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Frequency of Iron Deficiency Anemia as a Risk Factor for Febrile Seizures in Children Aged 6 Months to 5 Years

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ABSTRACT

Background: Febrile seizures (FS) are the most common seizure type in children, affecting 2-5% of the pediatric population, with potential long-term neurodevelopmental implications. Iron deficiency anemia (IDA), the most prevalent micronutrient deficiency globally, has been hypothesized to lower the seizure threshold due to its impact on neurotransmitter synthesis and brain function.

Objective: To determine the frequency of iron deficiency anemia as a risk factor for febrile seizures in children aged 6 months to 5 years.

Methods: A case-control study was conducted at the Department of Pediatrics, Balochistan Institute of Child Health Services, Quetta, from November 29, 2021, to May 30, 2022. A total of 200 children were enrolled, with 100 cases (children with febrile seizures) and 100 controls (children with febrile illnesses but no seizures). Demographic and clinical data were collected, and blood samples were analyzed for hemoglobin (Hb), mean corpuscular volume (MCV), hematocrit (HCT), and serum ferritin levels. Statistical analysis was performed using SPSS version 25, with a significance level of $p < 0.05$.

Results: The prevalence of IDA was significantly higher in cases (46.5%) compared to controls (28%) ($p = 0.003$). Mean Hb levels were 9.86 ± 2.28 g/dL in cases and 9.48 ± 1.86 g/dL in controls ($p = 0.104$). Mean MCV and HCT levels were significantly lower in cases (69.03 ± 10.84 fL and 29.75 ± 5.22%) than controls (72.91 ± 11.63 fL and 32.85 ± 11.86%) ($p = 0.016$ and $p = 0.035$). The odds ratio for IDA as a risk factor for febrile seizures was 2.23 (95% CI: 1.30–3.82).

Conclusion: IDA was significantly associated with febrile seizures, emphasizing the need for routine screening and management of iron deficiency in children to reduce seizure risk.

INTRODUCTION

Febrile seizures are the most frequently encountered type of seizures in pediatric populations, affecting approximately 2-5% of children globally. These seizures, which are characterized by their occurrence alongside febrile episodes in the absence of central nervous system infections or metabolic disturbances, present significant challenges to caregivers and healthcare systems alike. Their recurrence, estimated at 30-40%, adds to the psychological distress experienced by parents and guardians (1,2). Furthermore, febrile seizures are associated with a small but notable risk of progression to epilepsy, which is reported in 2-7% of cases, underlining the importance of identifying modifiable risk factors to prevent their occurrence (2,3).

Iron deficiency anemia (IDA), the most prevalent micronutrient deficiency worldwide, is both preventable and treatable but remains a significant public health challenge. It affects an estimated one-third of the global population, with particularly high prevalence among young children and women in developing countries. In Pakistan, the National Nutrition Survey 2011 reported that 33.4% of children suffer from IDA, with even higher prevalence in specific subpopulations (6). Iron plays a vital role in several critical physiological processes, including brain energy metabolism, neurotransmitter function, and myelination. Its deficiency can lead to neurodevelopmental impairments, cognitive dysfunction, and alterations in behavior, which are particularly concerning during the rapid growth and development phases of infancy and early childhood (7,8).

Emerging evidence suggests a potential association between iron deficiency anemia and febrile seizures in children. Several studies have proposed that iron deficiency may lower the seizure threshold due to its role in neurotransmitter metabolism and myelin synthesis, thereby predisposing children to febrile seizures. For instance, research has indicated that children with febrile seizures are more likely to exhibit iron deficiency anemia compared to their peers with febrile illnesses but without seizures (8,11). One local case-control study found that 31.85% of children with febrile seizures had IDA, compared to 19.6% of controls, with an odds ratio of 1.93 (11). However, other studies have reported conflicting findings, with some suggesting that iron deficiency does not confer a protective

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or predisposing effect on the development of febrile seizures (12,14).

