Serum zinc levels in children with simple febrile seizure

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ABSTRACT

Background: It has been postulated that children with low serum zinc level are more prone to febrile seizures. **Objectives:** The objectives of this study were to compare the serum zinc levels in children suffering from febrile seizures with the children with febrile illness without seizures and children with no seizure and fever. **Materials and Methods:** A prospective case–control study was conducted in the Department of Pediatrics, in a Medical Institution of Meerut, over a period of 2 years (March 2015–May 2017). A total of 150 candidates of age 6 months–60 months were recruited from the pediatric wards and were divided into three subgroups. Group A consisted of 50 children who neither had fever nor seizures. Group B consisted of 50 children who had fever but no seizures. Group C consisted of 50 children who suffered from simple febrile seizure. Here, the Groups A and B served as control while Group C was taken as case. Serum zinc level was assessed in each child after taking written consent from parents. Further, the value of serum zinc was compared among the group. The results were statistically analyzed using the Statistical Package for the Social Sciences Version 21.0 statistical analysis Software. **Results:** Of 50 children with febrile seizures, 29 (58%) were male. Mean serum zinc levels of all the children included in the study were low (55.42 µg/dl) as compared to the reference values. There was no significant difference in the serum zinc levels in the febrile seizure group and control groups. **Conclusion:** We found that the serum zinc level was not associated with febrile seizures.

Key words: *Febrile seizure, Pediatric population, Serum zinc levels*

A seizure occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizure is defined as febrile seizure [1]. International league against epilepsy in 2010 classified febrile seizures and febrile seizure plus under "electroclinical syndromes and other epilepsies" [2]. Febrile seizures occur in 2–5% of children 6 months–5 years of age.

Zinc is an important micronutrient that plays a significant role in growth and development, immune system response, enzymatic activity of different organs, proteins and cellular metabolism, neurological functions, nerve impulse transmission, and hormone release [3,4]. The possible role of zinc deficiency in provoking febrile seizures has been reported in different studies [5,6]. Zinc stimulates the activity of pyridoxal kinase, the enzyme that modulates GABA level, a major inhibitory neurotransmitter [7]. It also modifies the affinity of neurotransmitters and thus prevents the excitatory neuronal discharge [8]. In 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 [3,9].

Studies have revealed that the genetic factors [10,11], family backgrounds [10,11], iron deficiency [12,13], immunologic disorders [14], and zinc deficiency [7,15] may play a role in occurrence of febrile seizures. Some authors have reported that the serum zinc level in children with febrile seizure is lower than in control group and concluded that this trace element may have a role in febrile seizure [16-18]. Zinc deficiency is also found associated with other illnesses such as chronic liver disease [19-21], chronic diarrhea [22,23], pneumonia [24], and chronic renal disease [25-27].

Primary aim of the study was to compare the serum zinc levels in children suffering from febrile seizures those to age-matched children with febrile illness without seizures and to children with no seizure and fever and thus to evaluate any possible correlation between zinc levels and febrile seizures.

MATERIALS AND METHODS

This hospital-based prospective case–control study was conducted over a period of 2 years from March 2015 to May 2017 consisting of infants and children aged between 6 months and 60 months. This study was conducted in the Department of Pediatrics of a tertiary care teaching hospital of Meerut after getting approval from the Institutional Ethics Committee. Candidates were enrolled after taking informed consent from parents.

Sample size was calculated by formula - $n=\{(Z_{\alpha\backslash 2})^2pq\}/L^2\{(1.98)^2\times 3\times 97\}\div 5^2=45.6\sim 50$, where n=desired sample size, $Z_{\alpha\backslash 2}$=standard normal deviate (taken as 1.96 for confidence level

of 95%), p=proportion in the target population estimated to have a particular characteristic (prevalence in percentage), q=100-p, and L=allowable error (5–20% of p). Hence, to calculate, the prevalence taken was 3% and least allowable error was taken (5%). Hence, minimum sample size was calculated as 50.

