Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/2ges1797

THE ASSOCIATION OF IRON AND ZINC DEFICIENCIES WITH THE INCIDENCE OF FEBRILE CONVULSIONS

Dr. Akhilesh Kumar[1], Dr. Rajendra Kumar[2*]

[1]Associate Professor, Department of pediatrics, Autonomous State Medical College &Allied Pt. Ram Prasad Bismil Hospital Shahjahanpur, Uttar Pradesh, India
[2*]Associate Professor, Department of Pharmacology, Autonomous State Medical College, Kanpur Dehat, UP, India.

***Corresponding author:** Dr. Rajendra Kumar
*Email ID: dr.rajvns@gmail.com

ABSTRACT

Introduction: Febrile seizures occur in 2% to 5% of children younger than 5 years, with the highest frequency noted during the second year of life, rendering them the most common form of seizure.
Objective: To examine the correlation between febrile convulsions and the deficiencies of iron and zinc.
Methodology: This prospective observational study was conducted at Autonomous State Medical College & allied pt.Ram Prasad Bismil hospital Shahjahanpur, Uttar Pradesh. The study included 90 children who fulfilled the inclusion criteria, divided into two groups: 45 children with febrile convulsions as the study group and 45 febrile children without convulsions as the control group. A venous blood sample of 5 ml was obtained from all participants in both groups and sent to the laboratory for the evaluation of iron, zinc, and other hematological parameters. Children diagnosed with iron and zinc deficiencies were recommended to undergo supplementation of these minerals for duration of three months. After commencement of study, 3 ml of venous blood was collected from each participant and sent to the laboratory for assessment of serum iron and zinc level.
Results: The comparison between the groups revealed that the study group exhibited significantly lower levels of Hemoglobin (Hb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), as well as serum iron and zinc, with a statistical significance of 0.001. Following supplementation, a notable enhancement in serum iron and zinc levels was observed in comparison to baseline value.**($p<0.05$)**
Conclusion: The findings of the current study conclude that deficiencies in iron and zinc are contributing factors for the development of febrile convulsions. The current study recommends the inclusion of iron and zinc supplementation in children to aid in the prevention and management of febrile convulsions.

Key Words: Febrile convulsions iron and zinc

INTRODUCTION

Febrile convulsion (FC) is characterized as a seizure that takes place in children aged between 6 and 60 months, accompanied by a body temperature of 38°C or higher.[1] According to the American Academy of Pediatrics, FC occurs with fever with diseases in the absence of central nervous system (CNS) infections, metabolic disorders, or a history of febrile seizures.Essentially, it occurs in

individuals without a prior history of afebrile seizures.[2]These convulsions typically occur in children who have not previously experienced afebrile seizures.

Approximately one-third of children who experience a febrile seizure may have a subsequent episode. Among those with simple febrile seizures, the incidence of developing epilepsy is between 1% and 2%. In contrast, the risk is elevated for children with complex febrile seizures; with 6% to 8% later diagnosed with epilepsy.[3] FCs arise due to the brain's inability to tolerate elevated body temperatures, which can be influenced by the activity of enzymes, ion channels, and receptors. Research indicates that trace elements such as iron, zinc, magnesium, selenium, and copper play a significant role in the occurrence of this convulsions.4

Iron is the most crucial micronutrient utilized by nearly all cells within the human body. It serves as a cofactor in the synthesis of various enzymes and plays a significant role in the production and functioning of neurotransmitters. Additionally, iron is essential for the replication of deoxyribonucleic acid and the operation of hormones.[5, 6] It is also involved in numerous brain reactions, including myelin formation, energy metabolism, and the activity of certain enzymes, such as monoamine oxidase.The highest occurrence of iron deficiency anemia (IDA) is observed in children aged between 1 and 2 years.[7] Iron deficiency (ID) can stimulate neuronal activity, thereby elevating the likelihood of febrile seizures.[8] Changes in brain synaptic neurotransmitters, including an increase in glutamate excitatory neurotransmitters, a reduction in gamma-aminobutyric acid (GABA) inhibitory neurotransmitters, a decrease in monoamines, and hypoxemia resulting from iron deficiency, may contribute to the onset of convulsions.

