

Serum Zinc Level in Children Presenting with Febrile Seizures

Dr Nikhil Achanta, Dr Megha Sharma, Dr Ashok Sharma

Abstract: *Background:* Febrile seizures are seizures that occur between the age of 6 and 60 months with a temperature of 38.0°C (100°F) or higher, that are not the result of central nervous system infection, or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures. Febrile convulsions are the most common type of seizures in children. Zinc acts as a cofactor of glutamic acid decarboxylase, an enzyme which maintains the production of GABA in central nervous system. Serum Zinc levels are shown to be low in patients with febrile seizure in some studies. *Aims and Objectives:* The aim of the present prospective observational study was to estimate the levels of serum zinc in children with febrile convulsions and to compare serum zinc levels between children with febrile seizures and febrile children without seizures. *Methodology:* A prospective observational case control study was done in Department of Paediatrics, D.Y. Patil Hospital, Nerul, Navi Mumbai. A total of 30 cases of febrile seizure and 30 cases of fever without convulsion that visited OPD and were admitted to the hospital were included in the study. Detailed clinical history was taken. Serum zinc level was measured using Inductively Coupled Plasma Mass Spectrometry method between cases and controls. Normal serum zinc levels were taken as 70-120 µg/dl. The co-relation between serum zinc levels in relation to age, sex and duration of seizures were analysed by Chi square test and Unpaired t test. The p-value <0.05 was considered significant. *Results:* In our present study, majority of children were of the age group 13-24 months and least in 49-60 months in both the groups. Majority of children were males as compared to females. Upper Respiratory Tract Infection (URTI) was the most common cause of fever in both the groups. Majority of children in febrile convulsions group (73.3%) had serum zinc level less than or equal to 70 µgm/dl whereas majority of children in fever without seizures group (80.0%) had serum zinc levels by greater than 70 µgm/dl. The t-test showed mean serum Zn level of children with FS (56.95 ± 17.91) was significantly (p<0.001) more than the children with fever without seizures (78.94 ± 16.93). *Conclusion:* These findings revealed that there is correlation between serum zinc levels and occurrence of febrile seizures. Serum zinc level was significantly lower in children with febrile seizures in comparison with febrile children without seizure.

Keywords: febrile seizures, febrile convulsions, serum zinc levels, Zn levels

1. Introduction

Zinc, as a major element of some enzymes, plays an important role in the central nervous System (CNS) and can affect some inhibitory mechanisms of CNS.¹The highest concentrations of zinc in the brain are found in the hippocampus (approximately 30 pug/g dry weights).² Zn is a co-factor of glutamate decarboxylase which is an enzyme needed for gamma-aminobutyric acid synthesis in the central nervous system and reduced CSF zinc levels have also been noted in febrile convulsions. Recent evidences indicate that zinc deficiency plays a significant role in febrile seizures. The following mechanisms can be postulated. Zinc increases storage capacity of glutamate or slows down the release rate of glutamate.³Zinc increases the activity of glutamate decarboxylase which results in gamma-aminobutyric acid syntheses. Thus, decreased zinc levels lower GABA synthesis which would precipitate seizures.

Gamma-aminobutyric acid (GABA), a major inhibitory neurotransmitter, is produced by decarboxylation of L-glutamate. Glutamic acid decarboxylase is the rate limiting enzyme of GABA synthesis and requires pyridoxalphosphate or vitamin B6 for its activity. Zinc stimulates the activity of pyridoxal kinase, the enzyme that forms pyridoxal phosphate from pyridoxal, and thereby modulates the activity of glutamic acid decarboxylase and the synthesis of GABA.²

The GABA concentration in cerebrospinal fluid seems to be inversely related to seizure excitability. Low cerebrospinal fluid GABA values have been demonstrated in patients with intractable seizures. Low zinc concentrations have been found in the serum and cerebrospinal fluid of people with epilepsy.²In addition, zinc significantly reduces the severity

of illness and the duration of fever in children with pneumonia and diarrhea by the activation of immune enhancing T-cells.^{4,5}

Although several studies have been conducted in an attempt to determine the association of febrile convulsions with serum Zinc levels around the world such studies are lacking in India. This study will provide base line data and could aid in the formulation of guidelines for zinc supplementation as a part of management of febrile convulsions. There is urgent need to conduct and encourage studies with the purpose to investigate the plausible etiology of febrile convulsions with the Zn serum levels. Our study hypothesizes some concrete correlation of febrile convulsions with the Zn serum levels. This case control study is conducted with the purpose of investigating the role of Zinc in occurrence of febrile seizures in children.

