

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

Dr. URSILA ANWAR

Postgraduate Student, Department of Pediatric
Balochistan Institute of Child Health Services, Quetta, Pakistan

Email: ursilagul18@gmail.com

Dr. SHAROON JAVED

Dr. SHAMAYL MANDOKHAIL

Dr. NIMRA ZAFAR

Abstract

Background: Febrile seizure (FS) is the most commonly observed seizure type in children, with an incidence rate of 2-5%. Studies exploring the connection between iron deficiency and febrile seizures have reported conflicting outcomes.

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

Place & Duration of Study: Department of Pediatric, Balochistan Institute of Child Health Services, Quetta, Pakistan from 29th November, 2021 to 30th May 2022.

Methods: A total 200 children were included all patients were divided in to two groups, group a Cases and group b Controls (100 cases & 100 controls) in the study on the basis of presence or absence of seizures. Serum ferritin level, Hb, HCT and MCV levels were assessed. Children with febrile seizures and controls were included without seizures. Informed consent was taken from parents of each child.

Results: The average hemoglobin (Hb) levels in the case group and control group were recorded at 9.86 ± 2.28 mg/dl and 9.48 ± 1.86 mg/dl, respectively. The mean corpuscular volume (MCV) values were 69.03 ± 10.84 for the cases and 72.91 ± 11.63 for the controls. The mean hematocrit (HCT) level in the case group was 29.75 ± 5.22 , compared to a mean HCT level of 32.85 ± 11.86 in the control group. Among the children studied, 46.5% in the case group and 28% in the control group were diagnosed with iron deficiency anemia.

Conclusion: Iron deficiency anemia is considered as a risk factor for febrile seizures in children. Children with febrile seizures are almost twice as likely to have iron deficiency anemia as compared Iron deficiency anemia can be regarded as a risk factor that predisposes to febrile seizures in children to children with a febrile illness without seizures.

Keywords: Iron deficiency anemia, Simple febrile seizures, Hemoglobin

INTRODUCTION:

Febrile seizures represent the most prevalent type of seizures in pediatric patients, affecting approximately 2-5% of children. These seizures impose a significant burden on the healthcare system and contribute to considerable anxiety among parents.¹ Febrile seizure episodes can inflict significant distress and psychological trauma on parents.

Approximately 2-7% of children who experience febrile seizures may go on to develop epilepsy later in their lives.²

Iron deficiency represents the most prevalent micronutrient deficiency globally and is both preventable and treatable.³ It is classified as the foremost among the three global "hidden hungers which include Iron, Iodine, and Vitamin A characterized by sub-clinical deficiencies that do not exhibit visible symptoms.⁴ Approximately one-fifth of the world's population, particularly children in developing nations, suffers from iron deficiency, making it the most widespread single-nutrient deficiency.⁵

The prevalence of iron deficiency anemia (IDA) in Pakistan is alarmingly high. The National Nutrition Survey of Pakistan conducted in 2011 indicates that 33.4% of children nationwide are affected by this condition.⁶ Iron plays a crucial role in brain energy metabolism, neurotransmitter metabolism, and myelination.⁷

Numerous studies have indicated that children with iron deficiency are at a heightened risk of developing febrile seizures (FS).⁸⁻¹⁰ In one particular study, it was found that 31.85% of children experiencing FS exhibited signs of iron deficiency anemia (IDA), in contrast to 19.6% of those without FS, establishing a significant association (p-value = 0.014). The conclusion drawn was that children with FS are nearly twice as likely to suffer from IDA compared to those with febrile illnesses who do not experience seizures.¹¹ Thus, IDA can be considered a risk factor that predisposes children to febrile seizures. However, some studies have not corroborated these findings.¹² Additionally, a family history of febrile seizures or epilepsy among first-degree relatives was also associated with an increased incidence of febrile seizures in these children. These observations align with a recent case-control study conducted in Kenya involving children aged 3 to 156 months, which indicated that iron deficiency is a risk factor for simple febrile seizures but not for other forms of acute seizures.^{8,13}

The relationship between iron deficiency and the risk of febrile seizures remains a topic of debate. While several studies suggest a positive correlation, attributing it to the iron-dependent metabolism of various neurotransmitters, others indicate a negative or nonexistent association.¹⁴⁻¹⁶