Zinc is a trace element essential for growth, development, and proper brain function, serving as a key component in various enzymes, including deoxyribonucleic acid and ribonucleic acid polymerases.[9] Within the brain, zinc modulates the activity of glutamic acid and acts on the rate-limiting enzyme involved in GABA synthesis, thereby enhancing the inhibitory influence of calcium on N-methyl-d-aspartate receptors. These mechanisms collectively inhibit excessive neuronal firing. A reduction in zinc levels can diminish GABA production by increasing the activity of pyridoxine, which is necessary for GABA synthesis; potentially leading to convulsions.[10]Numerous studies have indicated a possible link between zinc deficiency and the onset of febrile seizures. Additionally, zinc influences the affinity of neurotransmitters, further preventing excitatory neuronal discharges.[11]

Febrile seizures, while generally considered a benign condition, often induce fear and anxiety in parents due to the nature of the seizures. It is crucial to assess modifiable risk factors associated with febrile seizures, including deficiencies in iron and zinc. Limited research has indicated a potential link between zinc deficiency and febrile seizures.[12, 13] Similarly, although a few studies have explored the connection between iron deficiency and febrile seizures, the findings have been inconsistent.[14, 15] Therefore, the current study aims to investigate the relationship between febrile seizures and deficiencies in iron and zinc.

MATERIALS& METHODS

A prospective, observational study was undertaken with febrile convulsions children at Autonomous State Medical College & allied pt. Ram Prasad Bismil hospital Shahjahanpur, Uttar Pradesh, India. Before starting the study, permission was granted by the institutional ethical committee. This study, which took place between October 2024 to February 2025, was a joint effort between the Department of pediatrics and pharmacology. Participants were chosen based on specific criteria for inclusion and exclusion.

Inclusion criteria:

- Patients above 6 months or below 5 years
- Febrile convulsions of both sexes
- Temperature of >38°C (100.4°F) with no evidence of Central nervous system (CNS) infection/metabolic abnormalities and no history of prior afebrile seizures

Exclusion criteria:

- Having CNS infection or other diseases
- Children on regular iron or zinc therapy
- Children with epilepsy or family history of epilepsy

Parents, legal guardians, or caregivers of the children meeting the selection criteria were chosen, and these guardians were informed about the study's nature in their native language. Written informed consent was then secured. Following the acquisition of this consent, interviews with the parents were conducted to gather sociodemographic information, as well as a comprehensive history of the child, particularly focusing on seizure occurrences and birth details. A thorough examination of the child was subsequently performed.

A total of 90 children who fulfilled the inclusion criteria were recruited for the study, consisting of 45 children with febrile convulsions designated as the study group and 45 febrile children without convulsions serving as the control group. Following aseptic protocols, 5 ml of venous blood was drawn from each child in both groups. Subsequently, 3 ml of this blood was centrifuged at 3000 rpm for 10 minutes to separate the serum for the assessment of serum iron, serum ferritin, total iron binding capacity, and serum zinc levels. The remaining 2 ml of blood was utilized for a complete blood count (CBC).

Children in both groups diagnosed with iron and zinc deficiencies were prescribed oral iron(3mg/kg/day) and zinc supplements (4mg/day) for duration of three months and parents were instructed to return for follow-up after three months, as well as to seek interim consultations if necessary.After 3 months supplementation of iron and zinc, 3 ml of venous blood was collected and estimated iron and zinc levels and compared with basal values.

Statistical Analysis: The obtained data were analyzed using the Statistical Package for the Social Sciences (SPSS) software, version 20. Unpaired‘t’ test was used to calculate the association between different groups. P value <0.05 was considered to be statistically significant and results were expressed as mean± SD.