2. Methodology

This hospital based study was conducted in the Department of Paediatrics, D.Y. Patil Hospital, Nerul, Navi Mumbai. A total of 30 cases of febrile seizure and 30 cases of fever without convulsion that visited OPD and admitted to the hospital were included in the study. The research protocol was approved by the ethical board of D.Y. Patil Hospital, Nerul, Navi Mumbai. This research was designed as prospective case control study. The inclusion criteria was subject with age ranging from 6 month to 5 years of either sex with clinical diagnosis of simple or complex febrile seizures. Exclusion criteria was seizures due to central nervous system infection or any other identifiable cause and presence of co-neurological morbidities during previous/present episode. Those children with abnormal

electroencephalogram and on zinc supplementation for therapeutic purposes were also excluded.

Before commencing the study, informed consent was taken from the legal representative of the patients satisfying the inclusion criteria. This study was conducted with a detailed history. Complete physical examination of the child was performed along with detailed neurological examination and all the findings were recorded in a predesigned proforma. Proforma was prepared in English and local language was used during interview to make it convenient for the study population. Selected cases and controls were subjected to evaluation of zinc level in blood.

Febrile seizures were defined as seizures accompanied with fever ($\geq 38^{\circ}\text{C}$) without central nervous system (CNS) infection. While normal fever without seizure was considered the characteristics of the controls. One single generalized seizure in 24 hours of fever period with duration less than 15 min and without focal features was defined as a simple FS. Whereas seizures were defined as complex if they lasted more than 15 min, had focal features, or occurred more than once in 24 hours.⁶

Blood samples were collected from the patients with FS and the control subjects. It was obtained from children with FS within a few hours after seizure attack. Venous blood samples were obtained from each subject and transferred to normal tubes. Serum was obtained by centrifugation at 2000 g for 10 min of blood samples taken without anticoagulant and stored at -20°C until analysis date. All chemicals and reagents used in this study were of analytical grade. Ultra-distilled water was used as the solvent

All 60 children were subjected to the investigation of serum zinc measured by inductively coupled plasmamass spectrometry method. The normal serum zinc level was considered 0.7–1.2 mg/L.

Statistical analysis

Data was analysed using Statistical Package for Social Sciences, version 23 (SPSS Inc., Chicago, IL). Results for continuous variables are presented as mean \pm standard deviation, whereas results for categorical variables are presented as number (percentage). The co-relation between serum zinc levels in relation to age, sex and duration of seizures were analysed by Chi square test and Unpaired t test. The p-value <0.05 was considered significant.

3. Results

All the patients were aged between 6 month to 5 years. It was noted that majority of patients were aged between 13-24 while the least were of age group 49-60 months in both the groups (Table 1). There were more males (60.0%) in FS group and in children with fever without seizures (56.7%) than females (Table 2).

The distribution of study subjects on the basis of causes of fever was evaluated (Table 3). It was found that majority of patients were of Upper Respiratory Tract Infection - URTI (50.0%) followed by acute gastroenteritis - AGE (23.3%),

lower respiratory tract infection – LRTI (16.7%) and viral fever (10.0%).

Table 4 shows distribution of children according to temperature and duration of fever. The majority of patients were having temperature $<102^{\circ}\text{F}$ in both the groups - children with FS (86.7%) and Children with fever without seizures (70.0%) while the temperature $\geq 102^{\circ}\text{F}$ was observed in 13.3% of children with FS and 30.0% of children with fever without seizures. The majority of patients having the duration of fever less than or equal to 24 hours with 70.0% in children with FS followed by greater than 24 hours with majority of patients of children with fever without seizures group (73.3%).