A local case-control study revealed that 31.85% of cases had IDA, whereas only 19.6% of controls were found to have the condition.¹¹ These findings imply that iron deficiency anemia is less prevalent among children with febrile convulsions compared to controls, suggesting that iron deficiency does not confer a protective effect against febrile convulsions.¹²

This study aims to explore the connection between iron deficiency anemia and simple febrile seizures among children presenting at a tertiary care hospital. Iron deficiency anemia is highly prevalent, and febrile seizures represent a significant challenge within pediatric emergency care in our setup

METHODOLOGY

This case-control study was conducted at the Department of Pediatrics, Balochistan Institute of Child Health Services in Quetta, Pakistan, from November 29, 2021, to May 30, 2022, with a total sample size of 200 children, comprising 100 cases in each group. The objective of this study is to investigate the relationship between iron deficiency anemia and simple febrile seizures in children admitted to a tertiary care hospital. The following operational definitions will be applied: simple febrile seizures are

characterized as brief generalized seizures lasting less than 15 minutes, which do not recur within a 24-hour timeframe in a febrile child (temperature exceeding 100°C) who is otherwise neurologically intact and shows no signs of neurological abnormalities before or after the seizure episode, nor any metabolic disturbances. Iron deficiency anemia is identified by hemoglobin levels below 10 g/dL, hematocrit below 33%, red cell distribution width exceeding 17%, and mean corpuscular volume below 70 fL in the blood of febrile children. The sample size was calculated with an 80% power of the test and a 5% significance level, based on the expected prevalence of iron deficiency anemia, which is 31.85% in cases and 19.6% in controls among children experiencing simple febrile seizures in a tertiary care setting. A non-probability purposive sampling technique was employed for sample collection. The inclusion criteria encompassed children aged between 6 months and 5 years of either gender presenting with febrile illness (temperature exceeding 100°C). GROUP A CASES: Children with Seizures (as per operational definition), GROUP B CONTROLS: Children without seizures.

The exclusion criteria encompassed children exhibiting atypical febrile seizures as determined by clinical examination, those with a febrile seizures identified through medical history and records, and children presenting signs of central nervous system infections, which were confirmed by clinical evaluation and positive bacterial findings in cerebrospinal fluid analysis. Additionally, children with chronic illnesses such as liver disease (indicated by AST levels exceeding 40 IU and ALT levels exceeding 40 IU), kidney disease (creatinine levels above 1.2 gm/dl), cardiac issues (assessed through medical records and clinical examination), a history of asthma, and that already undergoing iron therapy (as per medical records) were also excluded. Following approval from the hospital's ethical committee, a total of 400 children who met the selection criteria were enrolled in the study. Informed consent was obtained from the parents of each participant, and demographic information including name, age, sex, weight, and contact details was collected. The children were categorized into two groups: cases and controls, based on the presence or absence of seizures. Blood samples were then collected by a designated staff nurse using a 5cc BD syringe. These samples were sent to the hospital laboratory for the evaluation of serum ferritin levels, hemoglobin, hematocrit, and mean corpuscular volume (MCV). The results were reviewed and discussed with a senior consultant pathologist, and iron deficiency anemia was diagnosed according to the operational definition. All relevant data was documented on a pre-designed proforma.

Data entry and analysis were conducted using computer software, specifically SPSS version 20. The mean and standard deviation were calculated for continuous variables such as age, weight, hemoglobin, hematocrit, MCV and ferritin levels.

RESULTS:

The study comprised a total of two hundred children, with an equal distribution of one hundred cases and one hundred controls. The mean age of the cases was 1.04±1.07 years, while the controls had a mean age of 1.60±1.69 years. In the cases, there were 65 male and 35 female children, whereas the controls included 72 male and 28 female children. (Figure 1) Among the cases, 78 children weighed less than 10 kg, and 23 children weighed more than 10 kg. In contrast, the controls had 88 children weighing less than 10 kg and 13 children weighing more than 10 kg. The mean temperature recorded for the cases was 101.28±1.16, with a minimum of 100° and a maximum of

