

## Original Research Article

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

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## ABSTRACT

**Background:** Owing to the excessive susceptibility of the immature brain to temperature, febrile seizures remain one of the common neurological conditions of childhood. Although simple febrile seizures do not pose any increased neurological problems in adult life, but the anxiety, hospitalization and prophylaxis for the episode do call for a genuine concern. A correlation between zinc deficiency and febrile seizures has been proposed and a few studies undertaken have shown mixed conclusions. This case control study was undertaken to compare the serum Zinc levels in patients with simple febrile seizures against the controlled patients with short febrile illness without seizures and to find the correlation if any between simple febrile seizures and serum zinc levels.

**Methods:** The hospital based, observational case control study was done in Batra Hospital and Medical research Centre, New Delhi. A total of 200 children aged 6 months to 6 years admitted in the hospital with history of short pyrexia (fever for 2 days or less) and fulfilling our inclusion criteria were enrolled for the study after taking an informed consent from their attendants and classified into 2 groups of 100 each as cases and controls. Patients with history of simple febrile seizures as cases and those with fever without seizures as controls. A detailed history was taken, and complete physical examination was done on the patients and recorded on a precoded and pretested proforma. The data was analysed on SPSS 17.

**Results:** Our results showed a mean of serum zinc levels in cases as  $61.53 \pm 15.87$  mcg/dl which was found to be lower compared to controls as  $71.90 \pm 18.50$  mcg /dl. Further the difference was found to be statistically significant ( $P < 0.05$ ).

**Conclusions:** Low serum zinc levels in the patients of simple febrile seizures in association with other risk factors may enhance the occurrence of seizures triggered by fever. Thus, a possible correlation exists between the mean serum zinc level and simple febrile seizures.

**Keywords:** GABA, Hypozincemia, NMDA, Simple febrile seizures, Serum zinc levels

## INTRODUCTION

Febrile seizures defined as seizures occurring in the children in the age group of 6 to 60 months with a temperature of 38°C or more, in the absence of central nervous system infection or any metabolic derangement

or any previous history of non-febrile seizures. A number of factors have been implied to play a role in the pathophysiology of febrile seizures which include susceptibility of the immature brain to temperature, association with interleukins, circulating toxins and iron deficiency.<sup>1-4</sup>

Role of trace elements like selenium, magnesium, copper and zinc have also been described in association with febrile seizures which is to an extent explained by their ability to modulate neurotransmission by acting on ion channels and their coenzyme activity.<sup>4,5</sup>

Zinc has an important role in various processes at the cellular level. It is involved in cellular growth and differentiation, is an important cofactor in various enzymatic activities taking place in different organs, proteins and cellular metabolism. In brain, zinc is present in synaptic vesicles in a subgroup of glutaminergic neurons where it can be released by electrical stimulation and may serve to modulate responses at receptors level. These include both excitatory and inhibiting receptors particularly N-Methyl-D aspartate (NMDA) and Gamma aminobutyric acid (GABA) receptors respectively.<sup>6,7</sup> Glutamic acid decarboxylase is the rate limiting enzyme in the synthesis of Gamma Amino Butyric Acid (GABA). Its activity is modulated by zinc. GABA is a major inhibitory neurotransmitter and any abnormalities of GABAergic function, including synthesis, synaptic release, receptor composition, trafficking or binding, and metabolism, can each lead to a hyperexcitable state lowering the threshold for seizures.<sup>6-8</sup> Zinc has an inhibitory effect on N-Methyl-D aspartate receptors, which is responsible for excitatory phenomenon after binding with glutamate. This explains the possible role of zinc in pathogenesis of febrile seizures. Some of the studies have already reported low serum zinc levels in patients of febrile seizures.<sup>9-13</sup>

This study intends to compare the serum zinc levels in children with simple febrile seizure with those of acute febrile illness without seizures and to look for the correlation, if any, between the serum zinc level and simple febrile seizures.

**METHODS**

The study is a hospital based case control study with RCT code of AEARCTR-0000631 done at Department of Pediatrics, Batra Hospital and Medical Research Centre, New Delhi a tertiary care hospital.

