Original Article

An analysis on role of iron deficiency in febrile seizure among children in 6 months to 5 years: A case-control study

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Abstract

Background for the Study: This study looks into the relationship between febrile seizures in children between the ages of 6 months to 5 years who suffer from iron insufficiency. Febrile seizures, which are common in early life, are associated with abrupt temperature increases, and iron deficiency impacts neurological development in young infants. Understanding this relationship would lead to interventions that mitigate febrile seizure impact. **Aim:** To investigate the link between iron deficiency and febrile seizures in children between the ages of 6 months and 5 years. **Method:** A "retrospective case-control study" of 300 cases and 300 controls, including demographic, seizure, and laboratory data, was conducted. Descriptive statistics were computed using "Chi-square tests for proportions" and "*t*-tests for means" with $P \leq 0.05$ as the level of significance. **Result:** Significant findings emerged, including a notably younger mean age among cases (1.75 years) compared to controls (2.93 years). Cases showed higher rates of upper respiratory tract infections (3.7% vs. 0.3% in controls) and lower occurrences of viral febrile illnesses. Notably, cases had a lower prevalence of non-vegetarian diets and a higher incidence of family histories related to seizures. "Iron deficiency anemia" was more common in these instances, evident in blood parameters, alongside increased WBC counts. Recurrent seizures correlated with a lower mean RBC count ($P = 0.01$). **Conclusion:** The study confirms the link between "iron deficiency anemia" and "febrile seizures" among young children. Addressing iron deficiency emerges as a critical modifiable factor in potentially reducing the occurrence and impact of severe seizures, emphasizing the necessity of proactive efforts in pediatric treatment programs.

Keywords: Febrile seizures, iron deficiency anemia, pediatric neurology

Introduction

Understanding the complex relationship between iron deficiency anemia and febrile seizures in children between the ages of 6 months and 5 years is critical for improving pediatric care. Despite numerous studies, the correlation between these factors remains debated, with conflicting research outcomes. The absence of a standardized recommendation for iron supplementation in febrile seizure patients, irrespective of their anemic status, underscores the necessity for a comprehensive investigation.

Febrile seizures constitute the predominant form of seizures in children below the age of 5, accounting for a considerable burden on both affected children and their families.[1] Notably, iron deficiency anemia (IDA) is alarmingly prevalent in this demographic, affecting approximately 72.7% in urban and 81.2% in rural areas among children under 3 years of age

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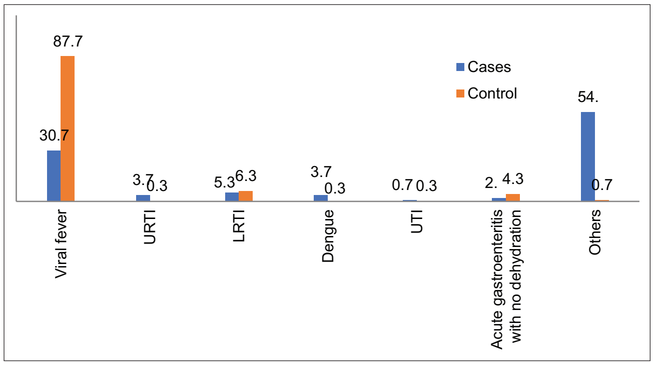
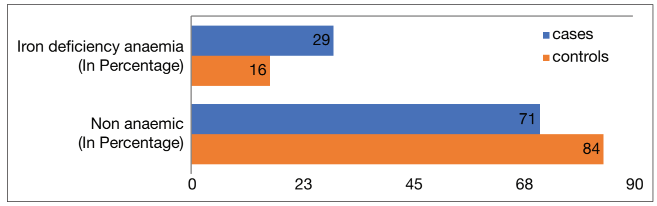
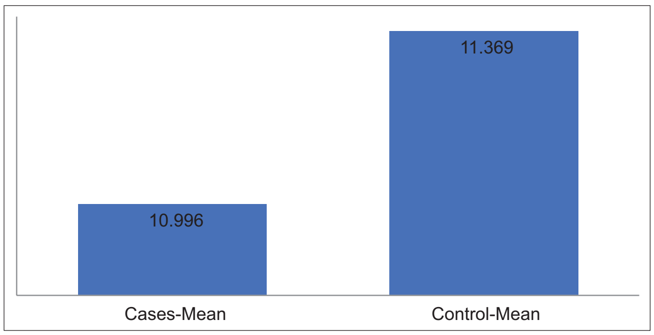


