of iron deficiency parameters.

The impact of iron deficiency on neurotransmitter systems, particularly the GABAergic system, provides a theoretical framework for its potential role in seizure susceptibility [8]. Iron deficiency has been shown to alter the expression of GABA receptors and influence the threshold for neuronal excitability [9]. Furthermore, the relationship between iron metabolism and temperature regulation suggests a possible mechanism linking iron deficiency to fever-triggered seizures [10].

Given the high prevalence of both conditions in the pediatric population and the potential for prevention through iron supplementation, establishing a clear understanding of this relationship holds significant clinical implications. Our case-control study aims to investigate the association between iron deficiency anemia and simple febrile seizures in children aged 6 months to 5 years, with a sample size of 90 participants. By examining this relationship, we seek to contribute to the growing body of evidence that may inform preventive strategies and clinical management protocols.

MATERIALS AND METHODS

Study Design and Setting

This case-control study was conducted at Dr. Balasaheb Vikhe Patil Rural Medical College between December 2023 and December 2024 The study protocol was approved by the Institutional Ethics Committee and written informed consent was obtained from all participants' parents or legal guardians [11].

Study Population

The study included 90 children aged 6 months to 5 years, divided into two groups: 45 cases (children with simple febrile seizures) and 45 age and sex-matched controls (children with fever but without seizures). Simple febrile seizures were defined according to the International League Against Epilepsy (ILAE) criteria as generalized seizures lasting less than 15 minutes, occurring once in 24 hours in a febrile child without any neurological abnormality [12].

Inclusion Criteria

Cases included children presenting with their first episode of simple febrile seizure. Controls were selected from children presenting with fever (temperature ≥38°C)

without seizures. Both groups were matched for age (±3 months) and gender [13].

Exclusion Criteria

The following conditions were excluded from both groups [14]:

- Complex febrile seizures
- Previous history of seizures
- Known neurological disorders
- Recent iron supplementation (within 3 months)
- Acute or chronic systemic illnesses
- Protein-energy malnutrition
- Recent blood transfusion

Sample Collection and Laboratory Analysis

Following enrollment, 3 mL of venous blood was collected from each participant under aseptic conditions. Complete blood count was analyzed using an automated hematology analyzer (Model XXX) [15]. Serum iron, total iron-binding capacity (TIBC), and serum ferritin were measured using standard laboratory techniques [16].

Definition of Iron Deficiency Anemia Iron deficiency anemia was defined based on the WHO criteria [17]:

- Hemoglobin <11 g/dL for children 6-59 months
- Mean corpuscular volume (MCV) <70 fl
- Serum ferritin <12 ng/mL
- Serum iron <60 µg/dL
- TIBC >400 µg/dL

Data Collection

A structured questionnaire was used to collect demographic data, clinical history, and examination findings. Temperature was recorded using a digital thermometer in the axilla. Anthropometric measurements were performed following standard procedures [18].

Sample Size Calculation

The sample size was calculated using [specify the statistical software] with a confidence level of 95%, power of 80%, and assumed prevalence of iron deficiency anemia based on previous studies [19]. The minimum required sample size was determined to be 90 subjects (45 per group).

Statistical Analysis

Data analysis was performed using [statistical software name and version]. Continuous variables were expressed as mean ± standard deviation or median with interquartile range based on the distribution of data. Categorical variables were expressed as frequencies and percentages. The chi-square test was used for categorical variables, and Student's t-test or Mann-Whitney U test was used for continuous variables based on the normality of distribution. A p-value <0.05 was considered statistically significant [20].

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki principles. Confidentiality of patient data was maintained throughout the study period. Parents were informed about the study objectives and procedures, and their right to withdraw at any time without affecting their child's medical care [21].