RESULTS

Table: 1- Socio demographic profile of the children

Variables		Control (n=45), n(%)	Cases (n=45), n(%)	p-value
Gender	Girls	16(35.5)	13(28.8)	>0.05
	Boys	29(64.4)	32(71.1)	
Age group	0-1 year	09(20)	12(26.6)	>0.05
	1-2 year	21(46.6)	24(53.3)	
	2-3 year	7(15.5)	5(11.1)	
	3-4 year	5(11.1)	3(6.6)	
	4-5 year	3(6.6)	1(2.2)	
Family history	Present	3(6.6)	9(20)	>0.05
	Absent	42(93.3)	36(80)	

P<0.05 = Statistically Significant

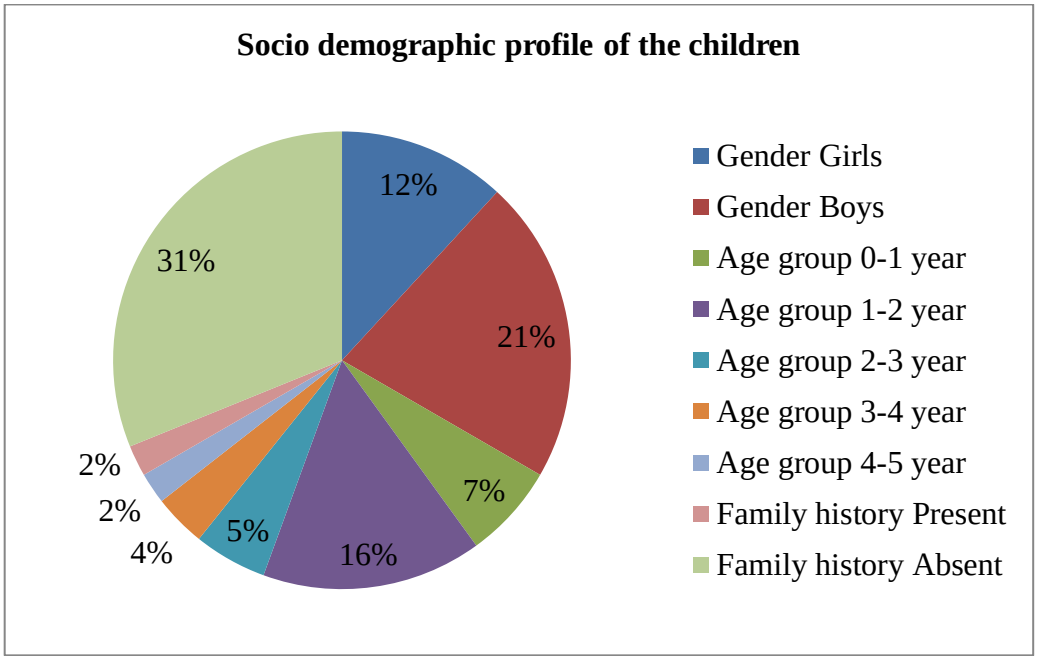

Image-1: Bardiagram showing Socio demographic profile of the children

The serum iron and zinc levels were assessed alongside the sociodemographic profiles of the children. The majority of participants in both the control group (29 boys) and the test group (32 boys) were male, and statistical analysis revealed no significant differences between the two groups ($p>0.05$). In terms of age distribution, most children in both groups fell within the 1-2 year age range, followed by those aged 0 to 1 year, with no significant age differences observed between the groups ($p>0.05$). Additionally, no significant correlation was identified between family histories of epilepsy and febrile convulsions in either group ($p>0.05$). **Table-1**

Table-:2-Comparison of mean hemoglobin, MCV, MCH, MCHC, serum ferritin, serum Iron and serumzinc levels in cases and control group

Variables	Control (n=45) Mean ± SD	Study (n = 45) Mean ± SD	p-value
Haemoglobin (%)	12.55 ± 1.55	10.38 ± 1.63	0.050
MCV (femtoliters)	85.27 ± 5.51	71.78 ± 6.98	0.001
MCH(pg/cell)	27.38 ± 4.10	24.62 ± 2.81	0.002
MCHC(gm/dl)	34.21 ± 2.01	32.12 ± 2.18	0.05
Serum ferritin (ng/ml)	158.34 ± 95.76	59.63 ± 80.55	0.000
Serum Iron(µg/dl)	71.33 ± 45.65	40.58 ± 19.21	0.000
Serum zinc (µg/dl)	75.20 ± 09.7	62.12 ± 7.1	0.001

P<0.05 = statistically significant

SD = standard deviation, **HB** = hemoglobin, **MCV** = Mean corpuscular volume, **MCH** = mean corpuscular hemoglobin and **MCHC** = mean corpuscular hemoglobin concentration.