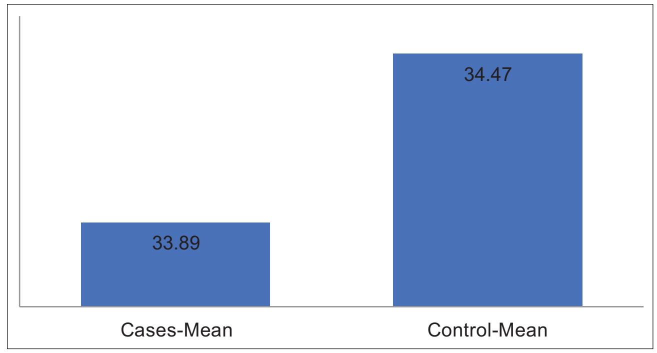
Graph 1: Etiological percentage of cases and controls



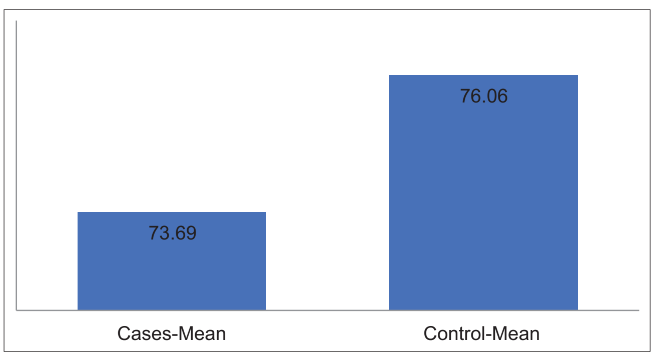
Graph 2: Prevalence of anemia among cases and controls



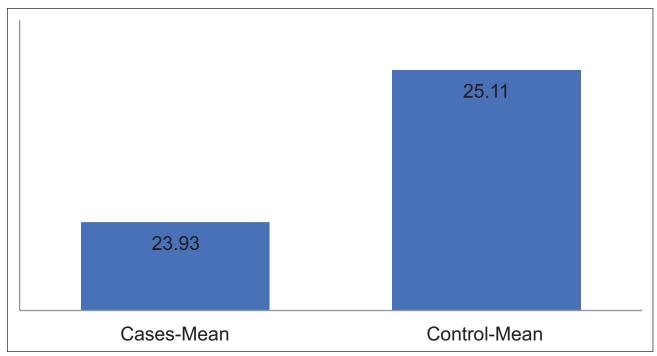
Graph 3: The mean value of hemoglobin of cases is lower than the controls and the difference is statistically significant. The mean value of hemoglobin of the cases is also less than the cut off value for the diagnosis of iron deficiency anemia (11 g/dl)



Graph 4: The mean value of packed cell volume of cases is lower than the controls and the difference is statistically significant. The mean value of PCV in the cases is not less than the diagnostic criteria for iron deficiency anemia (33%)



Graph 5: The mean value of mean cell volume of cases is lower than the controls and the difference is statistically significant. The mean value of MCV of the cases and the controls is less than the cut off value for the diagnosis of iron deficiency anemia (78 femtoliters per cell)



Graph 6: The mean value of mean cell hemoglobin of cases is lower than the controls and the difference is statistically significant. The mean value of MCH of the cases and controls is less than the cut off value for the diagnosis of iron deficiency anemia (27 picograms per cell)

group. Iron plays a crucial role in brain development and function exerting influence on neurotransmitter activity and the myelination of neurons.[2,3] Studies suggest iron deficiency affects neurotransmitter maturation, heightening brain seizure susceptibility.[4-7] Furthermore, it compromises immunity, escalating infection vulnerability.[2,7]

Iron's deep participation in neurological processes manifests as changes in neurotransmitter expression—lowering inhibitory neurotransmitters while increasing excitatory ones, thus encouraging a seizure-prone environment.[8] Iron deficiency is linked to increased brain excitability in many neurological problems, including "restless leg syndrome, breath-holding spells, and attention deficit hyperactivity disorder".[9] Studies on children between the ages of 6 and 24 months with iron-deficient anemia have shown impaired cognitive, motor, and socioemotional development, tying this disease even more closely to the febrile seizures that occur.