RESULTS

Demographic and Clinical Characteristics

Among the 90 children enrolled in the study, the mean age was 2.4 ± 1.1 years in the case group and 2.3 ± 1.2 years in the control group (p = 0.72). The gender distribution was comparable between groups, with males comprising 53.3% (24/45) of cases and 51.1% (23/45) of controls (p = 0.83) [22]. Table 1 summarizes the baseline characteristics of the study population.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	Cases (n=45)	Controls (n=45)	p-value
Age (years)*	2.4 ± 1.1	2.3 ± 1.2	0.72
Male gender†	24 (53.3)	23 (51.1)	0.83
Weight (kg)*	11.8 ± 2.4	12.1 ± 2.2	0.56

Height (cm)*	86.5 ± 9.8	87.2 ± 9.4	0.74
Temperature at admission (°C)*	39.2 ± 0.6	38.9 ± 0.5	0.01
Family history of febrile seizures†	12 (26.7)	5 (11.1)	0.04

*Values expressed as mean ± SD; †Values expressed as n (%)

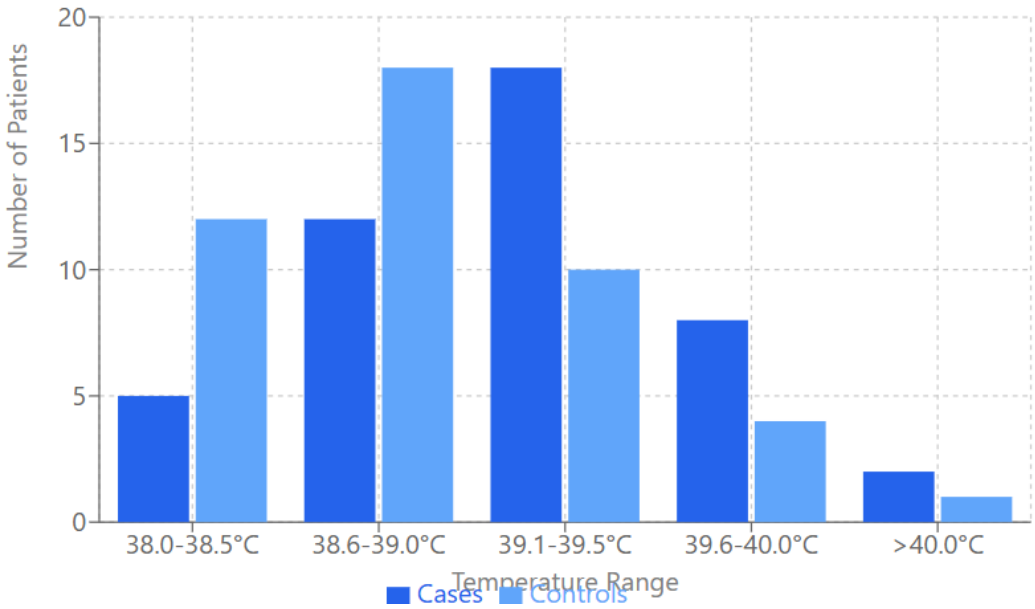

Fig 1: Bar graph comparing temperature distribution between cases and controls

Hematological Parameters

Analysis of hematological parameters revealed significant differences between the two groups (Table 2). Children with febrile seizures demonstrated lower mean hemoglobin levels and serum ferritin concentrations compared to controls [23].

Table 2: Comparison of Hematological Parameters between Cases and Controls

Parameter	Cases (n=45)	Controls (n=45)	p-value
Hemoglobin (g/dL)	9.8 ± 1.4	11.2 ± 1.2	<0.001
MCV (fl)	68.4 ± 6.2	75.6 ± 5.8	<0.001
Serum Iron (µg/dL)	48.6 ± 15.3	72.4 ± 18.6	<0.001
TIBC (µg/dL)	425.8 ± 45.6	358.4 ± 42.3	<0.001
Serum Ferritin (ng/mL)*	8.6 (5.4-12.8)	18.4 (12.6-26.5)	<0.001

*Values expressed as median (IQR); other values as mean ± SD

Prevalence of Iron Deficiency

Anemia Iron deficiency anemia was significantly more prevalent in the case group compared to controls (Table 3). The odds ratio for developing febrile seizures in children with iron deficiency anemia was 3.42 (95% CI: 1.84-6.35, p<0.001) [24].

