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Original Research Article

ASSOCIATION BETWEEN SERUM ZINC LEVELS AND FEBRILE SEIZURES IN CHILDREN: A CASE-CONTROL STUDY

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ABSTRACT

Background: Febrile seizures are among the most common seizure disorders of childhood and occur predominantly between 6 months and 5 years of age. Although generally benign, they are an important cause of pediatric emergency visits and considerable parental anxiety. The pathogenesis of febrile seizures is multifactorial, involving fever, central nervous system immaturity, genetic susceptibility, infection, and potentially nutritional and trace-element deficiencies. Zinc is an essential micronutrient involved in neurotransmission and modulation of neuronal excitability. The present study evaluated the association between serum zinc levels and febrile seizures in children.

Materials and Methods: A hospital-based case-control study was conducted in the Department of Paediatrics, St. Isabel's Hospital, Mylapore, Chennai, between April 2015 and March 2016. Eighty-four children aged 6 months to 5 years were enrolled, comprising 42 children presenting with a first episode of simple febrile seizure and 42 - age, sex, and nutritional-status-matched children with acute febrile illness without seizures. Children with atypical febrile seizures, intracranial infection, severe malnutrition, electrolyte abnormalities, structural brain lesions, neurodevelopmental disorders, previous afebrile seizures, or therapeutic zinc supplementation were excluded. Serum zinc was estimated using a colorimetric method, and serum zinc concentrations below 65 µg/dL were considered hypozincemia. We also assessed demographic, nutritional, haematological, infectious, and clinical variables.

Results: The mean serum zinc level was significantly lower among children with febrile seizures than among controls (63.12 ± 21.85 µg/dL versus 73.99 ± 19.68 µg/dL; $p = 0.019$). Hypozincemia was present in 26 (61.9%) children with febrile seizures compared with 16 (38.1%) controls ($p = 0.029$; odds ratio 2.64, 95% CI 1.094–6.371). Within the febrile seizure group, children with zinc deficiency experienced seizures at significantly lower temperatures than children without zinc deficiency (101.31 ± 0.837°F versus 102.19 ± 1.047°F; $p = 0.005$). Zinc deficiency was also significantly associated with protein-energy malnutrition ($p < 0.001$). Mean hemoglobin was lower among zinc-deficient children with febrile seizures than among those without zinc deficiency (10.61 ± 1.118 versus 11.25 ± 0.823 g/dL; $p = 0.05$). Regression analysis showed that serum zinc was the only variable among age, peak temperature, weight, zinc level, and haemoglobin that was significantly associated with the presence of febrile seizures ($p = 0.008$).

Conclusion: Children with febrile seizures had significantly lower serum zinc levels and a higher frequency of hypozincemia than febrile children without seizures. Zinc deficiency was also associated with lower seizure temperature and indicators of nutritional deficiency. These findings support an association between hypozincemia and febrile seizures; however, larger prospective studies

are required to determine causality and whether zinc supplementation can prevent first or recurrent febrile seizures.
Keywords: febrile seizure; febrile convulsion; zinc deficiency; hypozincemia; children; trace elements; nutritional deficiency.

INTRODUCTION

Febrile seizures are the most common seizure disorder encountered in childhood and generally occur between 6 months and 5 years of age. They are defined as seizures occurring in association with febrile illness in children without evidence of intracranial infection, metabolic disturbance, previous afebrile seizures, or another acute symptomatic cause. Most febrile seizures are simple, characterised by generalised tonic-clonic activity, a duration of less than 15 minutes, and no recurrence within 24 hours.[1,2]

Although febrile seizures are usually self-limited and have a favourable prognosis, they are a frequent reason for emergency pediatric consultation and can be highly distressing for parents and caregivers. Approximately one-third of affected children may experience recurrence, with recurrence influenced by factors such as young age at first seizure, family history, duration of fever before seizure, and other clinical characteristics.[3]

The precise pathophysiology of febrile seizures remains incompletely understood. The interaction of an immature brain, elevated body temperature, genetic susceptibility, and inflammatory responses is believed to contribute to neuronal hyperexcitability. Other proposed factors include viral infection, cytokine activation, iron deficiency, and trace-element abnormalities.[4]