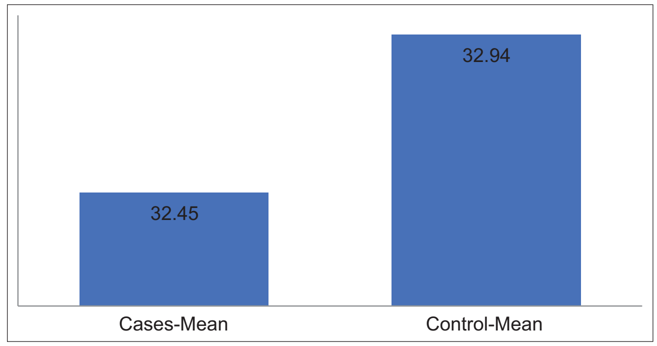
The impact of deficiencies in iron extends beyond seizure susceptibility, encompassing a spectrum of neurological issues in young children, such as developmental delays, strokes, and pseudo-tumor cerebri.[10] Studies on mice exposed to iron deficiency postnatally showed increased seizure susceptibility. Experimental studies using animal models exposed to postnatal iron deficiency have demonstrated an augmented susceptibility to seizures, shedding light on the potential mechanisms underlying this relationship.[11] Although the precise pathways linking iron deficiency to heightened brain excitability remain elusive, disruptions in neurotransmitter activity and brain metabolism are proposed culprits that may exacerbate the risk of febrile seizures.[9]

Beyond its role in neurological processes, iron status profoundly influences overall health, including "nutrition, growth, and immunity" in children. The correlation between poor general health and heightened susceptibility to febrile seizures, either through lower seizure thresholds or increased infection rates, underscores the multifaceted impact of iron deficiency.[12,13] Iron scarcity weakens the immune system, leading to reductions in T cell counts and antibody production, thereby increasing the likelihood of fever-induced febrile seizures.

Our study endeavors to establish a clearer understanding of the link between "IDA and febrile seizures in children aged 6 months to 5 years". By meticulously examining this relationship, we aim to ascertain the potential necessity for iron supplementation in this vulnerable demographic. This investigation holds promise in not only unraveling the intricacies of these intertwined factors but also in guiding future clinical strategies aimed at mitigating the burden of febrile convulsions in young children.

Material and Methods

The study, a "retrospective case-control investigation", underwent rigorous scrutiny and received ethical clearance from the "Sri Ramachandra Institute of Higher Education and Research (SRIHER) ethics committee", marked by the approval reference number CSP/18/MAY/70/177. It was conducted between January 2015 and April 2018, focusing on children between 6 months to 5 years of age admitted with febrile seizures or acute febrile illnesses. This research scrutinized medical records from SRIHER's repository, categorizing children based on their admission diagnoses into cases (febrile seizures) and controls (acute febrile illnesses). Strict criteria were applied,



Graph 7: The mean value of mean corpuscular hemoglobin concentration of cases is lower than the controls and the difference is statistically significant. The mean value of MCHC of the cases and controls is less than the cut off value for the diagnosis of iron deficiency anemia (33 g/dl)

Table 1: Descriptive statistics and frequency of background characteristics

	Type of entry	Cases, *n*=300 (%)	Control, *n*=300 (%)	*P*
Age	Mean	1.75	2.93	0.00*
	Standard deviation	1.048	1.352	
Sex	Male	166 (55.3)	155 (51.7)	0.368
	Female	134 (44.7)	145 (48.3)	
Residence	Rural	34 (11.3)	30 (10)	0.597
	Urban	266 (88.7)	270 (90)	
Etiology	Viral fever	92 (30.7)	263 (87.7)	0.00*
	URTI	11 (3.7)	1 (0.3)	
	LRTI	16 (5.3)	19 (6.3)	
	Dengue	11 (3.7)	1 (0.3)	
	UTI	2 (0.7)	1 (0.3)	
	Acute gastroenteritis with no dehydration	6 (2)	13 (4.3)	
	Others	162 (54)	2 (0.7)	
Type of delivery	Normal vaginal	145 (48.35)	150 (50)	0.683
	LSCS	155 (51.7)	150 (50)	
Twins	Single	295 (98.3)	297 (99)	0.477
	One of the twins	5 (1.7)	3 (1)	
Gestational age at delivery	Term	281 (93.7)	282 (94)	0.865
	Preterm	19 (6.3)	18 (6)	
Weight at delivery (kgs)	<1.5	4 (1.3)	5 (1.7)	0.733
	1.5-2.5	60 (20)	53 (17.7)	
	>2.5	236 (78.7)	242 (80.7)	
Immunization	Complete	300 (100)	300 (100)	Statistics constant
Family history of epilepsy	Yes	22 (7.3)	0 (0)	0.000*
	No	278 (92.7)	300 (100)	
Family history of febrile seizure	Yes	57 (19)	0 (0)	0.000*
	No	243 (81)	300 (100)	
Diet	Veg	39 (13)	18 (6)	0.003*
	Mixed	261 (87)	282 (94)	

