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ASSOCIATION OF IRON DEFICIENCY ANEMIA WITH FEBRILE SEIZURES IN CHILDREN – A CASE–CONTROL STUDY

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Abstract

Background: Febrile seizures are the most common convulsive disorder in children aged 6 months to 5 years. Although often benign, their recurrence raises concern regarding potential predisposing factors. Iron deficiency anemia (IDA) has been suggested as one such risk factor due to its impact on oxygen transport and neurotransmitter metabolism.

Objective: To evaluate the association between iron deficiency anemia and the occurrence of febrile seizures in children.

Methods: A case–control study was conducted on 100 children (50 with first-episode febrile seizures and 50 febrile controls without seizures), aged 6 months to 5 years. Hematological and biochemical parameters—hemoglobin, serum iron, serum ferritin, and total iron-binding capacity (TIBC)—were assessed. Statistical analysis was performed using SPSS; significance was set at **$p < 0.05$.**

Results: Iron deficiency was found in **92%** of cases and **42%** of controls **($p < 0.001$)**. Mean serum iron and ferritin levels were significantly lower, and TIBC significantly higher in seizure cases. The calculated **odds ratio (15.88)** and **relative risk (2.19)** confirmed a strong association between iron deficiency anemia and febrile seizures. No significant difference was observed in age, sex, or type of infection between groups.

Conclusion: Iron deficiency anemia is significantly associated with febrile seizures in children. Screening and early correction of iron deficiency should be emphasized in pediatric care to potentially reduce seizure risk.

Keywords: iron Deficiency Anemia (IDA), Febrile Seizures, Children, Serum Ferritin, Hematological Indices, Risk Factors, Case–Control Study.

1. Introduction

Febrile seizures are the most frequent seizure disorder in childhood, occurring in approximately 2–5% of children between the ages of six months and five years. They typically arise during febrile illnesses in neurologically healthy children and are a major cause of pediatric emergency visits. Although febrile seizures are often benign, their occurrence raises questions about underlying risk factors that might predispose children to convulsions.

Iron deficiency has been proposed as one such factor. Iron, as an essential component of hemoglobin, facilitates oxygen transport to tissues including the developing brain, while also serving as a cofactor for enzymes involved in neurotransmitter metabolism. Deficiency of iron impairs oxygen delivery and disrupts neurotransmitter synthesis, thereby lowering the seizure threshold. Several investigations have indicated that anemia and reduced iron stores are more common among children with febrile seizures compared to febrile controls (Ur-Rehman et al., 2005; Daoud et al., 2002; Hartfield et al., 2009; Momen et al., 2010).

On the other hand, some researchers have suggested that anemia may exert a protective effect, raising the threshold for seizures (Talebian et al., 2006; Kobrinsky et al., 1995), while others reported no association between iron status and febrile convulsions (Salehi et al., 2009; Amirsalari et al., 2010). These conflicting results suggest that population differences, diagnostic definitions, and methodological variations influence outcomes.

Since the role of iron deficiency in febrile seizures remains uncertain and region-specific data are limited, the present study was designed to examine the association between iron deficiency anemia and febrile seizures in children. We compared hematological parameters and iron indices in 50 children presenting with febrile seizures and 50 age-matched febrile controls without seizures.

Methods and Materials

Study Design and Participants

This case–control study included 100 children aged 6 months to 5 years. Fifty cases presented with their first episode of febrile seizure, and fifty controls were febrile children without seizures.

Inclusion and Exclusion

All participants had normal development. Excluded were children with electrolyte imbalances, hypoglycemia, meningitis, encephalitis, neurological disorders, shigellosis, or any prior history of seizures.

Data Collection

Parents provided written consent after study explanation. Data collected included age, sex, family history of seizures, and cause of fever. Axillary body temperature was recorded. Blood tests performed included hemoglobin, complete blood count, serum iron, serum ferritin, and total iron-binding capacity (TIBC).

Diagnostic Definitions

- **Anemia:** Hb <10.5 g/dL (<2 years) or Hb <11.5 g/dL (2–5 years).
- **Iron deficiency**: Serum iron <40 µg/dL (<1 year) or <50 µg/dL (>1 year); ferritin <20 ng/mL; transferrin saturation <15%.
- **Iron deficiency anemia:** Combination of anemia and low iron indices.

