International Journal of Contemporary Pediatrics
Ahmed S et al. Int J Contemp Pediatr. 2025 Jun;12(6):905-911
http://www.ijpediatrics.com
pISSN 2349-3283 | eISSN 2349-3291

DOI: https://dx.doi.org/10.18203/2349-3291.ijcp20251467

Original Research Article

Relationship between serum zinc levels and febrile seizures: a hospital based case control study

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Received: 18 March 2025
Revised: 06 May 2025
Accepted: 12 May 2025

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ABSTRACT

Background: Febrile seizures are common in children and are influenced by multiple factors, including micronutrient levels. Zinc is believed to play a crucial role in neuronal excitability and immune modulation. To compare serum zinc levels in children with febrile seizures and those with febrile illness without seizures and to examine associations between zinc levels and variables such as age, gender, seizure type, recurrence and clinical presentation.
Methods: A prospective case-control study was conducted at Sree Gokulam Medical College, Kerala, from December 2022 to June 2024. The study included 158 children aged 6 to 72 months: 79 with febrile seizures (cases) and 79 with febrile illness without seizures (controls), matched for age, sex and clinical presentation. Serum zinc levels were measured using colorimetry.
Results: Mean serum zinc levels were significantly lower in the case group (81.1 µg/dl) compared to the control group (142 µg/dl), with a mean difference of 61.3 µg/dl ($p<0.01$). Hypozincemia (serum zinc<65 µg/dl) was found in 48% of cases versus 6% of controls. No significant associations were observed between serum zinc levels and age, gender, seizure type, recurrence or clinical presentation.
Conclusions: Children with febrile seizures had significantly lower serum zinc levels compared to febrile controls. The higher prevalence of hypozincemia in the case group suggests zinc deficiency may contribute to febrile seizure risk, highlighting the need for further research on zinc's role in seizure prevention.

Keywords: Case group, Control group, Colorimetry, Febrile seizures, Hypozincemia, Serum zinc, Zinc supplementation

INTRODUCTION

A seizure is a sudden and temporary event caused by abnormal electrical activity in the brain. Febrile convulsions, represent a significant type of seizure occurring in children aged 5 months to 6 years, constituting about 30% of all seizures in this age group.[1] These convulsions are typically triggered by fever and are considered a reaction of the developing brain to elevated body temperature, occurring in children without underlying brain infections, metabolic disorders or a history of non-febrile seizures.[2] Most febrile seizures (80-85%) occur between the ages of 6 months and 3 years, with the highest frequency typically observed around 18 months of age.[3,4] Although majority of the children with simple febrile seizures do not develop epilepsy, a small percentage (2-7%) may later develop this condition during adolescence.[2,5] Zinc is a critical micronutrient involved in various physiological processes such as growth, immune response, enzymatic activities, protein metabolism, neurological functions, nerve signaling and hormone regulation. Zinc participates in modulating the activity of pyridoxal kinase, an enzyme that regulates levels of GABA (gamma-aminobutyric acid), a key neurotransmitter that inhibits neuronal activity in the brain.[6] By influencing neurotransmitter functions, zinc may help prevent excessive neuronal excitation and thereby reduce the likelihood of seizures.[2,7] While febrile

seizures are common in young children and are often associated with fever, zinc deficiency may contribute to their occurrence by affecting neurotransmitter balance and possibly exacerbating neuronal excitability. By exploring whether zinc deficiency correlates with the incidence or severity of febrile seizures, researchers could potentially uncover new insights into the mechanisms underlying these seizures and the potential benefits of zinc supplementation as a therapeutic strategy.

The findings from this study could potentially influence clinical practices, leading to recommendations for incorporating zinc supplementation into the management protocols for children susceptible to febrile seizures. This approach aims to improve outcomes by addressing nutritional factors that may contribute to seizure susceptibility during fever episodes. Therefore, conducting this study is pivotal in advancing our understanding and potentially enhancing the care and outcomes for children affected by febrile seizures.

METHODS

Study place

This study was conducted in the Department of Paediatric Medicine at Sree Gokulam Medical College, Trivandrum, Kerala, India.