*$P < 0.05$

including the inclusion of children specifically diagnosed with "febrile seizures in the 6-months-to-5-years age". Conversely, exclusions encompassed cases with seizures arising from causes not aligned with febrile episodes, such as poisoning or systemic illnesses, along with individuals below 6 months or above 5 years.

The study sample size, comprising 300 cases and 300 controls, was meticulously determined by referencing the study by Hartfield DS *et al.*[14] This sizable and diverse cohort encapsulated a broad spectrum of parameters for comprehensive analysis. These parameters encompassed multifaceted aspects, including demographic information, such as age, sex, and residence; birth-related specifics, such as type of delivery, twin status, gestational age, and birth weight; vaccination history; familial predisposition including a family history of epilepsy and febrile seizures; dietary habits; treatment records; and an extensive array of laboratory indices encompassing "hemoglobin, RBC count, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration(MCHC), peripheral smear details, WBC count, platelets, and parasites".

Seizure characteristics were meticulously classified into two categories: simple and complex seizures. Additionally, the study delved into nuanced characteristics like the nature of seizures, seizure types classified as generalized and focal seizures, episodes (first and recurrent seizures), and seizure duration classified based on time intervals (<5 minutes, 5-10 minutes, or >10 minutes). The statistical analysis employed in this comprehensive investigation was multifaceted, involving various methodologies. To describe the properties of the study information, descriptive metrics such as "mean, standard deviation, and proportions" were computed. "Chi-square tests" were used to examine differences in proportions between distinct groups, while *t*-tests were used to identify any mean discrepancies

Table 2: Prevalence of anemia based on peripheral smear among cases and controls

Anemia status	Cases (n=300)	Controls (n=300)	P
Iron deficiency anemia	86 (29%)	49 (16%)	0.001*
Nonanemic	214 (71%)	251 (84%)	

*$P<0.05$

Table 3: Comparison of laboratory parameters among cases and controls

Parameters	Cases, n=300		Controls, n=300		P
	Mean	Standard deviation	Mean	Standard deviation	
Hemoglobin (g/dl)	10.996	1.195861	11.36933	1.093761	0.000*
RBC count (million/mm^3)	4.595133	0.519453	4.545233	0.386898	0.183
PCV (%)	33.891	3.014261	34.47133	2.810238	0.015*
MCV (femtoliters per cell)	73.68933	7.559761	76.06233	5.653792	0.000*
MCH (picograms per cell)	23.93233	3.11433	25.11033	2.443993	0.000*
MCHC (g/dl)	32.4526	1.227628	32.945	1.153767	0.000*

*$P<0.05$

Table 4: Peripheral smear

Type of entry		Cases, n=300 (%)	Control, n=300 (%)	P
RBC size and color	Normocytic Normochromic	214 (71)	251 (84)	0.001*
	Microcytic Hypochromic	86 (29)	49 (16)	
WBC	Normal	166 (55.3)	189 (63)	0.000*
	Increased	130 (43.3)	83 (27.7)	
	Decreased	4 (1.3)	28 (9.3)	
Platelet	Normal	294 (98)	297 (99)	0.602
	Thrombocytopenia	2 (0.7)	1 (0.3)	
	Thrombocytosis	4 (1.3)	2 (0.7)	

*$P<0.05$

Table 5: Comparison of laboratory parameters within cases with 1st episode of seizure and recurrent seizure