103°. The mean temperature for both cases and controls was 9.67 ± 2.07 , with the controls showing a minimum and maximum temperature of 48 and 51, respectively. The mean hemoglobin (Hb) levels for cases and controls were 9.86 ± 2.28 and 9.48 ± 1.86 mg/dl, respectively, with minimum Hb levels of 5.50 and maximum levels of 13.50 and 13.30. The mean mean corpuscular volume (MCV) for cases and controls was 69.03 ± 10.84 and 72.91 ± 11.63 , respectively, with minimum values of 15 and 86. The mean hematocrit (HCT) level for cases was 29.75 ± 5.22 , with minimum and maximum levels of 20 and 38, while the controls had a mean HCT level of 32.85 ± 11.86 , with minimum and maximum values of 28.50 and 80. Iron deficiency anemia was defined according to the operational definition. Among the cases, 46.5% of the children had iron deficiency anemia, compared to only 28% among the controls, indicating a higher prevalence in the cases. The odds ratio of 2.235 suggests that children with seizures are 2.235 times more likely to have iron deficiency anemia than those without seizures.

DISCUSSION:

Febrile convulsions are defined as seizures that take place in conjunction with fever, without any indication of an underlying central nervous system infection, as determined by patient history, clinical assessment, and appropriate laboratory investigations. These convulsions are observed in 2-5% of the pediatric population, with a recurrence rate ranging from 30-40%. Typically, children aged between 6 months and 5 years are at a higher risk for this condition, with the peak incidence occurring between 14 to 18 months. This peak period coincides with the prevalence of iron deficiency anemia, which affects children from 6 to 24 months of age.^{11,17,18}

In low-income countries, it is reported that between 46% and 66% of children less than four years old are affected by anemia, with around 50% suffering from iron deficiency anemia. In Pakistan, the prevalence among children is approximately 65%.¹⁹ Iron is recognized as a critical component in various metabolic functions, making it essential to maintain adequate levels for the proper operation of the body. Furthermore, iron is necessary for the enzymes that participate in neurochemical processes. Insufficient iron can lead to dysfunction in several organs and systems, manifesting in neurological symptoms such as changes in behavior, reduced attention span, and hearing loss in young children.²⁰

One of the most common emergencies in pediatric care is febrile convulsion, which is reported in emergency rooms with a prevalence of approximately 2-5% in the United States and Europe, and 6-9% in Japan. This condition tends to occur more often in males, with the peak incidence observed in children aged 6 months to 5 years.²¹

The likelihood of recurrence is heightened by several factors, including a family history of febrile convulsions, the occurrence of the initial seizure before the age of 12 months, as well as the severity and duration of the fever. Iron deficiency stands as one of the most widespread nutritional issues globally. Recent research indicates that approximately 2.5 to 5 billion individuals, including infants aged 6 to 24 months, are impacted by this condition. Numerous studies have suggested a potential link between iron deficiency and the occurrence of febrile seizures.^{2,23}

The present study indicates that the mean ages for cases and controls were 2.08 ± 1.07 years and 3.21 ± 1.69 years, respectively. Gender analysis showed that the case group comprised 130 male and 70 female children, whereas the control group included 145 male and 55 female children, highlighting a greater number of male

children in this investigation. In contrast, other studies have yielded results that are inconsistent with our findings. For example, Bidabadi et al. reported a mean age of 22.86 months for cases and 21.91 months for controls. Additionally, the research by Susan et al. revealed a mean age of 39 months for cases and 35 months for controls, further illustrating the discrepancies.²⁴

A local case-control study assessed the association between iron deficiency anemia and febrile seizures in pediatric patients. The results revealed that 31.85% of the cases (50 out of 157) were diagnosed with iron deficiency anemia, compared to 19.6% of the control group (30 out of 153). This diagnosis was confirmed through low levels of hemoglobin, serum ferritin, mean corpuscular hemoglobin concentration, and mean corpuscular volume. The odds ratio calculated was 1.93. These findings are consistent with those of Sherjil A; however, this study reported a higher odds ratio and a greater prevalence of iron deficiency anemia.¹²

The findings of a case-control study conducted in Iran indicated that iron deficiency anemia was present in 44% of cases and 48% of controls. These results imply that the occurrence of iron deficiency anemia was lower among those with febrile convulsions compared to the control group, suggesting that iron deficiency does not provide a protective effect against such convulsions.¹² In a separate Indian case-control study, iron deficiency anemia was observed in 63.6% of cases and 24.7% of controls, with an odds ratio of 5.34 (3.27-8.73). The author of that study concluded that iron deficiency is a notable risk factor for simple febrile seizures in children aged between 6 months and 3 years.^{8,25}