Zinc is an essential micronutrient involved in growth, development, enzymatic activity, cellular metabolism, and normal brain function. It also has an important role in neuronal transmission. Zinc can modulate N-methyl-D-aspartate (NMDA) receptor activity and contributes to the synthesis and function of gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter. Consequently, reduced zinc availability may increase neuronal excitability and potentially lower the seizure threshold.[5]

Several previous studies have reported lower serum zinc concentrations in children with febrile seizures compared with febrile or healthy controls, although other studies have failed to demonstrate such an association. Differences in population characteristics, nutritional status, study design, and methods of zinc assessment may contribute to these conflicting findings.[6]

Relatively few studies from India have examined the relationship between serum zinc and febrile seizures. Therefore, the present study was undertaken to determine whether serum zinc levels differ between children with febrile seizures and children with acute febrile illness without seizures and to assess the association of zinc deficiency with demographic characteristics, nutritional status, anaemia, and infection.[7-10]

MATERIALS AND METHODS

Study Design and Setting: This hospital-based case-control study was conducted in the Department of Paediatrics, St. Isabel's Hospital, Mylapore, Chennai, from April 2015 to March 2016.

Study Population: The study included children aged 6 months to 5 years admitted with acute febrile illness.

The case group consisted of 42 children with a first episode of simple febrile seizure. The control group consisted of 42 children with acute febrile illness without seizures. Controls were matched for age, sex, and nutritional status.

Simple febrile seizure was defined according to the study criteria as a generalised tonic-clonic seizure lasting less than 15 minutes, occurring once within 24 hours in a child aged 6 months to 5 years.

Eligibility Criteria: Children with atypical or complex febrile seizures, intracranial infection, severe protein-energy malnutrition, therapeutic zinc supplementation, electrolyte abnormalities, hereditary metabolic disorders, structural brain lesions, cerebral palsy, intellectual disability, neurodegenerative disorders, or previous afebrile seizures were excluded.

Controls were children aged 6 months to 5 years with acute fever lasting less than 5 days without seizures and without the exclusion conditions described above.

Data Collection: After obtaining informed consent from parents, we recorded demographic and clinical information, including age, sex, duration and peak temperature of fever, seizure characteristics, family history of febrile seizures or seizure disorders, associated illnesses, dietary history, and breastfeeding history.

Anthropometric measurements included weight, height, and head circumference where appropriate. Nutritional status was classified using the Indian Academy of Paediatrics classification of protein-energy malnutrition. Children with Grade III or Grade IV malnutrition were excluded.

Laboratory Investigations: Hemoglobin, hematocrit, total leukocyte count, differential leukocyte count, peripheral smear, C-reactive protein, serum electrolytes, calcium, random blood glucose, liver enzymes, and serum zinc were assessed as appropriate.

Anaemia was defined as haemoglobin below 11 g/dL for children aged 6 months to 60 months. Peripheral smear findings were assessed for morphological evidence of anaemia.

Serum zinc was measured using a colorimetric assay. A serum zinc level below 65 µg/dL was considered indicative of hypozincemia.

Statistical Analysis: Data were entered into Microsoft Excel and analysed using SPSS version 20. Continuous variables were expressed as mean and standard deviation. Independent Student's t-test was used for comparison of means, while categorical variables were analysed using the chi-square or Fisher's exact test. Odds ratios with 95% confidence intervals were calculated to evaluate the association between zinc deficiency and febrile seizures. Regression analysis was performed to evaluate the relationship between febrile seizures and selected independent variables. A p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics: A total of 84 children were included, with 42 cases and 42 controls. The groups were comparable in age, sex, weight, height, protein-energy malnutrition, and peak temperature during illness.

The mean age was 22.9 ± 12.21 months among cases and 25.9 ± 15.47 months among controls (p = 0.327). Males constituted 59.5% of cases and 47.6% of controls, with no statistically significant difference in sex distribution.

The mean peak temperature during illness was also comparable between cases and controls (101.93 ± 0.92°F versus 101.73 ± 1.06°F; p = 0.360).

Serum Zinc Levels: The principal finding was a significantly lower serum zinc concentration among children with febrile seizures.

The odds ratio for zinc deficiency among children with febrile seizures compared with controls was 2.64 (95% CI 1.094–6.371).