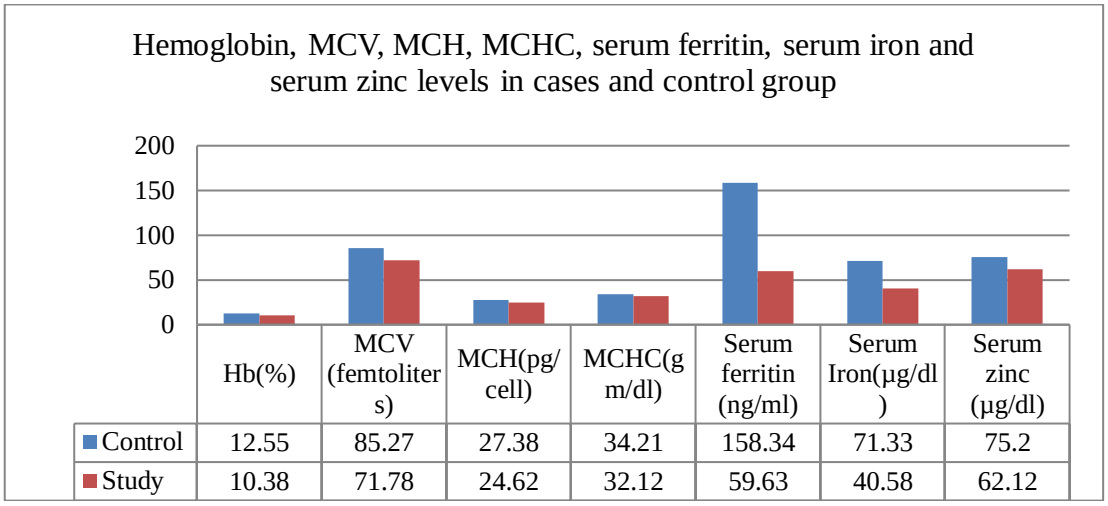

Image-2: Bardiagram showing the hemoglobin, MCV, MCH, MCHC, serum ferritin, serum Iron and serum zinc levels in cases and control group

When comparison was done between the groups, Study group had shown significantly lower levels of Hemoglobin (10.38 ± 1.63 gm/dl), MCV (71.78 ± 6.98 femtoliters), MCH (24.62 ± 2.81 pg/cell), MCHC(32.12 ± 2.18 gm/dl), serum ferritin(59.63 ± 80.55 ng/ml) and Serum iron (40.58 ± 19.21µg/dl)than control group (HB: 12.55 ± 1.55 gm/dl), MCV: 85.27 ± 5.51; MCH: 27.38 ± 4.10 pg/cell; MCHC: 34.21 ± 2.01 gm/dl; Serum ferritin: 158.34 ± 95.76 ng/ml and Serum iron (71.33 ± 45..65 µg/dl) than control group.(P<0.05)**Table-2**.Study group (62.12 ± 7.1) also had shown significant lower levels of serum zinc as compared to control group (75.20 ± 09.7). **(p<0.05)**
Children's in study group diagnosed with iron and zinc deficiency were advised iron and zinc supplementation for 90 days. After 90 days of supplementation, there was a significant rise in serum iron (58.21 ± 42.95) and zinc levels (70.14 ± 12.3) when compared with their base line values (serum iron: 40.58 ± 19.21**;** zinc**:** 62.12 ± 7.1**) (p<0.05) Table-3& Image-3**

Table 3: Serum iron and zinc levels in study group before and after supplementation

Variables	**Before treatment Mean**± SD	**After treatment Mean**± SD	**Mean difference**	**P value**
Serum Iron(3mg/kg/day)	40.58 ± 19.21	58.21 ± 42.95	17.63±23.74	0.002
Serum Zinc(4mg/day)	62.12 ± 7.1	70.14 ± 12.3	8.02±5.2	0.004