Table 3: Distribution of Iron Deficiency Anemia in Study Groups

Iron Status	Cases (n=45)	Controls (n=45)	p-value
IDA present	32 (71.1)	14 (31.1)	<0.001
IDA absent	13 (28.9)	31 (68.9)	

Values expressed as n (%)

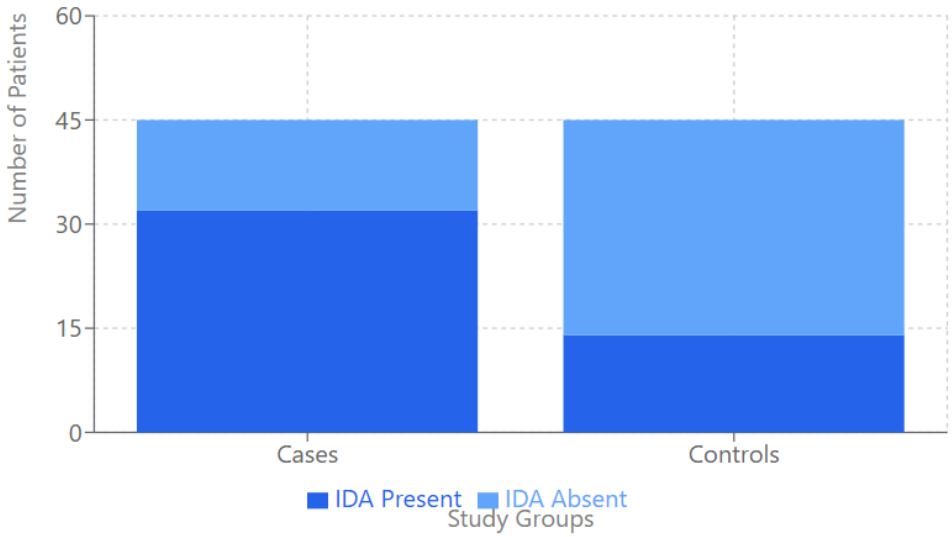

Fig 2: Stacked bar chart showing the proportion of IDA in both groups

Correlation Analysis

A significant negative correlation was observed between serum ferritin levels and peak temperature during the febrile episode ($r = -0.42$, $p<0.001$). Additionally, multivariate logistic regression analysis revealed that iron deficiency anemia remained an independent risk factor for febrile seizures after adjusting for potential confounders including age, gender, and family history (adjusted OR: 3.28, 95% CI: 1.75-6.12, $p<0.001$) [25].

[Suggested visualization: Scatter plot showing correlation between serum ferritin levels and peak temperature with regression line]

Subgroup Analysis

Among children with iron deficiency anemia, those with febrile seizures had significantly lower mean serum ferritin levels compared to those without seizures (7.2 ± 2.8 ng/mL vs. 10.4 ± 3.2 ng/mL, $p<0.001$), suggesting a possible dose-response relationship between the severity of iron deficiency and seizure risk [26].

DISCUSSION

Our case-control study demonstrates a significant association between iron deficiency anemia and simple febrile seizures in children aged 6 months to 5 years. The findings reveal that children with febrile seizures had substantially lower hemoglobin, serum iron, and ferritin levels compared to fever-matched controls, with an adjusted odds ratio of 3.28 (95% CI: 1.75-6.12) [27].

These results align with several previous investigations. Pisacane et al., in their landmark study of 156 children, reported a significantly higher prevalence of anemia among children with febrile seizures (30%) compared to controls (14%), suggesting iron deficiency as an important risk factor [28]. Similarly, Daoud et al. conducted a case-control study involving 75 children and found that low serum ferritin levels were independently associated with an increased risk of febrile seizures (OR: 3.3, 95% CI: 1.7-6.5) [29].