The variability in study results highlights the need for further exploration of this relationship. The pathophysiological mechanisms underpinning this potential association remain poorly understood, but hypotheses include the involvement of iron in critical enzymes required for normal brain function and the regulation of the seizure threshold (13,20). Notably, the prevalence of both febrile seizures and iron deficiency anemia is highest among children aged 6 months to 24 months, suggesting a potential overlap in their epidemiological determinants (17,18).

Given the high burden of febrile seizures in pediatric emergency care settings and the preventable nature of iron deficiency anemia, understanding the link between these conditions has significant implications for public health and clinical practice. This study seeks to investigate the association between iron deficiency anemia and febrile seizures in children aged 6 months to 5 years, with a focus on identifying whether IDA serves as a significant risk factor for febrile seizures. By addressing this gap, the findings aim to inform preventive strategies and improve outcomes in affected pediatric populations.

MATERIAL AND METHODS

This case-control study was conducted in the Department of Pediatrics, Balochistan Institute of Child Health Services, Quetta, Pakistan, over a six-month period from November 29, 2021, to May 30, 2022. A total of 200 children aged 6 months to 5 years were included in the study. The sample size was determined using an 80% power of the test, a 5% level of significance, and expected prevalence rates of iron deficiency anemia of 31.85% in cases and 19.6% in controls, as reported in prior studies (11). Non-probability purposive sampling was employed to recruit participants. The study adhered to ethical principles outlined in the Declaration of Helsinki, and approval was obtained from the institutional ethics committee before initiation. Written informed consent was acquired from the parents or legal guardians of all participating children.

Children were divided into two groups, each comprising 100 participants. The case group included children who experienced simple febrile seizures, defined as generalized seizures lasting less than 15 minutes, occurring in the context of febrile illness (temperature >100°F) in neurologically intact children with no history of previous afebrile seizures, central nervous system infections, or metabolic disturbances. The control group consisted of children with febrile illnesses but without seizures. Inclusion criteria required participants to be within the specified age range and presenting with febrile illnesses, while children with atypical febrile seizures, chronic illnesses (e.g., liver, kidney, or cardiac disease), central nervous system infections (determined by clinical evaluation and cerebrospinal fluid analysis), or ongoing iron therapy were excluded. Children with a history of asthma or any conditions affecting hematological parameters were also excluded.

Following recruitment, demographic data, including age, gender, weight, and contact information, were recorded on a standardized proforma. A thorough clinical evaluation was performed by a qualified pediatrician to confirm eligibility and group allocation. Blood samples were collected under aseptic conditions by a trained staff nurse using a 5cc BD syringe. The samples were immediately transported to the hospital laboratory for analysis of hemoglobin (Hb), hematocrit (HCT), mean corpuscular volume (MCV), and serum ferritin levels, which were interpreted by an experienced consultant pathologist. Iron deficiency anemia was diagnosed based on operational definitions, which included Hb levels below 10 g/dL, HCT levels below 33%, MCV values below 70 fL, and elevated red cell distribution width (RDW >17%) in the blood of febrile children.

The study ensured confidentiality and anonymity of participant data throughout the process. Data were systematically entered into a database and analyzed using SPSS version 25. Continuous variables such as age, weight, Hb, HCT, MCV, and serum ferritin levels were expressed as means and standard deviations. Categorical variables, including gender and the presence of iron deficiency anemia, were presented as frequencies and percentages. Comparative analyses between cases and controls were conducted using the chi-square test for categorical variables and an independent t-test for continuous variables. An odds ratio with a 95% confidence interval was calculated to assess the strength of association between iron deficiency anemia and febrile seizures. A p-value of less than 0.05 was considered statistically significant.

By employing rigorous methodological standards, the study aimed to generate reliable and clinically relevant insights into the association between iron deficiency anemia and simple febrile seizures in children, addressing a significant gap in pediatric research and healthcare practice.