P<0.05 significant**

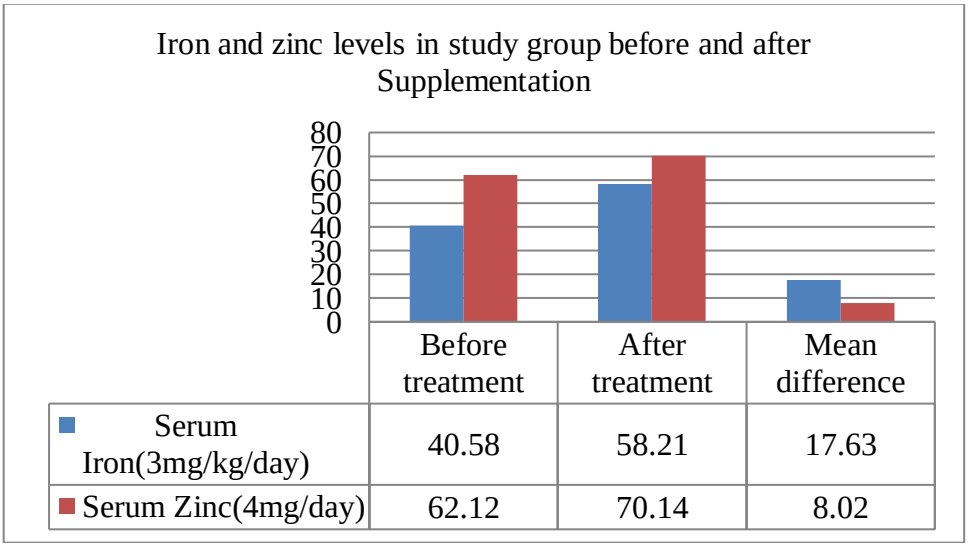

Image-3: Bardiagram showing serum Iron and zinc levels in study group before and after Supplementation

Although, when the levels of Hb, serum iron and serum zinc were seen within the group, in control group there were 6 children's who had shown low levels of serum Iron and ferritin and 5 children showed low levels of serum zinc. Similarly in study group, the levels of Hb, serum ferritin and serum iron were normal in 4 children's and zinc levels were normal in 2 children's.

DISCUSSION

Present study was aimed to find out the association between the serum iron and zinc deficiency and febrile convulsions. Along with the serum iron and zinc levels, child's sociodemographic profile also noted. In the present study, majority of children's were boys in cases and control, these findings were consistent with a previous study.[16] In the study group comprising 45 children who experienced febrile seizures, 71.10% were boys, while the remaining were girls. These results align with those of a prior study.[17] The distribution of children based on age and underlying medical conditions in both cases and controls was comparable, and similar findings were reported in another investigation.[17] However, in the current study, a comparison between the cases and controls revealed that 20% of children in the study group and 6.6% in the control group had a reported family history of febrile convulsions. This difference, although present, was statistically insignificant ($p > 0.05$) and does not correspond with the findings of a previous study.[17]**Table-1**

In the current study, the children in the study group exhibited markedly lower levels of hemoglobin (10.38 ± 1.63 gm/dl), mean corpuscular volume (71.78 ± 6.98 femtoliters), mean corpuscular hemoglobin (24.62 ± 2.81 pg/cell), mean corpuscular hemoglobin concentration (32.12 ± 2.18 gm/dl), serum ferritin (59.63 ± 80.55 ng/ml), and serum iron (40.58 ± 19.21 µg/dl) compared to the control group ($p<0.05$). These results align with findings from another study.[18]Similarly, the study group demonstrated significantly lower serum zinc levels (62.12 ± 7.1) in comparison to the control group (75.20 ± 09.7) ($p<0.05$), which is consistent with previous research.[17]In the present study it was found that, 13.3% of healthy children's from control group had shown lower levels of mean Hb, Serum ferritin and serum iron and 11.1% children's showed lower serum zinc levels. Similarly in the study group, the mean Hb, serum ferritin and serum iron values were normal in 8.8% of children's and zinc levels were normal in 4.4% children's.**Table -2**

The reduced serum ferritin levels were identified in the current study, which are align with findings of an another investigation,[18] which reported that serum ferritin levels in the studied group were lower than those in the healthy children (38.52 ± 11.38 vs. 54.32 ± 13.46; $P = 0.001$). Additionally, prior research indicated that the average plasma ferritin level in the febrile seizure group was significantly lower than that of the control group, suggesting a significant association between iron deficiency(ID) and the occurrence of febrile seizures.[19, 20, 21] Furthermore, another study noted that ferritin levels in healthy children were lower than those in both the febrile seizure group and the febrile group without seizures, although no significant difference was observed between the latter two groups.[22] In contrast, some studies have reported that the prevalence of iron deficiency in the febrile seizure group (44%) was lower than in the control group (48%), with no statistically significant difference.[23, 24, 25] It is stated that iron deficiency may contribute to the onset of convulsions by reducing the activity of the GABA inhibitory neurotransmitter, altering neuronal metabolism, and impairing brain oxygenation and energy metabolism.[26]