Study duration

The study was conducted from December 2022-June 2024 for 18 months.

It focused on children aged 6 to 72 months who visited the paediatric emergency and inpatient departments and met specific inclusion and exclusion criteria.

The case group comprised children within this age range who experienced simple, complex or status febrile seizures (seizures occurring in a developmentally normal child during a febrile illness) and presented to the paediatric emergency department during the study period.

Exclusion criteria

Excluded were patients with signs of central nervous system infections, a history of afebrile seizures, epilepsy, metabolic seizures, developmental delays or those already receiving zinc supplementation.

The control group included age-matched children who had febrile illnesses without seizures, such as urinary tract infections, acute upper and lower respiratory tract infections or viral fevers, who also came to the hospital.

The study was conducted with ethical approval from the Institutional Ethical Committee and informed consent was obtained from parents or guardians after explaining all details of the study. To determine the cause of fever, detailed histories, physical examinations and relevant investigations were performed. For the case group, a comprehensive history was collected, including information about the seizures (duration, type, onset, recurrence), family history of seizures and any additional symptoms accompanying the fever.

Blood samples were collected using a 22-gauge sterile needle under aseptic conditions, within 24 hours of the patient's visit. Serum zinc levels were measured using colorimetry, a photometric method where zinc reacts with Nitro-PAPS in an alkaline solution to form a coloured complex. The intensity of the colour, measured at 570 nm with a yellow filter, was used to determine zinc concentrations in the serum or plasma samples.

Statistical analysis

Data analysis was performed using SPSS software version 26. Qualitative variables were presented as percentages, while quantitative variables were expressed as mean±standard deviation. An independent samples t-test was used to compare the means of continuous variables and the chi-square test was employed to assess the association between recurrence rates and hypozincaemia (Zinc levels<µg/dl). Normal values of serum zinc level were defined from 70–120 µg/dl in paediatric age group (5 months to 6 years).

RESULTS

The study included 79 children with febrile seizures as the case group and 79 children with febrile illness but without convulsions as the control group, resulting in a total sample size of 158 children, matched for age (6 months to 72 months) and gender.

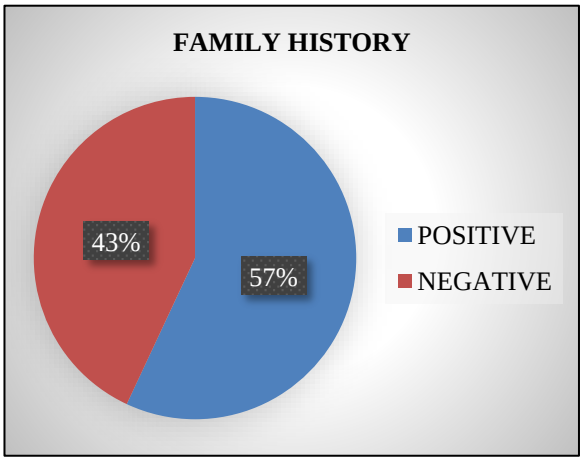

Figure 1: Representation of family history among case group.

Most of patients in our case group belonged to 6 months-12 months (41.8%) of age, whereas in control group, most of the patients belong to 25 months-72 months (53.2%) of age. Most of the patients in the case group

were dominated by females (53.2%), while males predominated most of the patients in the control group (53.2%). Family history of febrile seizures was positive in 45 patients (57%) and negative in 34 patients (43%) among the case group.

The average serum Zinc values in case group was 81.1µg/dl with a standard deviation of 42.1, whereas in control group, the average serum Zinc values were 142.4 µg/dl with a standard deviation of 69.8. The results of the independent sample t-test indicate that the mean serum zinc level was 61.3 ug/dl less in the case group as compared to control group and this difference is statistically significant at a 1% level of significance.