RESULTS

The study included 200 children aged between 6 months and 5 years, with an equal distribution of 100 cases and 100 controls. The mean age of children in the case group was 1.04 ± 1.07 years, while the mean age in the control group was 1.60 ± 1.69 years.

Table 1: Demographics and Baseline Characteristics of Cases and Controls

Variable	Cases (n=100)	Controls (n=100)	p-value
Age (years)	1.04 ± 1.07	1.60 ± 1.69	0.031*
Gender (Male/Female)	65/35	72/28	0.295
Weight <10 kg (%)	78	88	0.082
Temperature (°F)	101.28 ± 1.16	101.10 ± 0.85	0.432

(*Statistically significant at $p < 0.05$)

There was a higher proportion of male participants in both groups, with 65 males and 35 females in the case group and 72 males and 28 females in the control group. The weight distribution indicated that 78% of children in the case group and 88% in the control group weighed less than 10 kg. The descriptive statistics for demographic and clinical variables are summarized in Table 1. The hematological parameters, including hemoglobin (Hb), mean corpuscular volume (MCV), hematocrit (HCT), and serum ferritin levels, were assessed and compared between the two groups. The mean Hb levels in the case group were 9.86 ± 2.28 g/dL, while the control group had slightly lower levels at 9.48 ± 1.86 g/dL. The mean MCV values were 69.03 ± 10.84 fL in cases and 72.91 ± 11.63 fL in controls. Similarly, the mean HCT was 29.75 ± 5.22% in the case group compared to 32.85 ± 11.86% in the control group.

Serum ferritin levels were significantly lower in the case group (42.35 ± 15.28 ng/mL) compared to controls (58.14 ± 14.87 ng/mL). These findings are summarized in Table 2.

Table 2: Hematological Parameters of Cases and Controls

Parameter	Cases (n=100)	Controls (n=100)	p-value
Hemoglobin (g/dL)	9.86 ± 2.28	9.48 ± 1.86	0.104
MCV (fL)	69.03 ± 10.84	72.91 ± 11.63	0.016*
Hematocrit (%)	29.75 ± 5.22	32.85 ± 11.86	0.035*
Serum Ferritin (ng/mL)	42.35 ± 15.28	58.14 ± 14.87	<0.001*

(*Statistically significant at $p < 0.05$)

The prevalence of iron deficiency anemia, as defined by hemoglobin levels <10 g/dL, MCV <70 fL, and serum ferritin levels <50 ng/mL, was significantly higher in the case group (46.5%) compared to the control group (28%). The odds ratio (OR) for iron deficiency anemia as a risk factor for febrile seizures was calculated to be 2.23 (95% CI: 1.30–3.82, p = 0.003), indicating that children with febrile seizures were over twice as likely to have iron deficiency anemia compared to controls. Table 3 provides the summary of iron deficiency anemia prevalence and associated risk.

Table 3: Prevalence and Odds Ratio for Iron Deficiency Anemia

Group	Iron Deficiency Anemia Present (%)	Iron Deficiency Anemia Absent (%)	OR (95% CI)	p-value
Cases (n=100)	46.5	53.5	2.23 (1.30–3.82)	0.003*
Controls (n=100)	28.0	72.0		

(*Statistically significant at $p < 0.05$)

Further analysis revealed that the association between iron deficiency anemia and febrile seizures remained significant after adjusting for potential confounding variables, including age, gender, and weight. Multivariable logistic regression analysis confirmed that iron deficiency anemia independently increased the risk of febrile seizures with an adjusted odds ratio of 2.12 (95% CI: 1.18–3.80, p = 0.011).

These results support the hypothesis that iron deficiency anemia is a significant risk factor for febrile seizures in children aged 6 months to 5 years. Children with febrile seizures exhibited significantly lower hematological indices and a higher prevalence of iron deficiency anemia compared to controls, highlighting the need for routine screening and management of iron deficiency in pediatric populations to mitigate this risk.

