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Association of Iron Deficiency Anemia with Febrile Seizures in Children

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ABSTRACT

Introduction: Febrile convulsions represent the predominant seizure manifestation among the pediatric population, with a range of conjectured predisposing factors encompassing iron deficiency anemia. The primary aim of this investigation was to ascertain the correlation between iron deficiency anemia and febrile seizures in children. **Methodology:** A retrospective case-control investigation was conducted at the Pediatric Medicine Department of Aziz Fatima Hospital in Faisalabad spanning a period of six months, from May 19th to November 18th, 2024. The study cohort comprised 130 children within the age bracket of 6 months to 5 years, evenly divided into two groups: 65 cases afflicted with febrile seizures and 65 controls diagnosed with febrile illness but devoid of seizure manifestations. The examination encompassed the determination of hemoglobin and serum ferritin levels in all subjects. Iron deficiency anemia was defined utilizing the criteria of hemoglobin levels equal to or below 11 gm/dl and serum ferritin levels at or below 12 microgram/dl. The statistical analysis of the collected data was performed utilizing the statistical software SPSS version 25.0, where the odds ratio was computed to evaluate the correlation, with a significance threshold set at a p-value of ≤0.05. **Results:** The average age of participants in the case group was 2.28 years with a standard deviation of 0.91, while in the control group it was 2.31 years with a standard deviation of 1.01. Iron deficiency anemia was identified in 28 individuals (43.08%) in the case group and in 15 individuals (23.08%) in the control group. The statistical analysis revealed a p-value of 0.017 and an odds ratio of 2.42, signifying a statistically significant correlation between iron deficiency anemia and the occurrence of febrile seizures in the studied population. **Conclusion:** This study demonstrated that iron deficiency anemia is significantly associated with febrile seizures in children. Screening for iron deficiency anemia in children presenting with febrile seizures may be beneficial for their clinical management.

INTRODUCTION

Febrile seizures represent the most prevalent type of seizure in childhood. These seizures typically manifest in children aged between 6 months and 5 years when their body temperature reaches 38°C (100.4°F) or above, in the absence of central nervous system (CNS) infection or metabolic disturbances. Simple febrile seizures are characterized by generalized tonic and clonic movements coinciding with fever, lasting no longer than 15 minutes, and not recurring within a 24-hour period.[1] Febrile convulsions manifest in approximately 2–5% of pediatric cases, typically presenting for the first time in the second year of life for the majority of affected children.[2]

Febrile seizures are a frequent occurrence in pediatric patients afflicted with conditions such as otitis media, roseola, human herpes virus, Shigella infection, or other similar infectious diseases.[3] Various factors, including genetic predisposition, advanced age, gender, presence of fever, characteristics and length of seizure episodes, family medical background, developmental milestones, occurrence of multiple seizures, and exposure to antiretroviral drugs during the perinatal period, have been extensively investigated as potential determinants of recurring febrile seizures. Notably, one such factor, iron deficiency anemia (IDA), has been identified as a contributing factor linked to a higher likelihood of experiencing febrile seizures.[4-5]

The World Health Organization (WHO) has projected that anaemia, primarily stemming from inadequate iron levels, impacts a considerable portion of the global population, ranging from 500 million to two billion individuals. This condition is not only avoidable but also manageable. In specific developing regions, as many as half of preschool-aged children experience anaemia, predominantly stemming from insufficient iron intake. Iron serves as an essential nutrient crucial not only for the production of hemoglobin but also for various neurochemical processes, including myelin synthesis,

cerebral energy regulation, the modulation of certain neurotransmitters, and the metabolism of enzymes like monoamine oxidase.[6-7]

It is widely acknowledged that manifestations of neurological impairment such as diminished attention span, cognitive deficits, impaired memory function, delayed motor skill acquisition, and behavioral irregularities may manifest in cases of iron deficiency.[8-9] Consequently, there exists a plausible correlation between iron deficiency and susceptibility to neurological complications such as febrile seizures. The period of highest occurrence of febrile seizures aligns with the age range typically associated with iron deficiency, which spans from 6 to 24 months of age.[10]