Chi Square test was done to know if there is an association between hypozincaemia (serum zinc<65%) with respect to the recurrence of a febrile seizure.[8-10] P value of 0.354 shows that such an association is statistically insignificant in our study. Taking Hypozincaemia cutoff as 65µg/dl, 48% in our case group had hypozincaemia whereas only 6% in our control group had hypozincaemia.[8-10]

Mean zinc values are lower in febrile status group. There is not much difference in the mean Zinc values between simple febrile seizures and complex febrile seizures. The lowest mean zinc values in the febrile status group may be attributed to the smaller number of samples in the group.

Results of independent sample t test that compares the mean serum zinc values by types of febrile seizures

Due to smaller number of cases, the children with Febrile Status were dropped in this analysis. The p value of 0.926 indicates that there is no statistically significant difference in the mean zinc values between the children with Simple Febrile seizure and Complex Febrile seizure. Hence, the type of febrile seizures could not be influenced by the low levels of serum Zinc in our study.

Table 1: Mean serum Zinc values among cases and control group.

Groups	Mean±SD (µg/dl)
Cases	81.1±42.1
Controls	142.4±69.8
Total	111.8±65.1

Table 2: Independent sample test results from the values obtained among case and control group.

t	df	Mean difference	P value	95% CI for mean difference
-6.692	156	-61.3	<0.01	(-79.4, -43.2)

Table 3: Zinc deficiency by episode.

Parameters	Zinc values			Chi-square value	P value
	≥65	<65	Total		
Episode					
First episode	33	25	58	0.857	0.354
Second episode	8	10	18		
Total	41	35	76		

Group	Hypozincaemia		Total
	<65	≥65	
Case	38 (48.1%)	41 (51.9%)	79 (100%)
Control	5 (6.3%)	74 (93.7%)	79 (100%)
Total	43 (27.2%)	115 (72.8%)	158 (100%)

Table 4: Mean serum zinc levels obtained in various studies around the world.

Studies	Serum zinc level (µgm/dl)		Mean difference	P value
	Cases	Controls		
Ehsani et al[17]	76.8	90.12	13.32	<0.05*
Mahyar et al[18]	62.84	85.7	22.86	<0.05*
Ganesh et al[19]	32.17	87.6	55.43	<0.001 **
Okposio et al[20]	58.7	90.3	31.6	<0.001 **
Margaretha[1]	88.3	137.2	48.9	<0.001**
Burhangnoglu[21]	66	98	32	<0.05**
Gattoo et al[10]	61.53	71.99	10.46	<0.05*

Continued.

Studies	Serum zinc level (µgm/dl)		Mean difference	P value
	Cases	Controls		
Kafadar et al[22]	110.49	107.12	-3.37	0.673
Heyderian et al[23]	66.37	75.83	9.46	<0.001*
Modaressi et al[24]	93.39	130.54	37.15	<0.001**
Amiri et al[25]	66.13	107.8	41.67	<0.05*
Our study	81.1	142.4	61.3	<0.01*

*Significant, **Highly significant.

Table 5: Mean serum zinc levels among etiology of fever in case and control group and type of febrile seizures.

Parameters	Mean zinc values (µg/dl)	
	Cases	Controls
Diagnosis		
Acute lower respiratory infection	109.7	105.6
AURI (acute upper respiratory infection)	83.2	145.4
Bronchiolitis	50.9	137.7
UTI (urinary tract infection)	51.2	135.9
Viral fever	78.2	150.1
Type of febrile seizure	**No. of children**	**%**
Simple febrile seizure	65	82.30
Complex febrile seizure	11	13.90
Febrile status	3	3.80
Total	79	100

Table 6: Mean zinc values by type of febrile seizure.

Febrile seizure			Mean±SD (µg/dl)	
Simple febrile seizure			82±43.9	
Complex febrile seizure			80.7±36.8	
Febrile status			62.8±15	
t value	**df**	**Mean difference**	**P value**	**95% CI for mean difference**
-0.093	74	-1.31	0.926	(-29.23, 26.62)

Table 7: Demographic data among cases group: (General Overview).