Thus, children with febrile seizures had approximately 2.6 times the odds of hypozincemia compared with febrile children without seizures.

Table 1: Comparing the Serum Zinc values among cases and controls

Variable	Febrile seizure (n=42)	Controls (n=42)	p value
Serum zinc (µg/dL), mean ± SD	63.12 ± 21.85	73.99 ± 19.68	0.019
Zinc deficiency, n (%)	26 (61.9%)	16 (38.1%)	0.029

Age Distribution: More than half of the children in both groups were aged 24 months or younger. Among cases, 24 (57.1%) were ≤24 months, compared with 24 (57.1%) controls. The difference in age distribution was not statistically significant (p = 0.598).

Similarly, there was no significant difference in age distribution between children with and without zinc deficiency (p = 0.749).

Family History: Among the 42 children with febrile seizures, 11 (26.2%) had a family history of febrile seizures, and 4 (9.5%) had a family history of seizure disorder.

Temperature at the Time of Seizure

An important finding was the difference in seizure temperature according to zinc status.

Among zinc-deficient children with febrile seizures, 16 of 26 (61.5%) developed seizures at a temperature of ≤101°F, compared with 4 of 16 (25%) children without zinc deficiency (p = 0.038).

The mean temperature at seizure was:

- Zinc-deficient group: 101.31 ± 0.837°F
- Non-zinc-deficient group: 102.19 ± 1.047°F

This difference was statistically significant (p = 0.005).

Nutritional Status: Protein-energy malnutrition was strongly associated with zinc deficiency. Among children with zinc deficiency, 34 (81.0%) had Grade I/II protein-energy malnutrition compared with only 7 (16.7%) among children without zinc deficiency (p < 0.001).

Within the febrile seizure group, Grade I/II protein-energy malnutrition was present in 18 (69.2%) zinc-deficient children compared with only 1 (6.2%) child without zinc deficiency (p < 0.001).

The overall prevalence of Grade I/II protein-energy malnutrition did not differ significantly between cases and controls (p = 0.513).

Anemia: Peripheral smear abnormalities suggestive of microcytic anaemia were found in 5 (11.9%) cases and 5 (11.9%) controls (p = 1.000).

Among children with febrile seizures, microcytic changes were observed in 5 (19.2%) zinc-deficient children compared with none of the children without zinc deficiency. This difference did not reach statistical significance (p = 0.062).

However, mean hemoglobin was significantly lower among zinc-deficient children with febrile seizures:

- Zinc deficient: 10.61 ± 1.118 g/dL
- Zinc sufficient: 11.25 ± 0.823 g/dL
- p = 0.05

Associated Comorbidities and Infection: Upper respiratory tract infection was the most common associated clinical condition among zinc-deficient children with febrile seizures, occurring in 42.3% of this subgroup. Acute gastroenteritis was the most frequent condition among zinc-deficient controls.

No statistically significant difference in associated comorbidities was observed between the study subgroups.

Similarly, infection-related parameters did not differ significantly between cases and controls. The study findings suggested that viral illness was more common than bacterial illness based on peripheral smear findings and CRP results.

Regression Analysis: Regression analysis included age, peak temperature during illness, weight, serum zinc level, and hemoglobin.

Among these variables, serum zinc level was the only variable significantly associated with the presence or absence of febrile seizure (p = 0.008).

DISCUSSION

The present study demonstrated a significant association between lower serum zinc levels and febrile seizures in children aged 6 months to 5 years. Children with febrile seizures had a mean serum zinc concentration of 63.12 µg/dL compared with 73.99 µg/dL among febrile controls. Furthermore, hypozincemia was present in 61.9% of cases compared with 38.1% of controls.

These findings are consistent with several previous case-control studies cited in the thesis. Salehiomran and Mahzari reported significantly lower serum zinc levels among children with febrile seizures compared with febrile controls. Similarly, studies by Ehsanipour et al., Amiri et al., Mahyar et al., Gatoo et al., and Ganesh et al. reported lower zinc concentrations among children with febrile seizures.

The biological plausibility of this association is supported by zinc's role in neuronal function. Zinc participates in neurotransmitter regulation and can modulate NMDA receptor activity. It is also involved in pathways related to GABA synthesis, an inhibitory neurotransmitter system. Reduced zinc availability could therefore contribute to increased neuronal excitability and a lower seizure threshold during febrile illness.