Parameters	1st seizure, n=214		Recurrent seizure, n=86		P
	Mean	Standard deviation	Mean	Standard deviation	
Hemoglobin (g/dl)	10.98131	1.218067	11.03256	1.144855	0.738
RBC count (million/mm^3)	4.644252	0.506577	4.472907	0.533783	0.010*
PCV (%)	33.85608	3.017342	33.97791	3.022481	0.752
MCV (femtoliters per cell)	73.30187	7.787205	74.65349		6.910635
MCH (picograms per cell)	23.78411	3.247047	24.30116	2.73945	0.194
MCHC (g/dl)	32.4415	1.260982	32.48023	1.147049	0.805

*$P<0.05$. Comparison within the group of people who developed seizures, comparison between groups divided into two, first seizure and recurrent seizure (2nd episode or more): Laboratory parameters: Hemoglobin and complete blood count

between different categories. In all analytical studies, a stringent significance level of $P \leq 0.05$ was selected as the requirement for establishing statistical significance.

This comprehensive and multidimensional study sought to examine a wide range of data including demographics, seizure characteristics, and a large panel of laboratory markers. Statistical comparisons were made not just between cases and controls but also within different seizure subgroups. The goal was to uncover subtle differences in febrile seizures and iron insufficiency among kids from 6 months to 5 years. The study aims to find potential connections by methodically analyzing this vast range of factors, setting the framework for better-targeted therapies, refined clinical methods, and informed decision-making in pediatric care. This thorough investigation aimed to make a significant contribution to the knowledge and management of febrile seizures in this vulnerable pediatric group.

Result

The study, which included a substantial group of 300 cases and 300 controls, produced significant findings across numerous parameters, shedding light on the complex association between febrile seizures and various characteristics among children from six months to five years. One of the most notable findings was the significant age difference between cases and controls, with the mean age among patients being much lower at 1.75 years compared to controls at 2.93 years—a statistically significant discovery ($P = 0.000$*) [Table 1]. This disparity may point to age as a potential contributing factor to the onset or susceptibility to febrile seizures in this population.The mean age group of 86 anemic children in the cases group and 49 anemic children in the controls group were analysed and they were statistically significant (1.57 and 2.55 years respectively *P* -0.000) [Table 1], this denotes that younger children of age less than 2 years of age if having iron deficiency are more prone to febrile seizures , than older anemic children of age more than 2 years of age with febrile illness, this necessitates prompt nutritional care in the younger age group more than the older ones to prevent febrile seizures.

The investigation into the distribution of fever etiology between cases and controls revealed intriguing disparities. Notably, upper respiratory tract infections were significantly more prevalent in cases (3.7%) than in controls (0.3%), while other specific diseases like Kawasaki disease, pharyngitis, skin infections, and various other conditions demonstrated higher incidence rates in cases compared to controls. Conversely, certain febrile illnesses such as viral febrile illnesses, lower respiratory tract infections, and gastroenteritis were more prevalent in the control group. These disparities across specific disease categories highlight potential associations between certain illnesses and the occurrence of febrile seizures ($P = 0.000$*) [Table 1], warranting further investigation into their interplay.

Dietary habits emerged as another notable factor, with a significantly higher proportion of individuals consuming mixed diets (non-vegetarian) within the control group (94%) compared to the case group (87%)—a statistically significant difference ($P = 0.003$*) [Table 1]. This disparity raises questions about the potential impact of dietary choices on the susceptibility to febrile seizures, prompting further exploration into the role of nutrition in this context. Furthermore, family history of febrile seizures and epilepsy exhibited higher prevalence among cases than controls, with both disparities proving statistically significant ($P = 0.000$*)[Table 1]. These findings underscore the potential influence of genetic predisposition or familial factors in the manifestation of febrile seizures within this age group.

The assessment of blood parameters unveiled compelling disparities between cases and controls. Iron deficiency anemia, as diagnosed through peripheral smear analysis, was notably higher among cases than controls, demonstrating significant statistical differences ($P – 0.001$)[Tables 2-4]. Similarly, the comparison of WBC counts based on peripheral smear highlighted increased counts among cases and decreased counts among controls—a marked discrepancy of statistical significance [Table 4].These findings are highlighted graphically in [Graphs 1-7].These findings highlight possible links between altered blood parameters and the occurrence of febrile seizures in children of this age range, prompting additional investigation into the underlying mechanisms and ramifications of these changes.