DISCUSSION

This study investigated the association between iron deficiency anemia (IDA) and febrile seizures (FS) in children aged 6 months to 5 years and found that IDA was significantly more prevalent in children with febrile seizures compared to those with febrile illnesses but no seizures. The findings indicated that children with febrile seizures were more than twice as likely to have IDA, supporting the hypothesis that IDA is a significant risk factor for febrile seizures. These results align with previous studies that have suggested an association between IDA and febrile seizures. For instance, a study conducted in Pakistan reported a higher prevalence of IDA among children with febrile seizures, demonstrating an odds ratio of 1.93 (11). Similarly, Indian research revealed that 63.6% of children with febrile seizures had IDA, compared to 24.7% of controls, yielding an odds ratio of 5.34 (8). These findings highlight the global relevance of addressing iron deficiency as a modifiable risk factor for febrile seizures in pediatric populations.

The observed association between IDA and febrile seizures is likely rooted in the physiological role of iron in neurodevelopment and brain function. Iron is essential for the synthesis of neurotransmitters, myelination, and brain energy metabolism, and its deficiency can impair neuronal function and lower the seizure threshold (7,13). Additionally, low levels of hemoglobin and serum ferritin may contribute to hypoxia and oxidative stress, further exacerbating the risk of seizures. These mechanisms have been supported by studies demonstrating that iron supplementation improves neurodevelopmental outcomes and reduces seizure susceptibility in children with iron deficiency (9,13).

While this study adds to the growing body of evidence supporting the link between IDA and febrile seizures, it is not without limitations. One limitation was the use of non-probability purposive sampling, which may have introduced selection bias and limited the generalizability of the findings. Additionally, the cross-sectional design of the study precluded the determination of causality. Although the study adjusted for potential confounders such as age, gender, and weight, the possibility of residual confounding cannot be entirely ruled out. Another limitation was the reliance on a single measurement of hematological indices,

which may not fully capture the dynamic nature of iron status in young children.

Despite these limitations, the study had several strengths. The use of a well-defined case-control design allowed for a detailed comparison of hematological parameters between children with febrile seizures and controls. The rigorous operational definitions and inclusion criteria ensured the validity of the results, and the laboratory analyses were conducted under standardized conditions by experienced professionals, enhancing the reliability of the findings. Moreover, the study addressed an important public health issue in a developing country context, where both IDA and febrile seizures are highly prevalent and represent significant challenges for pediatric healthcare.

These findings have important clinical and public health implications. Routine screening for iron deficiency should be considered in children presenting with febrile seizures, especially in regions with a high prevalence of IDA. Early identification and management of iron deficiency may help reduce the risk of febrile seizures and improve neurodevelopmental outcomes in vulnerable populations. Public health interventions aimed at reducing the burden of IDA, such as iron supplementation programs, dietary education, and fortification initiatives, should be prioritized, particularly in resource-limited settings.

Future research should focus on longitudinal studies to establish causal relationships between IDA and febrile seizures and to explore the effectiveness of iron supplementation in reducing seizure recurrence. Additionally, studies investigating the interplay between genetic predisposition, nutritional deficiencies, and environmental factors in the pathogenesis of febrile seizures would provide a more comprehensive understanding of this complex condition. Addressing these knowledge gaps would contribute to the development of targeted preventive and therapeutic strategies to improve pediatric health outcomes globally.

CONCLUSION

This study demonstrated a significant association between iron deficiency anemia and febrile seizures in children aged 6 months to 5 years, with children experiencing febrile seizures being over twice as likely to have iron deficiency anemia compared to those with febrile illnesses without seizures. These findings underscore the critical need for routine screening and early management of iron deficiency in pediatric populations to mitigate the risk of febrile seizures. Addressing iron deficiency through public health initiatives, dietary interventions, and supplementation programs has the potential to improve neurodevelopmental outcomes, reduce the healthcare burden associated with pediatric emergencies, and enhance overall child health, particularly in resource-limited settings.

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