The mean serum Zn level ($\mu\text{g}/\text{dl}$) was compared between the two groups. The t-test showed statistically significant difference in mean serum Zn level between the two groups ($p < 0.001$). The mean serum Zn level of children with FS (56.95 ± 17.91) was significantly more than the children with fever without seizures (78.94 ± 16.93) [Table 5].

The mean serum Zn level ($\mu\text{g}/\text{dl}$) was compared between children with simple febrile convulsions and children with complex febrile convulsions. The t-test did not show statistically significant difference in mean serum Zn level between the two groups ($p = 0.372$). The mean serum Zn level of children with SFS was 59.50 ± 19.24 and in children with CFS was 53.62 ± 15.10 [Table 6].

4. Discussion

This case-control study was conducted to study the clinico-demographic profile of febrile seizures in children and to assess the relationship between serum Zinc levels and occurrence of fever.

The most common cause of fever in children with febrile convulsions was URTI followed by AGE, LRTI and viral fever. Similar pattern was also observed in children with fever without seizures. This was in accordance with Ingale SY et al⁷ (2018) study which found that common cause of fever was URTI (76.6%) children followed by AGE (13.33%), LRTI (6.66%) and 3.33% children were affected by CSOM (chronic suppurative otitis media). Another study done by Soni SP et al⁸ (2017) reported viral fever as the main cause followed by acute respiratory infection, acute suppurative otitis media and urinary tract infection. Margaretha L et al,⁹ Mahyar A et al¹⁰ and Gunduz Z et al.¹¹ in their respective studies have reported acute respiratory infection as the main cause of febrile convulsions.

Hirz DG et al.¹² reported that body temperature $>100^{\circ}\text{F}$ was a risk factor for occurrence of febrile seizures. In the present study, the majority of patients were having temperature $<102^{\circ}\text{F}$ in both children with febrile convulsions (86.7%) and children with fever without seizures (70.0%) while the temperature $\geq 102^{\circ}\text{F}$ was observed in 13.3% of children with febrile convulsions and 30.0% of children with fever without seizures. A recent study by Sampathkumar P et al¹³ showed that in the group of simple febrile convulsions, 45% had $100-100.9^{\circ}\text{F}$, 48% cases had $101-101.9^{\circ}\text{F}$ and 7% children had $102-103^{\circ}\text{F}$ temperatures. In the atypical febrile

convulsions group, 20, 14 and 6 children had temperature ranges of 100- 100.9, 101-101.9 and 102-103⁰F accounting to 51%, 33% and 15% respectively. In the fever without seizures group, 126, 44 and 30 children recorded the respective temperatures attributing to 63%, 21% and 15%.

Zinc acts as a neurotransmitter and improves the communicating and locomotive function and also evolution of nervous system. Hypozincemia leads to febrile seizures. (2006) In patients of febrile seizures the cause of low serum levels of zinc is not known, however the fever and acute infection plays a vital role in developing such conditions. (2006) It is believed that the release of tumor necrosis factor [TNF] and interleukin [IL] during fever or tissue injury may result in reduction of serum zinc level.¹⁴

In the present study, out of 60, abnormal serum zinc level was found in 28 children (≤ 70 $\mu\text{gm/dl}$) whereas 32 children were with normal level (>70 $\mu\text{gm/dl}$). Further, in the children with febrile convulsion group 22 (73.3%) children had serum zinc level below 70 $\mu\text{gm/dl}$ and 8 (26.7%) children had serum zinc level more than 70 $\mu\text{gm/dl}$. In the other group, children with fever without seizures, there were 6 (20%) and 24 (80%) children in ≤ 70 $\mu\text{gm/dl}$ and >70 $\mu\text{gm/dl}$ respectively of serum zinc level. Additionally, the difference between serum Zn levels in children with febrile convulsions and children with fever without seizures was found to be statistically highly significant ($p < 0.001$) as the mean Zn level of children with febrile convulsions group was 56.95 $\mu\text{gm/dl}$ while that of children with fever without seizures was 78.94 $\mu\text{gm/dl}$.