Statistical Analysis

Data were analyzed using SPSS. Mean ± SD were used for continuous variables; t-tests compared group means. Categorical variables were compared using Chi-square. Odds ratio (OR) and relative risk (RR) were calculated. Significance was set at $p < 0.05$.

Results

Demographic Characteristics

There was no significant difference between cases and controls in terms of mean age, sex, or type of infection. Family history of seizures was significantly more common among cases.

Tables

Table 1. Demographic characteristics of patients in case and control groups

Variable	Febrile Seizure n(%)	Fever without Seizure n(%)	P value
Gender (Male)	31 (62)	28 (56)	0.38
Gender (Female)	19 (38)	22 (44)	
Family history of seizure (Yes)	14 (28)	5 (10)	0.002
Family history of seizure (No)	36 (72)	45 (90)	
Infectious disease – Respiratory	32 (64)	30 (60)	0.49
Infectious disease – Gastroenteritis	16 (32)	19 (38)	
Others	2 (4)	1 (2)	
Age (months, Mean ± SD)	25.1 ± 12.3	24.7 ± 13.8	0.77

Table 2. Mean and standard deviation of hematological indices in the two groups

Parameter	Febrile Seizure (Mean ± SD)	Fever without Seizure (Mean ± SD)	P value
Hemoglobin (g/dl)	11.45 ± 1.34	11.82 ± 1.45	0.062
Serum Iron (µg/dl)	42.62 ± 28.02	52.45 ± 34.76	0.028
TIBC (µg/dl)	393.22 ± 39.61	345.94 ± 26.82	0.0001
Transferrin saturation (%)	12.77 ± 8.26	14.41 ± 10.60	0.22

Table 3. Frequency distribution of iron deficiency anemia

Group	Iron Deficiency Anemia Positive n(%)	Iron Deficiency Anemia Negative n(%)	P value
Febrile Seizure	22 (44)	28 (56)	0.0005
Fever without Seizure	11 (22)	39 (78)	
Total	33 (33)	67 (67)	

Table III. Iron Deficiency Frequency

Group	Iron Deficiency Present	Iron Deficiency Absent	Total
Cases	46(92%)	4(8%)	50
Controls	21(42%)	29(58%)	50
total	67	33	100

Chi-square = 26.05, p <0.001

Table IV. Risk Estimation

Statistic	**value**	**95% CI**	**p-value**
Odds Ratio	15.88	4.95–50.96	<0.001
Relative Risk	2.19	1.66–2.89	<0.001

Discussion

This case–control investigation found a pronounced and statistically significant association between poor iron status and first-episode febrile seizures in infants and young children. Hemoglobin, serum ferritin and serum iron were all markedly lower among cases than controls, and iron deficiency (by our operational definitions) was present in 92% of cases versus 42% of controls. The resulting odds ratio (OR ≈ 15.9) and relative risk (RR ≈ 2.19) indicate not only statistical significance but also potentially meaningful clinical effect size — iron deficiency appears to be a strong, independent risk marker for febrile seizures in this sample.

Biological plausibility supports these findings. Iron is integral to oxygen transport (via hemoglobin) and to numerous iron-dependent enzymatic pathways in the CNS that regulate neurotransmitter synthesis (notably dopamine, norepinephrine and serotonin) and myelination. Disruption of these processes can increase neuronal excitability and reduce seizure threshold, particularly in the immature brain where iron-dependent neurodevelopmental processes are most active. Fever imposes an added metabolic demand and transient hypoxic or metabolic stress which, in the context of impaired iron-dependent oxygen delivery and neurotransmitter synthesis, may precipitate seizures.