Age	Sex	Type	Serum zinc (µg/dl)	Family history	Fever duration	Episode of febrile seizure
0-1 year: 17	Males: 37	Simple: 65	20-40: 3	Positive:45	<3 days: 66	1st episode: 59
1-2 years: 23	Females:42	Complex: 11	41-60: 29	Negative:34	>3 days: 13	2nd episode: 13
2-4 years: 27		Status: 3	61-80: 18			3rd episode: 2
4-6 years: 12			81-100: 11			
			101-120: 9			
			121-140: 3			
			141-160: 1			
			161-180: 3			
			180-250: 2			

Table 8: Demographic data among control group (general overview).

Age (Years)	Sex	Serum zinc (µg/dl)	Fever duration
0-1: 5	Males: 42	41-60: 5	<3 days: 55
1-2: 33	Females: 37	61-80: 12	>3 days: 24
2-4: 25		81-100: 9	
4-6: 16		101-120: 16	
		121-140: 5	

Continued.

Age (Years)	Sex	Serum zinc (µg/dl)	Fever duration
		141-160: 5	
		161-180: 5	
		181-200: 6	
		201-220: 3	
		221-250: 6	
		250-300: 5	
		301-350: 2	

DISCUSSION

Febrile seizures are the predominant type of convulsion seen in childhood. Research has demonstrated that initial febrile seizures typically happen between 12 to 24 months of age, peaking specifically between 18 to 22 months.[11,12] Additionally, children with parents who are closely related (first-degree consanguinity) represent a previously unidentified high-risk group for recurrent febrile seizures.[13]

Similar to the literature, we have found that most of patients in case group belongs to 6-12 m (41.8%) whereas in control group, majority of the patients belong to 25-72 m (53.2%). Contrary to some studies, most of the patients in our case group were dominated by females (53.2%) and the rest were males (37%). Esch et al, studied 142 children with febrile convulsions prospectively and found a family history rate of 40%. In the same study, almost half of the patients with recurrent febrile convulsion were reported to have a prior family history. Supporting the literature, in our study, family history of febrile seizures was positive in 45 patients (57%) and negative in 34 patients (43%) among the case group.[14]

Zinc is considered crucial as it integrates into numerous metalloenzymes and functions as a neurotransmitter or neuro regulator within the central nervous system. Zinc is an important micronutrient vital for the normal function and development of the central nervous system. It plays a role in modulating neurotransmission by inhibiting the Glutaminergic NMDA receptor and acting as a cofactor for the enzyme crucial in GABA synthesis. Deficiency in zinc can disrupt the balance between excitatory and inhibitory neurotransmission, potentially triggering febrile seizures.

Variety of studies have explored the relationship between serum zinc levels and simple febrile seizures. While some of these studies indicate a correlation between low zinc levels (hypozincemia) and simple febrile seizures, others have reported contradicting results. Ghatoo et al found that children with simple febrile seizures had a significantly lower mean serum zinc level of 32.17 µg/dl (SD 15.05) compared to controls who had fever but no seizures, with a mean serum zinc level of 87.6 µg/dl (SD 17.63).[10] On the other hand, Uluhan et al, conducted a study at Akdeniz University involving 25 paediatric febrile convulsion patients and 20 healthy children.[15] They reported serum zinc levels of 86.76±4.04 µg/dl in the febrile convulsion group and 96±7.62 µg/dl in the control group. However, they did not find a statistically significant difference between the two groups. Similarly, Çelik et al, also studied 25 paediatric febrile convulsion patients and 20 healthy children but did not find a significant difference in serum zinc levels between the two groups.[16] In our study, the average serum Zinc values in the case group was 81.1µg/dl with a standard deviation of 42.1, whereas in control group, the average serum Zinc values were 142.4µg/dl with a standard deviation of 69.8. We did an independent sample t-test which indicated that the mean serum zinc level was 61.3 µg/dl less in case group as compared to controls and this difference is statistically significant at a 1% level of significance. In the present study significant difference of 61.3 µg/dl was obtained in mean serum zinc level in cases as compared to controls. Similar findings have been reported by other researchers as shown in table below.[1,10,17]