A total of 200 children falling in the age group of 6 to 60 months were enrolled for the study after obtaining an informed consent from the parents/guardians. They were distributed in two groups of 100 each as cases and controls. Patients with simple febrile seizure, normal development, were included as cases excluding those with complex febrile seizures, age younger than 6 months and older than 5 years, history of recent zinc intake, developmental delay and/or neurologic deficit, malnutrition, acute and chronic diarrhoea, electrolyte imbalance. Patients of the same age group matching all other criteria with the cases, with h/o short pyrexia (2days or less) without seizures were included as controls. A detailed history, thorough physical examination was done and the findings recorded on a pretested proforma. The

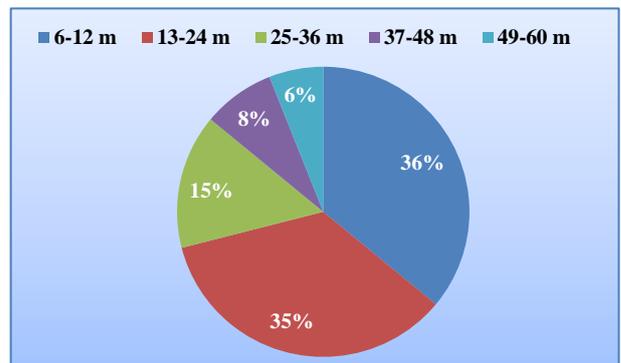
sample for zinc estimation was drawn within 24 hours of admission of patient in both the groups. The sample was centrifuged for 3-4 minutes at 3,000-4,000 rpm, serum thus obtain and preserved in sterile deionized vial. Estimation of serum zinc was done within 6 hours of collection using colorimetric test kits, with 2-(5-bromo-2-pyridylazo)-5-(N-propyl-N-sulphopropylamino) phenol as the reagent.

**Statistical analysis**

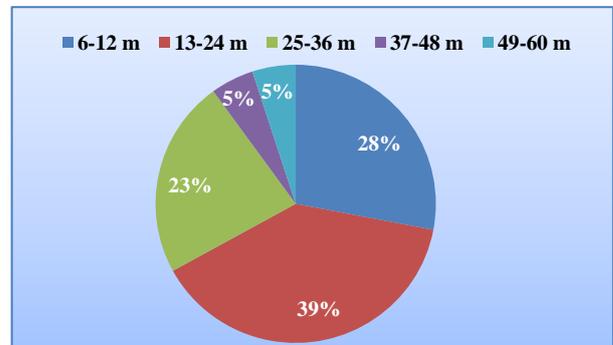
Data was analyzed using SPSS version 17.0. The difference in mean among the groups was assessed by ANOVA and t-test was used to analyze inter group difference. A p- value less than 0.05 was taken as statistically significant.

**RESULTS**

Figure 1 and 2, represents the mean age of group A and group B respectively. Mean age were nearly similar in the both Groups. The bulk of the patients in cases (Group A) were of age group 6-12 months (36%) followed by 13-24 months (35%), 25- 36 months (15%), 37 – 48 months, (49-60 months). In Controls (Group B) majority of the patients were from age group 13-24 months (39%) followed by 6-12 months (28%), 25-36 months (23%) and 37-48 months and 49-60 months (5% each).



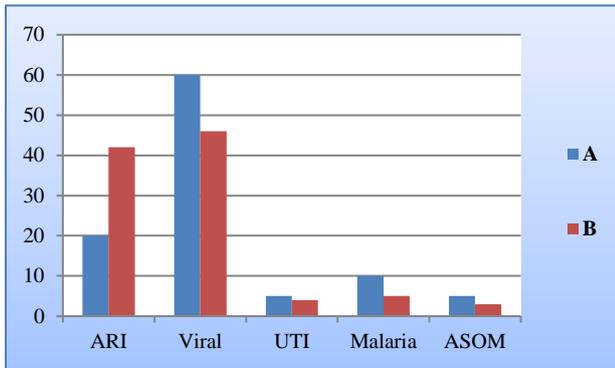
**Figure 1: Mean age distribution Group A.**



**Figure 2: Mean age distribution Group B.**

Figure 3, represents the distribution of diagnosis in group A and group B and shows that non localized fever (viral)

predominated as the cause of fever in the both groups with 60% and 46% in cases and controls respectively. This was followed by ARI (20% and 42%) and Malaria (10 and 5) in both the groups. The other diagnoses included UTI and ASOM.