A total of 150 children from 6 months to 60 months of age were recruited from the OPD/emergency of the department of pediatrics and three subgroups were made. Group A consisted of 50 children who neither had any fever nor seizures. Group B consisted of 50 children who had fever but no seizures. Group C consisted of 50 children who suffered from simple febrile seizure. Here, the Groups A and B served as control while Group C was taken as case. Following inclusion and exclusion criteria were used for recruiting cases and controls:

Inclusion Criteria

The following criteria were included in the study:

- Group A: Children aged between 6 months and 60 months having no febrile seizure or febrile illness with no evidence of undernutrition.
- Group B: Children between 6 months and 60 months of age having any kind of febrile illness and having normal growth and development with no evidence of undernutrition.
- Group C: Children between 6 months and 60 months of age having simple febrile seizures and having normal growth and development with no evidence of undernutrition.

Exclusion Criteria

The following criteria were excluded from the study:

- Group A: Children younger than 6 months and older than 60 months; children with a history or complaint of any febrile illness; children with a history of seizure-like activity; children having undernutrition; children with a history of recent zinc intake within previous 30 days; and children with any chronic illness such as chronic disease list (CLD), chronic diarrhea, prolonged steroid intake, and chronic renal disease.
- Group B: Children younger than 6 months and older than 60 months; children with any seizure-like activity; children having a history of recent zinc intake during previous 30 days; and children with any chronic illness such as CLD, chronic diarrhea, prolonged steroid intake, and chronic renal disease.
- Group C: Children younger than 6 months and older than 60 months; children with complex febrile seizure; children with neuroinfections or developmental delay and/or neurologic deficit or central nervous system malformations; children with family history of epilepsy; children having history of recent zinc intake during previous 30 days; and children with any chronic illness such as CLD, chronic diarrhea, prolonged steroid intake, and chronic renal disease.

Demographic data, seizure details, nature of febrile illness, family history of epilepsy/febrile seizures, temperature at admission, socioeconomic class, and nutritional status were recorded. All candidates were evaluated clinically for any signs of meningitis or any neurological deficit. Lumbar puncture was done, if indicated, to exclude meningitis. Electroencephalogram was done after 2 weeks of seizure episode in some cases where history was not reliable. Blood samples were collected within 24 h of hospitalization and were sent for the evaluation of serum zinc levels in plain vials 4 ml each for the evaluation of zinc levels. Atomic Absorption Spectrometer AAnalyst 400 was used for the determination of zinc in serum. Normal serum zinc level was found to be 64–118 µg/dl according to Nicholson and Pesce [28] and 64–124 µg/dl according to Lin *et al*. [29] in pediatric age group. The statistical analysis was done using the Statistical Package for the Social Sciences Version 21.0 statistical analysis software. $p<0.05$ was considered statistically significant.

RESULTS

The distribution of children in each group was even with reference to their age. The mean age of children included in the study was 34.2 months. Distribution of children in all three groups among various age groups and mean in each group is shown in Table 1.

Male-to-female ratio was 1.3 showing preponderance of boys (p=0.365). Most of the children (42.7%) were from lower socioeconomic class (Grade 5) according to modified Kuppuswamy scale. Lower respiratory tract infections (LRTI) (28%) and upper respiratory tract infections (URTI) (22%) were the predominant causes of febrile illness in Group B. The common causes of fever in febrile seizure group (Group C) were also LRTI and URTI.

Mean serum zinc level was 55.42±24.36 µg/dl of all children included in the study. Mean serum zinc levels were calculated in each individual groups and it was 52.16±22.35 µg/dl versus 61.39±11.76 µg/dl versus 52.64±33.31 µg/dl in Group A, B, and C, respectively (p=0.046). In this study, the mean serum zinc levels were not specifically found to be affected in febrile seizure group (p=0.046). Serum zinc levels were more in females (55.84 µg/dl) than in males (54.86 µg/dl), but the difference was not statistically significant (p=0.704).