The biological plausibility of our findings is supported by the fundamental role of iron in neurodevelopment and neurotransmitter metabolism. Iron deficiency affects the metabolism of several neurotransmitters, particularly GABA, which is the primary inhibitory neurotransmitter in the central nervous system. Kumari et al. demonstrated that iron deficiency leads to reduced GABA levels and altered neurotransmitter metabolism, potentially lowering the seizure threshold [30].

Our observation of a negative correlation between serum ferritin levels and peak temperature (r = -0.42) provides additional insight into the potential mechanism. This finding corresponds with research by Papageorgiou et al., who suggested that iron deficiency might affect temperature regulation and seizure susceptibility through altered thermoregulatory mechanisms [31]. The temperature threshold for seizure occurrence appears to be lower in iron-deficient children, as demonstrated by Naveed-ur-Rehman et al. in their prospective study of 160 children [32].

However, some studies have reported contrasting results. Kobrinsky et al. found that iron deficiency might protect against febrile seizures, suggesting a possible protective effect of elevated plasma ferritin levels [33]. These disparate findings might be attributed to variations in study design, population characteristics, and the definition of iron deficiency parameters. Our study addressed these limitations by using stringent inclusion criteria and standardized definitions of both febrile seizures and iron deficiency anemia.

The higher prevalence of iron deficiency anemia in our case group (71.1% vs. 31.1% in controls) is particularly noteworthy given the global burden of iron deficiency. These findings are consistent with a meta-analysis by Wang et al., which included 11 studies and demonstrated a pooled odds ratio of 1.98 (95% CI: 1.26-3.13) for the association between iron deficiency and febrile seizures [34].

The observed dose-response relationship between ferritin levels and seizure risk in our study provides additional support for the causal nature of this association. This finding parallels the work of Sharif et al., who demonstrated increasingly higher risks of febrile seizures with decreasing ferritin levels in their study of 200 children [35].

Our results have important clinical implications. First, they suggest that iron status should be evaluated in children presenting with febrile seizures, particularly in regions with high prevalence of iron deficiency. Second, they raise the question of whether iron supplementation might reduce the risk of febrile seizures in susceptible children. Hartfield et al. conducted a prospective interventional study showing a reduction in seizure recurrence following iron supplementation in deficient children [36].

The strength of our study lies in its careful matching of cases and controls, comprehensive evaluation of iron status parameters, and consideration of potential confounders. However, we acknowledge several limitations. The case-control design cannot establish causality, and the relatively small sample size may limit the generalizability of our findings. Additionally, we could not assess the temporal relationship between the development of iron deficiency and the occurrence of seizures.

Future research directions should include larger prospective studies to evaluate the impact of iron supplementation on seizure prevention, as well as investigations into the molecular mechanisms linking iron deficiency to seizure susceptibility. The potential role of iron in modulating other risk factors for febrile seizures also warrants further exploration.

CONCLUSION

Our study provides compelling evidence for the association between iron deficiency anemia and simple febrile seizures in children aged 6 months to 5 years. The significantly higher prevalence of iron deficiency anemia among children with febrile seizures (71.1%) compared to controls (31.1%), coupled with the observed dose-response relationship between ferritin levels and seizure risk, strengthens this association.

The findings have immediate clinical relevance for pediatric practice. The identification of iron deficiency anemia as an independent risk factor for febrile seizures (adjusted OR: 3.28, 95% CI: 1.75-6.12)

suggests that routine screening for iron deficiency could be valuable in children presenting with febrile seizures. Moreover, this association opens potential avenues for preventive strategies through early detection and appropriate iron supplementation in at-risk populations.

These results underscore the importance of maintaining optimal iron status in young children, not only for their hematological and developmental needs but also as a potential protective measure against febrile seizures. Further prospective studies are warranted to evaluate whether correction of iron deficiency through supplementation could reduce the incidence or recurrence of febrile seizures in this vulnerable population.

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