Similarly, in Ingale SY et al⁷ study, out of 30 controls with fever, 20 (66.7%) had normal Zinc levels (60-120 $\mu\text{gm/dl}$), 6 (20%) had low values (<60 $\mu\text{gm/dl}$) and 4 (13.3%) had high values and out of 30 controls without fever, 4 had low values and 26 had normal values. Out of 60 cases with febrile seizure, 40 (66.67%) had low serum Zinc levels.⁸⁹ The study done by Soni SP et al⁸ reported the number of cases with hypozincemia were 65% (<65 $\mu\text{gm/dl}$), while in control group were 30% (>65 $\mu\text{gm/dl}$) and highly significant difference of 9.64 mg/dl was obtained in mean serum zinc level in cases as compared to controls ($p < 0.0001$) as our findings. Some other studies also reported results similar to our findings.^{10,15,16}

In the present study, out of 30 children with febrile convulsions 17 (56.67%) were found as simple febrile convulsion and 13 (43.33%) cases of complex febrile convulsion. Children with febrile convulsions both simple and complex have statistically significant low serum zinc levels when compared control group ($p < 0.001$). Children with fever alone did not show a decrease in serum zinc level compared to other groups which are similar to findings of other studies.¹⁷ Also there was no significant difference in serum zinc levels between simple and complex febrile convulsions. The study done by Soni SP et al⁸ also reported similar findings. Hauser WA et al¹⁸ compared 50 cases of simple and complex febrile seizures each with a control which showed significant low zinc values in seizure group ($p < 0.002$). In a study done by Engel L et al¹⁹ serum zinc values were significantly lower in cases compared to controls with a p value of < 0.05 .¹⁰¹ Another study by

Sampathkumar P et al¹³ shows a statistically significant difference in the serum zinc levels measured in the children with simple and complex febrile seizures in comparison to febrile children without seizures. However, though serum zinc levels were found to be lower in simple febrile convulsions than complex febrile convulsions, statistically there was no significant difference between the two groups. Hitz et al (1983) conducted a study comparing both serum and CSF zinc levels in febrile seizures with nonconvulsive fever group. He showed a statistically significant difference of p value < 0.001 .¹²

Conclusion

The present study revealed that there is correlation between serum zinc levels and occurrence of febrile seizures. Serum zinc level was significantly lower in children with febrile seizures in comparison with febrile children without seizure. Future research should be directed towards the therapeutic trial of zinc supplementation in children with febrile seizures and to formulate a zinc treatment regimen including its dose and duration.

References

- [1] Salehiomran MR, Mahzari M. Zinc Status in Febrile Seizure: A Case- Control Study. Iran J Child Neurol. 2013;7(4):20-23.
- [2] Garty BZ, Olomucki R, Tally LS, Nitzan M. Cerebrospinal fluid zinc concentrations in febrile Convulsions. Archives of Disease in Childhood 1995;73:338-341
- [3] Kumar S, 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;5:977-982.
- [4] Bhandari N, Bahl R, Taneja S, Strand T, Molbak K, Ulvik RJ, et al. Effect of routine zinc supplementation on pneumonia in children aged 6 months to 3 years: randomised controlled trial in an urban slum. BMJ. 2002;324(7350):1358-1359..
- [5] Raqib R, Roy SK, Rahman MJ, Azim T, Ameer SS, Chisti J. Effect of zinc supplementation on immune and inflammatory responses in pediatric patients with shigellosis. Am J Clin Nutr. 2004;79:444-450.
- [6] 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):740-3.
- [7] Ingale SY, Karguppikar M, Kakar R. The association between serum zinc level and febrile seizures in childhood. 2018;Vol.4(5):22-25
- [8] Soni SP, Une L. Role of serum zinc level in simple febrile seizures: A hospital based study from rural area of Maharashtra. Med Pulse International Journal of Pediatrics, 2017;Vol.3:2:36-38
- [9] Margaretha L, Masloman N. Correlation between serum Zinc level and simple febrile seizure in children. PediatrIndones 2010;50(6):326-30.
- [10] Mahyar A, Pahlavan A, Varasteh-Nijad A. Serum Zinc level in children with febrile seizure. Acta Medica Iranica 2008;46(6):67-9.