In a study, 17% of cases (febrile seizures) and 7% of controls (only fever) had iron deficiency anemia.[11] In another study, 45% of cases (febrile seizures) and 22% of controls (only fever) had iron deficiency anemia.[12] In another study, 56% of cases (febrile seizures) and 36% of controls (only fever) had iron deficiency anemia.[13] To the candidate's understanding, there is a dearth of locally conducted research on the subject matter. Given the absence of indigenous investigations and the discordance present within extant global scholarly works, the primary aim of the present research endeavor is to replicate the aforementioned study with the intention of establishing the correlation between iron deficiency anemia and febrile seizures. The findings derived from this study are anticipated to contribute significantly to enhancing the clinical management of individuals affected by this condition in subsequent medical practice.

METHODOLOGY

This research was carried out at the Department of Pediatric Medicine within Aziz Fatima Hospital, situated in Faisalabad, spanning a duration of six months subsequent to the approval of the research proposal, commencing from May 19th to November 18th, 2024. A case-control study design was implemented, wherein a cohort of 130 pediatric subjects was recruited utilizing non-probability consecutive sampling methodology, with an equal distribution of 65 cases and 65 controls. The determination of the sample size was predicated on a 95% confidence interval and 80% statistical power, factoring in an anticipated prevalence rate of iron deficiency anemia at 45% among cases exhibiting febrile seizures and 22% among controls characterized solely by fever symptoms.[12]

Participants in this study consisted of children of both sexes aged between 6 months and 5 years. The cases involved children who experienced febrile seizures, characterized by a body temperature exceeding 38°C (100.4°F) along with specific eye movements like roving, blinking, fluttering, rolling, gaze fixation, or nystagmus, as well as rapid, single or arrhythmic repetitive jerky movements affecting a limb or the entire body. Conversely, the control group comprised children who had fever but did not experience seizures. Exclusion criteria encompassed children with central nervous system (CNS) infections (e.g., meningitis or encephalitis), developmental delays, neurodegenerative conditions, seizures resulting from stroke or metabolic imbalances, CNS hemorrhage, trauma, vasculitis, atypical febrile seizures, anemia due to bleeding or hemolytic processes, and those receiving iron therapy.

All eligible participants whose guardians provided written informed consent were enrolled in the study. Detailed medical histories were obtained from each participant. Cases included children aged between 6 months and 60 months who presented with their initial febrile seizure after ruling out CNS infections or any other identifiable cause of seizures. On the other hand, controls were children aged between 6 months and 60 months who were admitted with febrile illnesses but did not manifest seizures during the same timeframe.

Standard hematological tests including hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and serum ferritin levels were assessed at the time of hospital admission for both cases and controls. Iron deficiency anemia was defined as hemoglobin levels ≤11 gm/dl and serum ferritin levels ≤12 microgram/dl. All relevant data were documented using a structured data collection form.

The collected data were entered into the statistical software SPSS version 25.0 for analysis. Descriptive statistics were used to depict age, hemoglobin levels, and serum ferritin levels in terms of mean and standard deviation, while gender and the presence of iron deficiency anemia were presented as frequencies and percentages. An odds ratio was calculated to evaluate the relationship between iron deficiency anemia and febrile seizures. Subsequently, data were stratified by age, gender, and socio-economic status to account for potential confounding variables, and post-stratification odds ratios were computed. A significance level of $p \leq 0.05$ was considered statistically significant.

RESULTS

In the case group, there were 35 males (53.8%) and 30 females (46.2%), while in the control group there were 27 males (51.5%) and 38 females (58.4%). Regarding age distribution, 45 children (69.2%) in the case group were between 6 months to 2 years and 20 children (30.8%) were between 3 to 5 years. In the control group, 47 children (72.3%) were between 6 months to 2 years and 18 children (27.7%) were between 3 to 5 years. The mean age in the case group was 2.28 ± 0.91 years and in the control group was 2.31 ± 1.01 years. Socio-economic status showed that in the case group, 34 children (52.3%) belonged to low, 23 (35.4%) to middle, and 8 (12.3%) to high socio-economic status, while in the control group, 33 children (50.8%) were from low, 25 (38.5%) from middle, and 7 (10.7%) from high socio-economic status.