To delve deeper into seizure features, the study classified people based on their seizure profiles. Notably, while there was a statistically significant difference in mean RBC counts between those who had their first seizure and those who had recurrent seizures ($P = 0.010$*)[Table 5], the distinction between simple and complex seizures yielded no statistically significant differences across various lab parameters. These subtle changes reflect a complicated interplay between different seizure features and blood measures, necessitating further research into these connections to better understand their clinical consequences.

Overall, the complete examination of several parameters across cases and controls revealed intriguing relationships and disparities, suggesting further research into the complex variables causing febrile seizures among children from six months to five years. These findings will be used to improve diagnostic methods, therapeutic tactics, and preventive actions aimed at reducing the burden of febrile seizures in this vulnerable paediatric group.

Discussion

The discussion focuses on a "case-control study" that looked at the possible link between febrile seizures and IDA among children from 6 months to 5 years. This extensive study intended to establish potential correlations between these illnesses by comparing 300 cases of febrile seizures to 300 controls with only feverish sickness. To find significant changes between the case and control groups, the study relied heavily on peripheral smear analysis.

The prospective case-control research conducted by Ali M. ElShafie *et al.*[15] looked at children of the same age range. When compared to controls, children experiencing febrile seizures had lower levels of "hemoglobin, mean corpuscular volume (MCV), and mean corpuscular hemoglobin (MCH)". These findings suggested a possible link between iron factors and seizure frequency. Similarly, Pisacane *et al*.'s[16] study of 156 febrile seizures in children from 6 to 24 months echoed ElShafie *et al*.'s findings, indicating a significant incidence of iron deficiency among patients compared to controls. This convergence of findings across research strengthens the case for an association between "iron deficiency and febrile seizures" in young children.

The "systematic review and meta-analysis" conducted by Kwak BO *et al*.,[17] which included 17 research, found a clear association between iron deficiency and an increased risk of experiencing febrile seizures. The study emphasized the importance of employing precise criteria in detecting iron deficiency and its connection with febrile seizures, such as plasma ferritin and mean corpuscular volume.

Similarly, Kumari *et al*.'s[18] prospective case-control study, with children ranging in age from 6 months to 3 years suffering from uncomplicated febrile seizures or febrile illness without seizures. They diagnosed IDA using WHO criteria, indicating a significant difference between patients (63.6%) and controls (24.7%) ($P = 0.001$). Meanwhile, Narges Habibian *et al*.[19] found a 1.52 overall odds ratio for febrile seizures in children with iron-deficient anemia, with changes dependent on diagnostic criteria—1.84 for iron studies and 1.26 for hemoglobin and packed cell volume. Another study by Mohammad Reza Sharif *et al*.[20] revealed a significant difference in anemia prevalence between cases (45%) and controls (22%), with specific hemoglobin levels and altered fever etiology as differentiators ($P = 0.00$*). Their findings emphasized the importance of family history and various laboratory indicators in identifying links.

However, research such as Kunwar Bharat *et al*.'s[21] investigation found no significant evidence to substantiate the link between iron deficiency and febrile seizures. Their study included 50 children in each group and failed to demonstrate a relevant link between iron deficiency and seizure occurrence. Similarly, Salehi Omran MR *et al*. found no significant variations in major iron values between patients and controls in their investigation.[22] Furthermore, Hartfield DS *et al*.'s[14] study found a higher prevalence of iron insufficiency and IDA in patients compared to controls. Intriguingly, their research found that gestational age had no effect on the development of iron deficiency or IDA, emphasizing the relevance of the postnatal period in this setting.[23]

Jang *et al*.'s[9] study compared febrile seizure cases to febrile illness controls and found decreased "serum iron, plasma ferritin, and transferrin" saturation in the febrile seizure group. However, their investigation found no variations in mean hemoglobin levels, indicating some variances in several iron indicators between trials.

Furthermore, family history is revealed as a key determinant. In our investigation, we discovered a statistically significant link between a family history of febrile seizures and epilepsy in cases versus controls. This discovery is congruent with the findings of Syndi A. Seinfeld *et al*.[1]", who found an increased risk of seizures and neurological problems in twins with a family history of febrile seizures.