A study conducted in India using a case-control design identified that iron deficiency anemia was present in 63.6% of the cases, whereas it was observed in 24.7% of the controls, leading to an odds ratio of 5.34 (3.27-8.73). The author concluded that iron deficiency is a significant risk factor for the occurrence of simple febrile seizures in children within the age range of 6 months to 3 years.^{8,26,27}

A recent research study from Rawalpindi, Pakistan, identified a link between iron deficiency anemia and the occurrence of febrile seizures. The results showed that 64% of the affected individuals had low serum ferritin levels, in contrast to 42% of the control participants who also had low serum ferritin levels. Furthermore, an Iranian study found that iron deficiency anemia was observed in 44.6% of the cases, while 58.4% of the controls were affected ($p < 0.016$).^{28,29}

Ghasem Miri-Aliabad from Iran reported in his study that the prevalence of iron deficiency anemia was 44% among cases and 36% among controls.³⁰ The findings of this research align with those of a study conducted in India; however, the odds ratio presented in the Indian study was higher than that observed in this study, specifically 5.34 compared to the current study's findings.^{12,31,32}

In conclusion, evaluating iron deficiency anemia in children who have experienced febrile seizures is essential to prevent immediate complications, alleviate the public health burden, and lessen the financial strain on both parents and government healthcare systems. Anemia is particularly common among children with febrile seizures in developing countries. Furthermore, iron is critical for normal brain development and metabolic functions; therefore, its deficiency may impair several important physiological processes and could initiate febrile convulsions.

CONCLUSION:

Iron deficiency anemia is considered as a risk factor for febrile seizures in children. Children with febrile seizures are almost twice as likely to have iron deficiency anaemia as compared Iron deficiency anaemia can be regarded as a risk factor that predisposes to febrile seizures in children to children with a febrile illness without seizures.

TABLE-I AGE FOR CASES & CONTROLS
(age in years)

	Cases	Controls	Total
N	100	100	200
Mean	1.04	1.60	2.64
SD	0.54	0.85	1.39
Minimum	0.50	0.50	0.50
Maximum	4.00	5.00	5

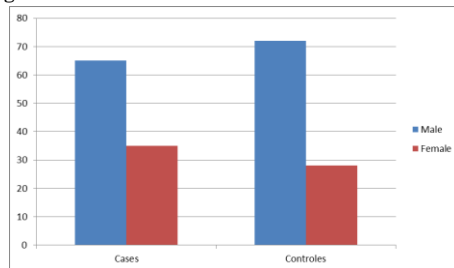
TABLE-II HEMOGLOBIN (gm/dl) OF CASES & CONTROLS

	Cases	Controls	Total
N	100	100	200
Mean	4.93	4.74	9.67
SD	1.14	0.93	2.07
Minimum	1.25	1.25	2.50
Maximum	6.75	6.65	13.4

TABLE-III CONTROLS (Percent)

	Cases	Controls	Total
N	100	100	200
Mean	29.75%	32.85%	31.30
SD	5.22%	11.86%	9.28
Minimum	20.00%	18.50%	18.50
Maximum	38.00%	80.00%	80

Figure No. 1 Distribution Gender Cases and Control



REFERENCES:

1. Pediatrics AAo. Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures. Febrile seizures: clinical practice guideline for the long – term management of the child with simple febrile seizures. Pediatrics. 2008;1(21):1281-6
2. Seizures. MMF. Nelson textbook of pediatrics. In: Kleigman RM SB, Schor NF, St. Geme JW, Behrman RE, editor. 19th Edition ed. Philadelphia: lsevier/Saunders; 2011. p. 2017.
3. UNICEF, Organization WH. Iron deficiency anemia: assessment, prevention, and control: a guide for programme managers: WHO; 2001.
4. Siddiqui MS, Siddiqui MK. Public health significance of iron deficiency anaemia. Pak Armed Forced Medical Journal. 2008;58:219-330.