[11] Günduz Z , Yavuz I, Koparal M, Kurnanda S. Saraymen R. Serum and cerebrospinal fluid Zinc levels in children with febrile convulsions. Acta PaediatrJpn 1996;38(3):273-41.

[12] Hirtz DG, Nelson KB, Ellenberg JH. Seizures following childhood immunizations. J Pediatr. 1983;102:14-8.

[13] 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. **International Journal of Contemporary Pediatrics** 2018; 5(3): 977-982.

[14] Haspolat S, Mihçi E, Coşkun M, Gumuslu S, Özbenm T, Yegin O. Interleukin-1β, tumor necrosis factor-α, and nitrite levels in febrile seizures. J Child Neurol. 2002;17(10):749-51.

[15] Ehsoni F, Vahid-Harandi M, Kany K. Determination of serum Zinc in children affected by febrile convulsion and comparison with control group. The journal of Iranian Medical sciences University 2006;12:219-76

[16] TalebianA,VakiliZ.TalarSA,KazerniM.MousaviGA.As sessmentofthe relation between serum Zinc and magnesium levels in children with febrile convulsion. Iranian Journal of Pathology 2009;4:157-60.

[17] Haspolat S, Mihçi E, Coşkun M, Gumuslu S, Özbenm T, Yegin O. Interleukin-1β, tumor necrosis factor-α, and nitrite levels in febrile seizures. J Child Neurol. 2002;17(10):749-51.

[18] Hauser WA. Prevalence and incidence of convulsive disorders in children. Epilepsia. 1994;35(2):1-6.

[19] Engel J, Pedley TA. Epilepsy: a comprehensive textbook 2nd ed. Philadelphia: Pennsylvania, Wolters Kluver, Lippincott Williams, and Wilkins; 2007:659-60.

Table 1: Age wise distribution of studied children

Age Groups	Febrile convulsions	Fever without seizures
6 – 12 months	6 (20.0%)	8 (26.6%)
13 - 24 months	13 (43.3%)	12 (40.0%)
25 - 36 months	7 (23.3%)	5 (16.7%)
37 - 48 months	3 (10.0%)	3 (10.0%)
49 -60 months	1 (3.3%)	2 (6.7%)
Total	30 (100.0%)	30 (100.0%)

Table 2: Gender wise distribution of studied children

Gender	Febrile convulsions	Fever without seizures
Male	18 (60.0%)	17 (56.7%)
Female	12 (40.0%)	13 (43.3%)
Total	30 (100.0%)	30 (100.0%)

Table 3: Distribution of studied children on the basis of the causes of fever

Cause of Fever	Febrile convulsions	Fever without seizures
URTI	15 (50.0%)	20 (66.7%)
LRTI	5 (16.7%)	3 (10.0%)
AGE	7 (23.3%)	5 (16.7%)
Viral Fever	3 (10.0%)	2 (6.6%)
Total	30 (100.0%)	30 (100.0%)

Table 4: Distribution of children according to temperature and duration of fever

Variable	Febrile convulsions	Fever without seizures
Temperature		
≥102 ⁰ F	26 (86.7%)	21 (70.0%)
≥102 ⁰ F	4 (13.3%)	9 (30.0%)
Duration of fever		
≤24 hours	21 (70.0%)	8 (26.7%)
>24 hours	9 (30.0%)	22 (73.3%)

Table 5: Comparison of serum Zn level in children with febrile convulsions and children with fever without seizures

Groups	Zn level (µg/dl)		p-value
	Mean	S.D.	
Febrile convulsions (n=30)	56.95	17.91	<0.001
Fever without seizures (n=30)	78.94	16.63	

Table 6: Comparison of children with fever without seizures with type of febrile convulsions

Groups	Zn level (µg/dl)		p-value
	Mean	S.D.	
Fever without seizures(n=30)	78.94	16.63	0.0007
Simple febrile convulsions (n=17)	59.50	19.24	
Fever without seizures (n=30)	78.94	16.63	0.0001
Complex febrile convulsions (n=13)	53.62	15.10	