We analyzed whether there was any difference in mean Zinc value in relation to gender. In the case group, the average Zinc values in males were 80.3µg/dl with a standard deviation of 39.7, compared to 81.9µg/dl with a SD of 44.6 in females and a total (case+control) mean value of 81.1µg/dl with a SD of 42.1. Our study did not reveal any significant difference in mean serum zinc level in relation to gender. Other researchers have reported similar findings regarding serum zinc levels in relation to febrile convulsions.[20]

In our study, it was observed that mean serum Zinc levels are lowest in the age group of 13-24 months among the case group. Among our case group, the clinical presentation comprised of mainly non localized fevers, majority of which had clinical evidence to suggest viral aetiology (48%), followed by acute upper respiratory infections (45%), UTI (1%) and bronchiolitis (1%). Margaretha have reported acute respiratory infections (ARI) as the most common cause.[1] Many authors who have investigated the correlation between serum zinc levels and simple febrile seizures have typically compared the mean serum zinc levels between cases and controls.

Mean serum Zinc values were compared among both groups in relation to their clinical presentation. Our study

did not reveal any significant difference in mean serum zinc level in relation to the clinical presentation. Authors also wanted to know whether low levels of serum Zinc had anything to do with respect to type of febrile seizures (simple, complex, status) among our cases group. Mean serum zinc levels for the groups are. Simple febrile seizures: 82 µg/dl (standard deviation±43.9). Complex febrile seizures: 80.7 µg/dl (standard deviation±36.8). An independent sample t test was conducted, resulting in a p value of 0.926.

The p value of 0.926 indicates that there is no statistically significant difference in serum zinc levels between children with simple febrile seizures and those with complex febrile seizures. The likelihood of a febrile seizure recurring is associated with several factors, the age of the child when they first experience a febrile seizure, whether there is a family history of epilepsy and the nature of the initial febrile seizure. A complex initial febrile seizure is particularly predictive of future episodes. Additionally, children with parents who are closely related (first-degree consanguinity) represent a previously unidentified high-risk group for recurrent febrile seizures.[13]

We aimed to investigate whether low serum Zinc levels are associated with the recurrence of febrile seizures, considering hypozincemia cutoff of 65 µgm/dl as suggested by WHO.[8-10] A Chi-square value of 0.857 with a corresponding p value of 0.354. These statistical results indicate that there is no significant association between hypozincemia and the recurrence of febrile seizures in our case study.

Hypozincemia (zinc levels<65%) was present among 48% in our case group, compared to 6% in our control group, though no statistically significant difference was found in the mean age, gender distribution, physical parameters and nutritional status between the patients of hypozincemia and normal zinc level.[8-10] Mahyar et al, were reported the similar findings.[18] In our study, low serum zinc levels were found to be more prevalent among children with febrile seizures. Hypozincemia (Zinc levels<65 µgm/dl) was present in around 48% in our case group.[8-10] There is a need for further research to elucidate its precise role and clinical significance in this specific population and the role of Zinc supplementation in the febrile seizure group to prevent recurrence.

Authors did not assess the efficacy of zinc supplementation in preventing the recurrence of febrile seizures, which presents a potential area for future research. Investigating this aspect could contribute valuable insights into preventive strategies. No other limitations were encountered during the study.

CONCLUSION

In this study, we observed a statistically significant lower serum zinc levels in children who experienced febrile seizures compared to febrile children without seizures. Hypozincaemia (Zinc levels<65µgm/dl) was present in around 48% in our case group, compared to 6% in our control group.[8-10] In our study, there was no statistically notable link between low serum zinc levels and the type of febrile seizures (simple and complex febrile seizures).We could not find a substantial relationship between low serum zinc levels and the recurrence of febrile seizures statistically in our study. There was no significant association of low serum zinc levels and age group or gender. A significant connection could not be determined between serum zinc levels and the causative factor of febrile seizures in our patients in the case group.

This distinction underscores the complexity of zinc metabolism and its implications in the context of febrile seizures, highlighting the need for further research to elucidate its precise role and clinical significance in this specific population and the role of Zinc supplementation in the febrile seizure group to prevent recurrence.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Ahmed S, Kailas L, Nair RS. Relationship between serum zinc levels and febrile seizures: a hospital-based case control study. Int J Contemp Pediatr 2025;12:905-11.