In our study, the mean serum zinc level was significantly lower in the study group(62.12 ± 7.1) than that in the control group(75.20 ± 09.7), and 95.6% of patients had low level of serum zinc, whereas 11.1% of controls had low level with a great difference, which was in agreement with many other studies.[27, 28]A case-control study conducted in Iran found that the average serum zinc levels in the patient group were 62.84 ± 18.40 µg/dL, while in the control group, they were 85.7 ± 16.76 µg/dL ($P < 0.05$). This suggests that hypozincemia is a contributing factor to the occurrence of febrile seizures.[29] A case-control study indicated that the average serum zinc levels in the case group were 32 µg/dL, while in the control group, they were 87.6 µg/dL ($P < 0.001$). The study concluded that Indian children experiencing febrile seizures exhibited lower serum zinc levels.[30]A prior case-control study indicated that the average serum zinc level was considerably lower in children experiencing febrile seizures compared to the control group ($P < 0.05$).[31] Additionally, another

investigation suggested that zinc deficiency may serve as a potential risk factor for febrile seizures in pediatric patients. However, contrary to the results of the current study, an earlier research effort did not support the hypothesis linking febrile seizures to diminished zinc levels.[32] In the present study, following a three-month supplementation period with iron and zinc in the study group, notable improvements were observed; however, no comparable studies have been carried out.

CONCLUSION

The findings of this study suggest that a lack of iron and zinc may play a crucial role in the development of febrile convulsions. After supplementation of iron and zinc for 3 months, the study grouphad shown notable improvements.Hence, it is recommended to incorporate iron and zinc supplementation in children as a preventive strategy against febrile convulsions, in addition to addressing iron deficiency anemia and hypozincemia.

ACKNOWLEDGEMENT: We would like to acknowledge the Department of Pediatrics & Biochemistry for their technical support.

REFERENCES

1. Hubaira, Wani ZA, Qadri SMR. Relationship between serum zinc levels and simple febrile seizures: hospital based case control study. Int J ContempPediatr 2018;5:42.
2. Smith DK, Sadler KP, Benedum M: Febrile seizures: risks, evaluation, and prognosis. Am Fam Physician. 2019, 99:445-50.
3. Eilbert W, Chan C: Febrile seizures: a review. J Am Coll Emerg Physicians Open. 2022, 3: 10.1002/emp2.12769.
4. Rehman U, Khan SA, Saldanha PR. Estimation of serum zinc levels in children with febrile convulsions. Int J ContempPediatr 2018;5:1518-22.
5. Habibian N, Alipour A, Rezaianzadeh A. Association between iron deficiency anemia and febrile convulsion in 3- to 60-month-old children: A systematic review and meta-analysis. Iran J Med Sci 2014;39:496-505.
6. Hartfield D. Iron deficiency is a public health problem in Canadian infants and children. Paediatr Child Health 2010;15:347-50.
7. 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 (Phila) 2009;48:420-6.
8. Heydarian F, Vatankhah H. The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old. Neurosciences (Riyadh) 2012;17:226-9.
9. Mahyar A. The preventive role of zinc from communicable and non-communicable diseases in children. 2005. NCD Malaysia. 2005;4:21-5.
10. Sampathkumar P, Kannan KS. A comparative study of serum zinc levels in children with febrile seizures and children with fever without seizures in an urban referral hospital. Int J ContempPediatr 2018;5:977-82.
11. Waqar Rabbani M, Ali I, Zahid Latif H, Basit A, Rabbani MA. Serum zinc level in children presenting with febrile seizures. Pak J Med Sci 2013;29:1008-11.
12. Lee JH, Kim JH. Comparison of serum zinc levels measured by inductively coupled plasma mass spectrometry in preschool children with febrile and afebrile seizures. Ann Lab Med 2012;32:190-3.
13. Heydarian F, Ashrafzadeh F, Ghasemian A. Serum zinc level in patient with simple febrile seizure. Iran J Child Neurol 2010;4:41-3.
14. Derakhshanfar H, Abaskhanian A, Alimohammadi H, ModanlooKordi M. Association between iron deficiency anemia and febrile seizure in children. Med Glas (Zenica) 2012;9:239-42.
15. Habibian N, Alipour A, Rezaianzadeh A. Association between iron deficiency anemia and febrile convulsion in 3- to 60-month-old children: A systematic review and meta-analysis. Iran J Med Sci 2014; 39: 496-505.