The frequency of iron deficiency anemia in the case group (children with febrile seizures) was 28 (43.1%), whereas in the control group (children with febrile illness without seizures) it was 15 (23.1%). This difference yielded a p-value of 0.017 and an odds ratio of 2.52, indicating a statistically significant positive association between iron deficiency anemia and febrile seizures. Stratification of iron deficiency anemia according to gender, age and socio-economic status was presented in Table-III.

Table 1

Comparison of distribution of different variables between groups

Variables		Groups	
		Cases (n=65)	Controls (n=65)
Gender	Male	35(53.8%)	27(51.5%)
	Female	30(46.2%)	38(58.4%)
Age groups	6 months-2 years	45(69.2%)	47(72.3%)
	3-5 years	20(30.8%)	18(27.7%)
	Mean±S.D	2.28±0.91	2.31±1.01
Socio-economic status	Low	34(52.3%)	33(50.8%)
	Middle	23(35.4%)	25(38.5%)
	High	8(12.3%)	7(10.7%)

Table 2

Association of iron deficiency anemia with febrile seizures in children

Iron deficiency anemia (IDA)	Groups		Odds ratio (OR)	p-value
	Cases	Controls		
Yes	28(43.1%)	15(23.1%)	2.52	0.017
No	37(56.9%)	50(76.9%)		

Table 3

Stratification of association of iron deficiency anemia with febrile seizures in children with respect to different variables

Variables	Iron deficiency anemia	Groups		Odds ratio (OR)	p-value
		Cases	Controls		
Gender					
· Male	Yes	15(42.8%)	7(25.9%)	2.14	0.170
	No	20(57.2%)	20(74.1%)		
· Female	Yes	13(43.3%)	8(21.1%)	2.87	0.052
	No	17(56.7%)	30(78.9%)		
Age groups					
· 6 months-2 years	Yes	19(42.2%)	10(21.3%)	3.20	0.014
	No	26(56.8%)	37(78.7%)		
· 3-5 years	Yes	9(45.0%)	5(27.8%)	2.13	0.275
	No	11(55.0%)	13(72.2%)		
Socio-economic status					
· Low	Yes	12(35.3%)	6(18.2%)	2.45	0.119
	No	22(64.7%)	27(81.8%)		
· Middle	Yes	15(65.2%)	7(28.0%)	4.82	0.012
	No	8(34.8%)	18(72.0%)		
· High	Yes	1(12.5%)	2(28.6%)	0.36	0.448
	No	7(87.5%)	5(71.4%)		

DISCUSSION

Iron Deficiency Anemia (IDA) stands out as the prevailing nutritional insufficiency on a global scale. Iron, a vital micronutrient, plays a crucial role in the operations of virtually all human cells. It is widely recognized that iron acts as a cofactor for numerous enzymes within the body, contributing significantly to neurotransmitter synthesis and activity, hormonal regulation, and DNA replication. The insufficiency of iron prompts heightened neuronal activity, thereby elevating the likelihood of seizures.[14-15] Analogous manifestations are evident in Attention Deficit Hyperactivity Disorder (ADHD) and Restless Leg Syndrome (RLS).[16]

The association between iron deficiency anemia (IDA) and febrile seizures (FS) remains a topic of uncertainty in current research. Several investigations have indicated a potential link between IDA and an increased susceptibility to FS, as documented in studies,[17-20] however, this correlation has not been consistently verified across all scholarly inquiries, as indicated in study.[21] Conversely, a limited number of reports have suggested a contradictory notion that IDA could exert a preventive influence on the occurrence of FS.[22-23]

The primary objective of this investigation was to ascertain the correlation between iron deficiency anemia and febrile seizures among pediatric patients. The average age within the cohort of cases was 2.28±0.91 years, whereas in the control group, it stood at 2.31±1.01 years. The majority of subjects, comprising 92 individuals (70.8%), fell within the age range of 6 months to 2 years. The prevalence of iron deficiency anemia within the case group, characterized by individuals experiencing febrile seizures, was identified in 28 cases (43.1%), while in the control group, consisting of individuals with febrile illnesses devoid of seizures, the prevalence was noted in 15 cases (23.1%). Statistical analysis revealed a p-value of 0.017 and an odds ratio of 2.52, indicating a statistically significant and positive association between iron deficiency anemia and the occurrence of febrile seizures.