5. Baker RD, Greer FR. Diagnosis and prevention of iron deficiency and iron-deficiency anemia in infants and young children (0–3 years of age). *Pediatrics*. 2010;126(5):1040-50
6. Pakistan NNSo. 2011:63.
7. Beard JL. Why iron deficiency is important in infant development. *The Journal of nutrition*. 2008;138(12):2534-6.
8. Kumari PL, Nair M, Nair S, Kailas L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures—a case control study. *Indian pediatrics*. 2012;49(1):17-9.
9. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The association between iron deficiency and febrile seizures in childhood. *Clinical pediatrics*. 2009.
10. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. *Indian pediatrics*. 2010;47(5):437-9.
11. Sherjil A, Saeed Z, Shehzad S, Amjad R. Iron deficiency anaemia—a risk factor for febrile seizures in children. *J Ayub Med Coll Abbottabad*. 2010;22(3):71-3.
12. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. *Seizure*. 2009;18(5):347-51
13. Carlson ES, Tkac I, Magid R, O'Connor MB, Andrews NC, Schallert T, et al. Iron is essential for neuron development and memory function in mouse hippocampus. *The Journal of nutrition*. 2009;139(4):672-9.
14. Idro R, Gwer S, Williams TN, Otieno T, Uyoga S, Pegan G, et al. Iron deficiency and acute seizures: results from children living in rural Kenya and meta-analysis. *PLoS One*. 2010;5(11):e14001.
15. Millar JS. Evaluation and treatment of the child with febrile seizure. *American family physician*. 2006;73(10):1761-4.
16. Jones T, Jacobsen SJ. Childhood febrile seizures: overview and implications. *International journal of medical sciences*. 2007;4(2):110.
17. Lozoff B, Beard J, Connor J, Felt B, Georgieff M, Schallert T. Long-Lasting Neural and Behavioral Effects of Iron Deficiency in Infancy. *Nutrition reviews*. 2006;64(s2):S34-S43.
18. Lozoff B, Georgieff MK, editors. Iron deficiency and brain development. *Seminars in pediatric neurology*; 2006: Elsevier.
19. Hesdorffer DC, Benn EK, Bagiella E, Nordli D, Pellock J, Hinton V, et al. Distribution of febrile seizure duration and associations with development. *Annals of neurology*. 2011;70(1):93-100.
20. Shinnar S, Glauser TA. Febrile seizures. *Journal of child neurology*. 2002;17(1suppl):44-52.
21. Daoud AS, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron status: a possible risk factor for the first febrile seizure. *Epilepsia*. 2002;43(7):740.
22. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The association between iron deficiency and febrile seizures in childhood. *Clin Pediatr*. 2009;48(4):420-6.
23. Kobrinsky NL, Yager JY, Cheang MS, Yatscoff RW, Tenenbein M. Does iron deficiency raise the seizure threshold? *J Child Neurol*. 1995;10(2):105-9.
24. Stoltzfus RJ. Defining iron-deficiency anemia in public health terms: a time for reflection. *The Journal of nutrition*. 2001;131(2):565S-7S.
25. Ambruso DR HT, Goldenberg NA. Iron deficiency anemia. Current diagnosis and treatment –Pediatrics Denver USA: Mc Graw Hill; 2009. 810-11 p.
26. Abbaskhanian A, Vahidshahi K, Parvinnezhad N. The association between iron deficiency and the first episode of febrile seizure. *JBUMS* 2009.
27. Habib Z, Akram S, Ibrahim S, Hasan B. Febrile seizures: factors affecting risk of recurrence in Pakistani children presenting at the Aga Khan University Hospital. *Group*. 2003;1(73):32.
28. Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association between iron deficiency anemia and febrile seizure in children. *Med Glas*. 2012.
29. Beard J. Iron deficiency alters brain development and functioning. *The Journal of nutrition*. 2003; 133(5): 1468S-72S.
30. Asadi-Pooya AA, Ghetmiri E. Red blood cell indices in children with idiopathic epilepsy: A case-control study. *Clinical neurology and neurosurgery*. 2006;108(6):614-5.
31. Saeed T, Haq MZU, Kanwal A, Zulfqar R, Raja TM. Association of Iron Deficiency Anaemia and Febrile Seizures in Children. *Journal of Rawalpindi Medical College (JRMC)*. 2013;17(2):175-7.
32. Miri-Aliabad G, Khajeh A, Arefi M. Iron Status and Iron Deficiency Anemia in Patients with Febrile Seizure. *Zahedan Journal of Research in Medical Sciences*. 2013;15(9):14-7.