16. Sharif MR, Kheirkhah D, Madani M, Kashani HH. The relationship between iron deficiency and febrile convulsion: A case-control study. Glob J Health Sci 2015;8:185-9.
17. Mallela J, Metgud T, Kamate M, Kadeangadi DM. Iron and zinc deficiency in children with febrile convulsions aged 6–60 months – A 1-year hospital-based case–control study. J Sci Soc 2022;49:288-93.
18. Fallah R, Tirandazi B, Akhavan Karbasi S, Golestan M. Iron deficiency and iron deficiency anemia in children with febrile seizure. Iran J Ped Hematol Oncol 2013;3:200-3.
19. 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;43:740-3.
20. Rehman N, Billoo AG. Association between iron deficiency anemia and febrile seizures. J Coll Physicians Surg Pak 2005;15:338-40.
21. Momen AA, Nikfar R, Karimi B. Evaluation of iron status in 9 months to 5 year old children with febrile seizures: A case control study in the south west of Iran. Iran J Child Neurol 2010;4:45-50.
22. Ghasemi F, Valizadeh F, Taee N. Iron-deficiency anemia in children with febrile seizure: A case-control study. Iran J Child Neurol 2014;8:38-44.
23. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, et al. Iron deficiency anaemia and febrile convulsions: Case-control study in children under 2 years. BMJ 1996;313:343.
24. Vaswani RK, Dharaskar PG, Kulkarni S, Ghosh K. Iron deficiency as a risk factor for first febrile seizure. Indian Pediatr 2010;47:437-9.
25. Idro R, Gwer S, Williams TN, Otieno T, Uyoga S, Fegan G, et al. Iron deficiency and acute seizures: Results from children living in rural Kenya and a meta-analysis. PLoS One 2010;5:e14001.
26. Lozoff B, Jimenez E, Smith JB. Double burden of iron deficiency in infancy and low socioeconomic status: a longitudinal analysis of cognitive test scores to age 19 years. Arch PediatrAdolesc Med 2006;160:1108-13.
27. Srinivasas S, Manjunath M. Serum zinc levels in children with febrile seizures. J Evol Med Dent Sci 2014;3:2983-8.
28. Abdel Hameed ZA, El-Tellawy MM, Embaby M, Kamel YS. Relation of iron and zinc deficiencies to the occurrence of febrile convulsions. J PediatrNeurosci 2019; 14: 61-4.
29. Kumar L, Chaurasiya OS, Gupta AH. Prospective study of level of serum zinc in patients of febrile seizures, idiopathic epilepsy and CNS infections. People's J Sci Res 2011;4:1-4.
30. Ganesh R, Janakiraman L. Serum zinc levels in children with simple febrile seizure. Clin Pediatr (Phila) 2008;47:164-6.
31. Waqar Rabbani M, Ali I, Zahid Latif H, Basit A, Rabbani MA. Serum zinc level in children presenting with febrile seizures. Pak J Med Sci 2013;29:1008-11.
32. Garty BZ, Olomucki R, Lerman-Sagie T, Nitzan M. Cerebrospinal fluid zinc concentrations in febrile convulsions. Arch Dis Child 1995;73:338-41.

The authors confirm contribution to the paper as follows:

- **Study conception and design**: Dr Akhilesh Kumar, Dr. Rajendra kumar
- **Data collection**: Dr Akhilesh Kumar
- **Statistical analysis & results interpretation of results:** Dr. Rajendra kumar
- **Draft manuscript preparation**: Dr Akhilesh Kumar & Dr. Rajendra kumar

Both authors reviewed the results and approved the final version of manuscript.