However, the relationship between zinc and febrile seizures has not been consistently demonstrated across all studies. Garty et al. found no significant difference in cerebrospinal fluid zinc concentrations among children with febrile seizures, febrile illness without seizures, and aseptic meningitis. Amouian et al. also reported no significant difference in serum zinc between cases and controls, with low zinc concentrations observed in both groups. These conflicting observations indicate that zinc deficiency may represent one component of a multifactorial process rather than an independent cause of febrile seizures.

A notable finding in the present study was that zinc-deficient children developed seizures at significantly lower temperatures than children without zinc deficiency. Although peak temperature during the overall febrile illness was similar between cases and controls, the temperature at seizure onset differed by zinc status. This finding raises the possibility that hypozincemia may lower the seizure threshold in susceptible children.

The strong association between zinc deficiency and protein-energy malnutrition is also important. More than four-fifths of zinc-deficient children had Grade I/II protein-energy malnutrition. This suggests that hypozincemia may occur as part of a broader nutritional deficiency state rather than as an isolated micronutrient abnormality. Similar considerations apply to anemia, as zinc-deficient children with febrile seizures had lower mean hemoglobin levels.

The study also identified a family history of febrile seizures in 26.2% of cases, supporting the established contribution of genetic susceptibility to febrile seizures. Nevertheless, the regression analysis indicated that among the variables examined in this study, serum zinc was the only factor significantly associated with febrile seizure occurrence.

Importantly, the present study establishes an association rather than causation. Serum zinc was measured during an acute febrile illness, and baseline zinc concentrations before illness were unavailable. Consequently, it cannot be determined whether hypozincemia predisposed children to febrile seizures or whether acute illness itself contributed to reduced serum zinc concentrations.

Strengths and Limitations: The study used a case-control design with a febrile control group rather than healthy controls, allowing comparison of zinc levels in children experiencing fever with and without seizures. Cases and controls were also comparable on several important demographic and nutritional characteristics.

However, the study had several limitations. First, the sample size was relatively small, with only 42 children in each group. Second, complete iron studies, including serum ferritin, were not performed, limiting assessment of the relationship between iron deficiency and febrile seizures. Third, CSF zinc concentrations were not evaluated. Fourth, the serum zinc cutoff used to define deficiency may not accurately represent the optimal threshold for Indian children, given differences in dietary patterns and nutritional status. Finally, baseline serum zinc levels before the febrile illness were unavailable, preventing determination of whether hypozincemia preceded the seizure or resulted from acute illness.

CONCLUSION

This case-control study found that children with febrile seizures had significantly lower serum zinc concentrations and a significantly higher prevalence of hypozincemia than febrile children without seizures.

The mean serum zinc level was 63.12 ± 21.85 µg/dL in children with febrile seizures compared with 73.99 ± 19.68 µg/dL in controls. Zinc deficiency was associated with approximately 2.6-fold higher odds of febrile seizure. Within the febrile seizure group, zinc-deficient children also developed seizures at significantly lower temperatures.

Zinc deficiency was strongly associated with protein-energy malnutrition and was accompanied by lower hemoglobin concentrations, suggesting that hypozincemia may form part of a broader nutritional deficiency state.

Overall, the findings support an association between low serum zinc and febrile seizures in young children. However, the results should not be interpreted as evidence that zinc deficiency independently causes febrile seizures or that zinc supplementation prevents them. Larger prospective studies assessing pre-illness zinc status and using standardised, population-specific zinc thresholds are

needed to clarify the causal relationship and determine whether zinc supplementation has a preventive role.

Recommendations

Future studies should:

1. Enrol larger numbers of children through multicenter or prospective cohort designs.
2. Measure serum ferritin and other iron parameters alongside zinc.
3. Establish appropriate serum zinc reference and deficiency thresholds for Indian children.
4. Assess baseline zinc status before the onset of febrile illness where feasible.
5. Investigate whether correction of documented zinc deficiency reduces the incidence or recurrence of febrile seizures.
6. Further evaluate the interaction between zinc deficiency, nutritional status, infection, anaemia, and other established risk factors for febrile seizures.

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