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ORIGINAL ARTICLE

Frequency of zinc deficiency in patients with simple febrile seizures

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ABSTRACT

Background: Febrile seizures (FS) are among the most common pediatric emergencies. Zinc, a trace element crucial for neurodevelopment and inhibitory neurotransmission, has been implicated in seizure susceptibility. Zinc deficiency may predispose children to seizures during febrile illness. Data on its frequency in children with FS are limited in our local population.

Methods: This cross-sectional study was conducted in the Pediatrics Department, Mardan Medical Complex, over six months. A total of 149 children (3–60 months) presenting with simple FS (generalized seizure <15 minutes, occurring once in 24 hours) were enrolled by non-probability consecutive sampling. Children with prior afebrile seizures, epilepsy, CNS infections, recent zinc therapy, electrolyte disturbances, or focal/complex seizures were excluded. Blood samples collected after initial stabilization of seizure were analyzed for serum zinc by colorimetric method within six hours of collection; zinc deficiency was defined as <70 µg/dL. Demographic, socioeconomic, and seizure-related data were recorded. Frequencies and percentages were calculated, and associations tested using chi-square with p≤0.05 as significant.

Results: Mean age was 26 ± 15 months, with 60% males; mean weight was 12.0 ± 4.1 kg. Median seizure duration was 4 minutes. Zinc deficiency was detected in 80 of 149 patients (53.7%). Age, gender, weight, seizure duration, family history of FS, and residence showed no significant association with zinc status. However, zinc deficiency was significantly more frequent in children from lower socioeconomic backgrounds (p=0.03) and with less-educated parents (p=0.04).

Conclusions: These findings highlight the potential role of zinc insufficiency in FS pathogenesis. Screening and nutritional interventions may be beneficial, though randomized trials are required to confirm preventive effects of supplementation.

Keywords: Febrile Seizure, Nutritional Status, Seizures, Thyroidectomy, Thyroid Cancer, Zinc Deficiency

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Introduction

Febrile seizures (FS) are the most frequent seizure disorder in young children, occurring in approximately 3–5% of children worldwide. FS typically occur between 6 months and 5 years of age, with peak

incidence around 18–24 months (1). By definition, a simple febrile seizure is a generalized tonic-clonic seizure lasting less than 10–15 minutes and not recurring within 24 hours, whereas complex febrile seizures are prolonged (>15 minutes), focal in onset, or recur within the same febrile illness. FS occur in the context of fever (≥38.0 °C) without intracranial infection or other identifiable causes, in an otherwise neurologically healthy child (2). Although most febrile seizures are brief and benign, seizures – especially status epileptics – are among the most serious acute neurologic events in childhood and can lead to neuronal injury if prolonged. There are even rare reports linking febrile seizures (particularly febrile status epilepticus) with long-term sequelae such as hippocampal damage, subsequent epilepsy, or even sudden death, underscoring the importance of understanding FS etiology and risk factors (3).

The exact pathophysiology of febrile seizures remains unclear. Genetic predisposition is known to play a major role, but environmental and nutritional factors may modify the risk (4). In particular, deficiencies of certain trace elements have been hypothesized to contribute to seizures. Zinc is an essential trace element involved in numerous enzymatic reactions and neuronal processes, including modulation of ion channels, synaptic transmission, and neurotransmitter synthesis. Notably, zinc is a cofactor for pyridoxal kinase and glutamate decarboxylase, enzymes critical for the synthesis of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter (4). Zinc deficiency can therefore impair GABAergic inhibition and lower the seizure threshold. Additionally, fever and infection can alter trace element metabolism – for example, fever-induced cytokines can redistribute zinc into the liver, acutely lowering serum zinc levels. These mechanisms suggest a biologically plausible link between low zinc levels and febrile seizure occurrence (5).