**Figure 3: Distribution of diagnoses in Group A and Group B.**

Table 1, represents the mean serum zinc level in the both groups. Mean serum zinc level was 10.45 µg/dl less in cases of simple febrile seizure as compared to controls and the difference was found to be statistically significant (P<0.005).

**Table 1: Mean serum zinc levels in Group A and Group B.**

	Serum zinc level mcg/dl	Mean difference	P value
Group A	61.53±15.87	-10.45	<0.05
Group B	71.90±18.50		

Table 2 represents the number of patients in both groups with bio-chemical hypozincemia and shows that 60% of the cases and 34% of the controls had bio-chemical hypozincemia. Hypozincemia was found to be significantly predominant in cases compared to controls (P=0.001).

**Table 2: Biochemical hypozincemia in Group A versus Group B.**

Zinc level	Group A		Group B		Total	
	No.	%	No.	%	No.	%
<65 µgm/dl	60	60	34	34	94	47
>65 µgm/dl	40	40	66	66	106	53
Total	100		100		200	

**DISCUSSION**

Zinc has an essential role in the normal function and development of the central nervous system. It is present in synaptic vesicles in a subgroup of glutaminergic neurons where it can be released by electrical stimulation and may serve to modulate responses at receptors level. These include both excitatory and inhibiting receptors

particularly N-Methyl-D aspartate (NMDA) and Gamma aminobutyric acid (GABA) receptors respectively. Hence its deficiency can lead to the excitation inhibition imbalance precipitating a febrile seizure.

A number of studies have been done in this regard with some demonstrating an association of hypozincemia with simple febrile seizures, while few concluding no association. Majority of the studies have compared the mean serum zinc level between cases and controls, while few others have studied this correlation by determining the number of patients having hypozincemia in subject population. In present study, both methods to analyse the data were used. The cut off value for hypozincemia was taken as 65µgm/dl as per the World Health Organization (WHO) recommendation.<sup>14</sup>

Patient profile in present study comprised mainly of non localized fevers with clinical evidence to suggest viral etiology (60%), followed by ARI (20%), Malaria (10%), UTI (5%) and ASOM (5%). Margaretha and Günduz have also reported ARI as most common cause.<sup>10,15</sup>

Overall Hypozincemia was present in 60% of the patients, but no statistical significant difference was seen in the mean age, gender distribution, physical parameters, and nutritional status between the patients of hypozincemia and normal zinc level. Mahyar et al. and few other researchers have also reported similar findings in their studies suggesting that no specific age group or gender is particularly predisposed to develop hypozincemia.<sup>16-20</sup>

A significant difference of 10.46 µg/dl in the mean serum zinc levels in cases(lower) compared to controls was also noted in the present study. The findings are consistent with some previous studies.<sup>5,9-13,19,20</sup>

Hypozincemia in present study was found to be more prevalent in children with simple febrile seizures compared to the control group. However, no classical clinical manifestations of hypozincemia like diarrhoea, impaired appetite, decreased growth velocity, acro-orrificial skin lesions, delayed wound healing, dysguesia and hypoguesia were present in these patients, demonstrating purely biochemical hypozincemia.

**CONCLUSION**

The higher prevalence of hypozincemia in children with simple febrile seizures compared to the control group suggests a possible correlation between low serum zinc levels and simple febrile seizures. Hypozincemia in presence of other risk factors may enhance the occurrence of febrile seizures. However, large randomized control trials are recommended to prove the association or otherwise, and discuss the possibility of prophylactic zinc supplementation in reducing the risk of febrile seizures, particularly in developing countries.

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