Furthermore, when subjects were divided into subgroups based on seizure complexity or recurrence, our study and others found no significant variations in iron measurements. Nonetheless, the lack of significant variations between these subgroups supports the overall link with IDA and febrile seizures. While several studies produced contradictory or unclear results, the overall body of data points to a link between iron deficiency and febrile seizures in children aged 6 months to 5 years. Notably, certain research indicate that iron shortage, even in the absence of anemia, may raise the chance for febrile seizures, highlighting the importance of monitoring iron status beyond typical anemia definitions. A study by Kumari *et al*. showed iron deficiency, family history of febrile seizure, family history of epilepsy is more linked to the development of the first febrile seizure episode, indicating the correction anemia at an earlier age group even before the febrile seizure occurs is more important, and iron deficiency correction must be a part of routine pediatric care, as also shown by our research with statistically significant age group differences in anemic children in cases and controls group with the occurrence of febrile seizure in younger anemic children.[24]

In summary, despite differences between individual research, the combined evidence suggests to a possible link between iron deficiency and febrile seizures in young infants. These findings highlight the significance of treating iron deficiency as a modifiable risk factor in controlling and potentially avoiding febrile seizures in this susceptible population. However, more research with larger sample numbers and elegant methodology is needed to establish this relationship conclusively and investigate potential causal pathways.

Conclusion

The study, which looked at the complex link between febrile seizures and iron deficiency in children aged 6 months to 5 years, provided a wide range of insights across multiple parameters. The study of 300 cases and 300 controls found startling discrepancies and connections, providing light on crucial factors influencing febrile seizures in this age group. This analysis revealed a major finding: a strong link between IDA with febrile seizures in young children. Febrile seizures in newborns and young children are generally cause for anxiety due to their abrupt onset, even though they rarely cause long-term injury. The newly discovered link between iron deficient anemia and these seizures has significant implications for pediatric care, warranting further investigation.

Febrile seizures, convulsions occurring in infants and young children during fever, can be alarming for caregivers but often do not lead to lasting consequences. The study's findings highlight a notable difference in mean age between cases and controls, suggesting age might play a crucial role in susceptibility to febrile seizures and younger anemic children are more prone to febrile seizures than older anemic children of age >2 years. This insight, coupled with the distinct distribution of fever causes among the groups, hints at intriguing associations between specific illnesses and seizure occurrence. Variations in disease prevalence between cases and controls warrant deeper investigation into their potential impact on febrile seizures.

Dietary habits were found to be an important predictor, with a substantial difference in mixed diet consumption between cases and controls. This discrepancy calls for more research into nutrition's potential role in modifying susceptibility to febrile seizures in this age range. Furthermore, the increased prevalence of family history of febrile seizures and epilepsy among subjects highlights the potential role of genetic susceptibility or familial variables in seizure manifestation.

Blood parameter analysis revealed significant differences between cases and controls, indicating a higher frequency of IDA among cases. Furthermore, differences in white blood cell counts between groups suggest possible linkages between altered blood parameters and febrile seizure occurrence, necessitating further investigation into their consequences. Furthermore, when people were classified based on their seizure profiles, subtle disparities emerged. There were differences in mean RBC counts between those who had their first seizure and those who had recurrent seizures. However, no statistically significant variations in key laboratory measures were found between simple and complex seizures. This shows a complex interaction between different seizure types and blood factors, needing additional research.

The review of several studies strengthens the case for a possible link in IDA and febrile seizures in children. While individual studies produced conflicting or inconclusive results, the collective evidence points to an overarching link between IDA and febrile seizures, arguing for iron deficiency to be considered as a modifiable risk factor in managing and potentially preventing seizures in this vulnerable population.

In short, this study found a link between IDA and febrile seizures among children of 6 months to 5 years. The findings highlight the critical role of age, dietary habits, familial history, and altered blood parameters in influencing febrile seizure occurrence within this demographic. This comprehensive understanding emphasizes the need for targeted interventions addressing iron deficiency and exploring broader preventative strategies in pediatric care for mitigating febrile seizures. This study also demonstrates how relevant iron deficiency correction is important in routine pediatric care to prevent febrile seizures. However, the variations in findings across individual studies warrant further comprehensive research with refined methodologies. Larger sample sizes and more detailed analyses are essential to firmly establish the iron deficiency-febrile seizure relationship. Such efforts are crucial in unraveling underlying mechanisms and devising more personalized interventions, ultimately advancing pediatric care strategies.

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Conflicts of interest

There are no conflicts of interest.

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