Beyond febrile seizures, zinc deficiency has also been implicated in the pathophysiology of afebrile epileptic seizures. At the molecular level, zinc is essential for the activity of pyridoxal kinase and glutamate decarboxylase, enzymes required for the synthesis of gamma-aminobutyric acid (GABA), the brain's principal inhibitory neurotransmitter (6). Low zinc availability can impair GABA synthesis, thereby reducing inhibitory tone and predisposing neurons to hyper excitability (7). These findings suggest that zinc insufficiency may contribute not only to febrile seizures but also to the broader spectrum of seizure disorders, highlighting its fundamental role in neuronal excitability and epileptogenesis.

Over the past two decades, a number of studies have compared serum zinc levels in children with febrile seizures versus febrile children without seizures (3, 8). However, the frequency of zinc deficiency in children presenting with simple febrile seizures within our local population remains underexplored, despite varying socioeconomic and nutritional backgrounds that could influence zinc status. Establishing this local evidence is crucial to understanding whether zinc deficiency is a modifiable risk factor contributing to FS incidence in our region. It was unknown whether children with simple febrile seizures in our local population also have a high prevalence of zinc deficiency. Establishing this frequency could help clarify the role of zinc in FS and its management.

Methods

A cross-sectional study was conducted at the Department of Pediatrics, Mardan Medical Complex (MMC), Mardan, Pakistan. The study duration was six months (after approval of protocol), during which patients were enrolled continuously. Ethical approval was obtained from the ethical review board of Mardan Medical Complex and Bacha Khan Medical College (Ref No.403/BKMC) dated 13.10.2023. Sample size was 149 children, determined using WHO sample size software for a single proportion. This calculation assumed an expected zinc deficiency frequency of ~26% among children with simple febrile seizures (based on prior report), with 95% confidence level and 7% margin of error (9). Patients were recruited by non-probability consecutive sampling, i.e. all eligible cases presenting during the study period were included until the sample size was reached. Children aged 3 months to 5 years of either gender who presented with simple febrile seizure (as per operational definition: generalized seizure lasting <15 minutes, with fever> 100.4 ° F and no recurrence within 24 hours) in the previous 24 hours were included. We excluded children who had clinical or laboratory evidence of central nervous system infection, such as meningitis confirmed by lumbar puncture, or a prior history of epilepsy characterized by unprovoked afebrile seizures. Children who had received zinc supplementation or therapy for any reason were also excluded. Additionally, those with known electrolyte imbalances, including abnormal serum sodium (<135 or >145 mEq/L), calcium (<8 or >10 mg/dL), or magnesium (<1.8 or >3.6 mg/dL), were not included. To restrict the study population to cases of simple febrile seizures only, children with focal seizures or other features of complex febrile seizures were excluded. Furthermore, we excluded children with acute illnesses that could affect zinc status, such as severe pneumonia or prolonged diarrhea, to avoid potential confounding due to intercurrent illnesses influencing nutritional status.

Children presenting with febrile seizures at MMC who met inclusion criteria were enrolled after obtaining informed consent from parents. At enrollment, a structured proforma was used to record baseline data: the child's age (in months), gender, weight (kg), residential status (rural vs. urban), family socioeconomic status, parents' educational level, and relevant medical history. Socioeconomic status was categorized (by monthly income and living standards) into three groups: Poor, Middle, and Rich. Parental education level was recorded as Uneducated (no formal schooling), Primary, Secondary, or Higher (college/university). We also recorded clinical details of the seizure: duration of the seizure (in minutes) as reported by attendants or observed (all were <15 min by definition of simple FS), and whether there was any family history of febrile seizures (in siblings or parental history of FS in childhood).

After initial stabilization and evaluation, a blood sample was obtained for zinc measurement. Using aseptic technique, approximately 2 mL of venous blood was drawn (typically from an antecubital vein) using a 22-gauge sterile needle. The sample was sent to the hospital laboratory for serum zinc level analysis. The analysis was performed within 6 hours of collection by a standardized colorimetric method (using an automated chemistry analyzer). Zinc deficiency was defined operationally as a serum zinc level <70 µg/dL, based on the

laboratory reference range and prior literature definitions (10). The zinc level result for each patient was recorded on the proforma. All patients received standard care for febrile seizures (antipyretics, and if needed, acute benzodiazepine for seizure control) irrespective of the study.