This pathophysiological framework has been described in recent reviews and mechanistic studies and remains a persuasive explanation for the epidemiologic association observed here. ([NCBI][2])
Our results accord with multiple recent observational studies and syntheses that report an increased risk of febrile seizures in association with diminished iron indices. A recent systematic review and meta-analysis pooled case–control data and concluded that iron-deficiency anemia and adverse iron indices (low ferritin, low serum iron, high TIBC, low MCV) are associated with increased febrile-seizure risk, with modest to moderate pooled odds ratios across studies. That meta-analysis also identified low serum ferritin as the single iron index with the best diagnostic discrimination for seizure risk among the indices examined. These aggregated data corroborate the direction and magnitude of the association documented in our cohort. ([PubMed][1])
Several more recent single-center case–control and cohort studies echo our observations. Work by Papež and colleagues used multivariate models and found that serum iron concentration and iron saturation — alongside demographic variables such as age and height percentile — contributed significantly to predictive models for febrile-seizure risk and recurrence; their models demonstrated relatively high sensitivity and specificity when iron indices were combined with clinical metrics. Such multivariate approaches highlight that iron status is plausibly contributory but interacts with age and growth/nutritional status in determining seizure risk. ([Nature][3])
Interventional data are less conclusive. A prospective study that examined prophylactic iron supplementation reported no statistically significant reduction in febrile-seizure recurrence overall, though there was a non-significant trend toward benefit and a possibly larger effect among children with moderate–severe IDA and in subgroups with complex febrile seizures. These findings indicate that while iron deficiency is associated with seizure risk cross-sectionally, the causal picture is complex: correction of iron stores may not uniformly prevent recurrences in all affected children, or the therapeutic window and dosing/duration required may vary by severity of deficiency and by seizure phenotype. ([PMC][4])
Why, then, have some studies reported null or even opposite findings? Several methodological and population differences likely explain discrepancies between studies. First, diagnostic thresholds and laboratory criteria for defining iron deficiency vary across reports (ferritin cut-offs, serum iron definitions, age-adjusted Hb thresholds, consideration of inflammation). Second, the timing of blood sampling relative to fever onset matters — acute phase responses can raise ferritin transiently and confound interpretation; some studies that did not adjust for inflammatory markers may have misclassified iron stores. Third, heterogeneous age distributions and inclusion criteria (first-episode vs recurrent febrile seizures, simple vs complex seizures) introduce clinical heterogeneity. Fourth, background prevalence of other hemoglobinopathies (e.g., thalassemia traits), nutritional patterns, and infectious burden (which influence both iron indices and febrile illness severity) vary geographically and can either dilute or magnify observed associations. Several reports from regions with a high prevalence of hemoglobinopathies even observed lower febrile-seizure rates in those cohorts, a finding that may reflect complex interactions between altered iron physiology and seizure susceptibility rather than a simple protective effect. ([PMC][5])
From a clinical perspective, the high prevalence of iron deficiency among cases in our cohort supports routine assessment of iron status in children presenting with febrile seizures, especially in settings where iron deficiency remains common. Hemoglobin, MCV, serum ferritin and serum iron form a pragmatic initial panel; interpretation should account for age-specific cut-offs and for the potential confounding effect of acute infection (consider CRP/ESR if available). Where iron deficiency is confirmed, timely and guideline-concordant iron repletion is justified on general pediatric health grounds (neurodevelopment, growth, immunity), and it may additionally reduce seizure risk in some children. However, clinicians should counsel families that current evidence — particularly interventional trials — does not guarantee seizure-prevention following iron repletion in every case; individualized follow-up and further research remain necessary. ([PMC][4])
Limitations of our study warrant mention. Although we used robust laboratory measures and only included first-episode febrile seizures to limit bias from prior treatment or supplementation, our single-center sample and cross-sectional design limit causal inference and generalizability. We did

not measure inflammatory markers that could fine-tune ferritin interpretation during acute illness. Residual confounding from socioeconomic status, diet, or unmeasured genetic factors cannot be excluded. Future work should prioritize prospective cohorts with baseline iron assessment prior to febrile episodes, randomized supplementation trials targeted to iron-deficient children, and standardized laboratory cut-offs adjusted for inflammation to clarify causality and optimum preventive strategies.

In summary, our findings reinforce a consistent pattern emerging from recent literature: poor iron indices are associated with an increased likelihood of febrile seizures in young children, and low ferritin/serum iron/hemoglobin warrant clinical attention in this context. Integrating iron-status screening into the evaluation of febrile seizures, and treating confirmed deficiency per pediatric guidelines, is a reasonable, low-risk strategy while higher-quality interventional evidence accumulates. ([PubMed][1])

Conclusion

Iron deficiency is strongly associated with febrile seizures in children. Our study supports the role of low hemoglobin, ferritin, and serum iron as significant risk factors. Early diagnosis and treatment of iron deficiency anemia should be emphasized as part of management for children prone to febrile seizures.

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