Table 1: Distribution of children in all three groups

Age (months)	Group A (%)	Group B (%)	Group C (%)	Total (%)	p value
6–12	11 (22.00)	5 (10.00)	7 (14.00)	23 (15.33)	0.237
13–60	39 (78.00)	45 (90.00)	43 (86.00)	127 (84.67)	
Mean±SD	32.46±18.23	40.34±17.34	29.26±15.08		0.079

Table 2: Comparison of mean serum zinc levels in each group with other studies

Studies	No fever and no seizure group	Any febrile illness but no seizure group	Simple febrile seizures group	Significance
Present study	52.16	61.39	52.64	Insignificant
Joshi [30]	132.04	-	155.09	Insignificant
Lee *et al*. [31]	109.6	-	106.5	Insignificant
Cho *et al*. [32]	90.38	-	97.16	Insignificant
Gattoo *et al*. [16]	-	71.9	61.53	Significant
Choudhury and Sidharth [17]	88.00	65.84	40.41	Significant
Bonu *et al*. [18]	-	90.1	76.8	Significant
Kumar *et al*. [33]	120	-	79.55	Significant
Soni *et al*. [34]	72.14	-	62.5	Significant

DISCUSSION

In this study, we compared the serum zinc levels in three groups of children, i.e., (a) children who neither had fever nor seizures, (b) children who had fever but no seizures, and (c) children with simple febrile seizures. Here, the Groups A and B served as control while Group C was taken as cases; however, we could not find any significant difference in the serum zinc levels between the three groups.

Of total 50 children with febrile seizures, 29 (58%) were with a significant male preponderance which also has been seen in many previous studies [15,16,30]. Whether there is a biological basis for the gender-specific differences in febrile seizure susceptibility, or whether boys just contract more fevers and therefore are at greater risk, are currently not established. The presence of more male children even in both control groups might be due to the fact that in India male children are more cared for by families so are brought more to hospital. However, difference in the mean serum zinc levels was not significant between females (55.84 µg/dl) and males (54.86 µg/dl).

In our study, the mean serum zinc levels in control Group A (children with no seizure and no fever) were 52.16 µg/dl while in Group B (children suffering from any febrile illness), mean serum zinc levels were 61.39 µg/dl and in Group C (children suffering from febrile seizure), it was 52.64 µg/dl. Therefore, there was no significant difference in the mean serum zinc levels between control and case groups. Many previous studies have shown that zinc deficiency [7,15] may play a role in occurrence of febrile seizures. Results of the previous studies conducted to assess the role of the zinc deficiency have been given in Table 2.

Some authors have reported that the serum zinc level in children with febrile seizure is lower than in control group and concluded that this trace element may have a role in febrile seizure. Gattoo *et al*. [16] in Jammu and Kashmir concluded that the presence of hypozincemia in the presence of other risk factors of febrile seizures may enhance the occurrence of febrile seizures. In their study, the mean serum zinc level in cases was 61.53±15.87 µg/dl, and in controls, it was 71.90±18.50 µg/dl. Choudhury and Sidharth [17] in Odisha found that mean serum zinc was significantly low in febrile seizure group compared to febrile illness group and normal children. Another study, conducted by Bonu *et al*. [18], revealed that serum zinc level decreases during infections. This decrease was more significant in patients with febrile convulsion. However, many other studies have shown the contradictory results as they could not find any significant difference in zinc levels between cases and controls [30-32].

The main limitation of this study was a small sample size and a study of large sample size will be needed to prove the association. Moreover, most of the children in the study sample were moderately nourished, who may already have zinc deficiency. Therefore, further studies on serum zinc levels in a cohort of well-nourished children with febrile seizure will be needed.

CONCLUSION

The present study concludes that serum zinc levels are not associated with febrile seizure.

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