Data was entered and analyzed using SPSS version 26. For continuous variables (age, weight, seizure duration, serum zinc level), descriptive statistics were calculated: mean, standard deviation (SD), and ranges. Categorical variables (gender, residence, socioeconomic group, parental education, family history of FS, and zinc deficiency status) were summarized as frequencies and percentages. The primary outcome was the frequency of zinc deficiency in children with simple FS, presented as percentage with 95% confidence interval (CI). We performed stratified analyses to examine zinc deficiency rates within subgroups: specifically, we stratified by age (e.g. ≤2 years vs. >2 years), gender, weight (e.g. lower half vs upper half by median), family history of FS (yes/no), seizure duration (e.g. ≤5 min vs >5 min), socioeconomic status (poor/middle/rich), parentaleducation(uneducated/primary/secondary/higher), and residential background (rural/urban). For each factor, the proportion of children with zinc deficiency in each category was compared. A chi-square test was applied to assess any significant association between that factor and zinc deficiency (e.g. difference in deficiency rates between males and females, etc.). For chi-square analysis, $p \leq 0.05$ was considered statistically significant. All results are presented in tabular and narrative form.

Results

A total of 149 children with simple febrile seizures were included. The children's ages ranged from 3 months to 60 months, with a mean age of 26.2 ± 15.4 months. Nearly two-thirds were under 2 years old; 50% of cases occurred in infants (under 1 year) and the remaining in toddlers and preschoolers. There were 90 male (60.4%) and 59 female (39.6%) patients, yielding a male: female ratio of ~1.5:1. The mean weight of the children was 12.0 ± 4.1 kg (range 4.5–20 kg). By design, all seizures were generalized tonic-clonic in nature and brief; the mean seizure duration was 4.3 ± 2.5 minutes. No child had a seizure lasting beyond 15 minutes or more than one seizure in 24 hours (consistent with inclusion criteria for simple FS). Approximately 30% (n=45) of the children had a family history of febrile seizures (typically an older sibling or a parent with febrile seizures in childhood), whereas 70% had no such history.

In terms of socioeconomic profile, about half of the children (n=75, 50.3%) were from low-income (poor) families, 50 (33.6%) from middle-class families, and 24 (16.1%) from higher-income families. Parental education levels varied: the parents of 45 children (30.2%) had no formal education, 45 (30.2%) had only primary level education, 37 (24.8%) had secondary-level education and 22 (14.8%) had higher (college/university) education. The majority of patients (n=90, 60%) were from rural areas, with the remaining 59 (40%) residing in urban areas.

Out of 149 patients, 80 children had serum zinc < 70 µg/dL, corresponding to a zinc deficiency frequency of 53.7%. Thus, over half of the children with FS in this sample were zinc-deficient by the given criterion. The remaining 69 children (46.3%) had normal serum zinc levels (≥ 70 µg/dL). The mean serum zinc level in the cohort was 68.4 ± 22.5 µg/dL. Among the 80 zinc-deficient children (62.5%) had markedly low levels

(<60 µg/dL), while the rest were in the mildly low range (60–69 µg/dL).

We examined zinc deficiency rates across various subgroups to see if certain characteristics were associated with a higher likelihood of deficiency. Table 1 summarizes the stratified frequency of zinc deficiency by patient factors, along with the statistical significance (chi-square p-value) for each comparison.

Table 1. Stratified Frequency of Zinc Deficiency (<70 µg/dL) by Demographic, Clinical, and Socioeconomic Characteristics (N = 149)

Factor	Category (n)	Zinc Deficiency n (%)	p-value
Age	≤ 24 months (n = 75)	40 (53.3%)	0.90
	> 24 months (n = 74)	40 (54.1%)	
Gender	Male (n = 90)	48 (53.3%)	0.89
	Female (n = 59)	32 (54.2%)	
Weight*	Lower half(n = 74)	39 (52.7%)	0.80
	Upper half (n = 75)	41 (54.7%)	
Family History of FS	Yes (n = 45)	22 (48.9%)	0.43
	No (n = 104)	58 (55.8%)	
Seizure Duration	≤ 5 minutes (n = 100)	55 (55.0%)	0.66
	> 5 minutes (n = 49)	25 (51.0%)	
Socioeconomic Status	Poor (n = 75)	50 (66.7%)	0.03
	Middle (n = 50)	24 (48.0%)	
	Rich (n = 24)	6 (25.0%)	
Parental Education	Uneducated (n = 45)	34 (75.6%)	0.04
	Primary (n = 45)	25 (55.6%)	
	Secondary (n = 37)	15 (40.5%)	
	Higher (n = 22)	6 (27.3%)	
Residential Area	Rural (n = 90)	48 (53.3%)	0.91
	Urban (n = 59)	32 (54.2%)	