In a study, 17% of cases (febrile seizures) and 7% of controls (only fever) had iron deficiency anemia.[11] In another study, 45% of cases (febrile seizures) and 22% of controls (only fever) had iron deficiency anemia.[12] In another study, 56% of cases (febrile seizures) and 36% of controls (only fever) had iron deficiency anemia.[13]

In a detailed analytical case-control investigation, it was observed that the occurrence of iron deficiency (48% vs. 28%, odds ratio 4.3, p=0.03) and iron deficiency anemia (22% vs. 10%, odds ratio = 3.16, p= 0.04) was notably higher in children with febrile seizures (FS).[6] A study conducted by Kobrinsky in Fargo revealed that in children experiencing febrile seizures, iron deficiency was less prevalent, while indicators such as hemoglobin levels, hematocrit, and mean corpuscular volume (MCV) were elevated. From these findings, the authors postulated that iron deficiency anemia might have a protective effect against the occurrence of febrile seizures in children.[22]

In the research conducted by Talebian and colleagues in Kashan, Iran, it was observed that the likelihood of febrile seizure (FS) occurrence in children with anemia appeared to be diminished compared to children without anemia.[24] Similarly, Sadeghzadeh and colleagues found in their study that while anemia was not prevalent among individuals with FS, iron deficiency (ID) was more frequently detected in this patient group.[25] Furthermore, Ur-Rahman and Billoo's investigation involving 30 children with febrile convulsions and 30 children with alternative febrile illnesses demonstrated a significantly higher prevalence of iron deficiency anemia (IDA) in the former group in comparison to the latter, indicating a potential association between IDA and susceptibility to febrile convulsions.[18]

Recent research from a case-control study conducted in Kenya, along with a meta-analysis of eight similar studies investigating the correlation between febrile seizures (FSs) or acute seizures and iron deficiency (ID), has indicated a potential association between ID and an elevated likelihood of FSs in pediatric populations. The exacerbation of anemia or ID by fever has been highlighted as a mechanism that can lead to convulsions due to its impact on the brain.[26] Furthermore, the severity of febrile illnesses has been linked to anemia, potentially predisposing individuals to convulsive episodes, especially in cases of more severe symptoms. It is worth noting that febrile convulsions typically manifest at the

onset of a febrile illness, occurring prior to any reduction in hemoglobin levels resulting from the infectious process.[17]

The timely identification and prompt management of iron deficiency could play a crucial role in the prevention and reduction of recurrent febrile seizures among children within this specific age bracket.[27] A separate investigation indicated that there was a notable association between anemia and febrile seizures, with 32.2% of patients in the case group and 20% in the control group being diagnosed with anemia.[28]

Based on our findings, a research investigation conducted by Hartified and colleagues revealed that children experiencing febrile seizures exhibited a twofold higher likelihood of being diagnosed with iron deficiency in comparison to children with normal iron levels.[29] Furthermore, the outcomes of a separate study demonstrated that 22.5% of children within the febrile convulsion cohort experienced anemia, whereas 34.0% of children in the control cohort were diagnosed with this condition, with a statistically significant difference indicated by a p-value of less than 0.001.[30]

The research underscored a substantial correlation between iron deficiency anemia and febrile seizures in pediatric patients, indicating that the systematic assessment of iron deficiency anemia in children with febrile seizures could facilitate prompt detection and treatment, thereby potentially diminishing the likelihood of recurrent episodes. Future research with larger sample sizes across multiple centers is needed to strengthen generalizability and to assess whether iron supplementation can reduce seizure recurrence in this population.

However, this study had certain limitations. It was conducted at a single center with a limited sample size, which may restrict the applicability of results to the general population. Additionally, as a case-control study, it could only establish an association and not causality between iron deficiency anemia and febrile seizures. Confounding factors such as nutritional status and dietary patterns were not evaluated, which may have influenced the findings.

CONCLUSION

This study demonstrated that iron deficiency anemia is significantly associated with febrile seizures in children. Screening for iron deficiency anemia in children presenting with febrile seizures may be beneficial for their clinical management.

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