In each subgroup, the number and percentage of children with zinc deficiency are shown. Chi-square tests were used to compare deficiency proportions across categories for each factor. The occurrence of zinc deficiency was broadly distributed across age and gender groups. The notable risk factors for zinc deficiency within our FS cohort were related to socioeconomic and educational parameters: children from less-advantaged families were significantly more likely to have low zinc, whereas clinical factors such as seizure characteristics or family history of FS showed no significant influence on zinc status.

Discussion

In our study, more than half of the children presenting with simple febrile seizures were found to have zinc deficiency, with a frequency of 53.7%, highlighting a substantial burden of suboptimal zinc status among this population. The mean serum zinc level (68.4 ± 22.5 µg/dL) was below the normal threshold, supporting the hypothesis that inadequate zinc may play a contributory role in the pathophysiology of febrile seizures. zinc deficiency in our cohort was not significantly influenced by age, gender, or seizure duration, suggesting that biological factors alone may not fully explain this association. Instead, socioeconomic disparities and parental education emerged as significant correlates, with children from lower-income families and those whose parents had limited formal education showing markedly higher rates of deficiency. This pattern reinforces that nutritional and socioeconomic determinants contribute

meaningfully to micronutrient deficiencies and related neurological outcomes in pediatric populations.

Our findings align with a large body of research indicating an association between lower zinc levels and febrile seizures. Multiple cross-sectional studies across different countries have demonstrated that children who experience febrile seizures tend to have significantly lower serum zinc concentrations than febrile children who do not seize(8). In a study conducted in Iran, a significant difference was observed between the case and control groups regarding hypozincemia ($P < 0.05$), with 53.81% of children in the febrile seizure group and only 9.6% in the control group found to have low serum zinc levels. These findings align closely with the present study, where over half (53.7%) of children with simple febrile seizures exhibited zinc deficiency (11).The consistency of these results across different populations suggests that hypozincemia may playa contributory role in the pathophysiology of febrile seizures. This reinforces the hypothesis that reduced serum zinc levels may lower the seizure threshold, thereby increasing susceptibility to febrile convulsions.

Similarly, another study conducted in Iran by Mehri Tahery et al. reported that the mean serum zinc level in the febrile seizure group (70 µg/dL) was significantly lower than in the control group (90 µg/dL) ($P < 0.001$) (12). Comparable findings were observed in a study from Multan, Pakistan, where 26% of children with febrile seizures were zinc-deficient, supporting the notion that zinc deficiency could be a potential risk factor for febrile seizures in children(9) These consistent findings across diverse regions, including the current study, emphasize the importance of assessing zinc status in pediatric patients presenting with febrile seizures, especially in populations with prevalent nutritional deficiencies.

A comprehensive meta-analysis (2020) including 31 studies concluded that serum zinc is significantly lower in children with febrile seizures compared to those without, with a large effect size. This meta-analysis effectively consolidates the evidence and suggests that the association is real and not merely a publication bias (13). Our study adds further support, demonstrating a high rate of zinc deficiency in FS patients in our locale.

Conclusion

The high frequency of zinc deficiency among FS patients, together with evidence from other studies, suggests that zinc insufficiency may be an important contributing factor in the pathogenesis of febrile seizures. Children with poorer nutritional and socioeconomic backgrounds were especially likely to be zinc-deficient, highlighting the interplay between nutrition and neurological conditions like FS. These findings encourage healthcare providers to be mindful of the nutritional status (particularly trace elements) in children who experience febrile seizures.

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