

Determinants of Febrile Seizures with special reference to Serum Electrolytes, Glucose, Calcium and Zinc: A Case Control Study

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Abstract

Background: Febrile seizure is an important cause of hospitalisation and morbidity among toddlers and young infants. Various studies have been undertaken in the past to find the association between febrile seizures and several biochemical parameters such as serum Sodium, serum Albumin etc.

Objectives: To study the association between levels of serum sodium, calcium, potassium, glucose, zinc and febrile seizures.

Methods: This hospital based case control study included patients aged 6 months to 5 years admitted with fever and seizures at a tertiary care teaching hospital over a period of 6 months. Baseline demographic parameters were collected and serum Sodium, Potassium, Calcium, Zinc and random blood sugar estimation was done.

Results: A total of 100 cases and 100 controls were included (boys:girls = 2:1). Mean age of cases was 22.39 months while that of controls was 23.29 months. Mean Serum Sodium, Serum Potassium and Serum Zinc levels were found to be lower among cases which was statistically significant. No significant difference could be found between the two groups with respect to mean Random blood sugar and mean serum Calcium.

Conclusions: Serum Sodium, serum Potassium and serum Zinc levels are significantly lower among children with febrile seizures in comparison to children with fever without convulsion, indicating that deficiency of Sodium, Potassium and Zinc play significant role in the pathogenesis of febrile seizures. There is significant lack of awareness regarding febrile seizure and intermittent prophylaxis of febrile convulsion among the parents. Serum sodium level and serum calcium level are predictors of recurrence of febrile seizure.

Keywords: Febrile Seizure; Serum Calcium; Serum Potassium; Serum Sodium; Serum Zinc.

Introduction

Febrile seizures are the seizures that occur between the ages of 6 and 60 months (peak 12-18 months) with a temperature of 38°C (100.4°F) or higher, that

are not the result of Central Nervous System (CNS) infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures.¹ Between 2-5% of neurologically healthy infants and children experience at least one, usually simple febrile seizure. Although approximately 15% of children with epilepsy have had febrile seizures, only 5% (range 1-33%) of children who experience febrile seizures proceed to develop epilepsy later in life.^{2,3} A positive family history for febrile seizures can be elicited in 25-40% of children with febrile seizures, and the reported frequency in their siblings ranges from 9-22%.⁴

Among the serum electrolytes, sodium is an important factor in neuronal cell depolarization and production of electrical discharge and

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finally seizures.⁵ Even in animals, reduced serum sodium levels have been shown to lower the threshold to convulsive stimuli. No study to date has demonstrated a benefit of anti-pyretic use in decreasing the incidence of recurrence of febrile seizures. This suggests that fever is not the only factor involved in the etiology of febrile convulsion. However, American Academy of pediatrics (AAP) does not recommend blood evaluations such as serum electrolytes, calcium, zinc and blood glucose unless clinically indicated.⁶

Considering the contradictory reports and the importance of pediatric febrile seizures, this study was conducted to investigate the role of serum sodium in febrile seizures. If relative hyponatremia is predictive of seizure recurrence in febrile seizures, sodium replacement and fluid restriction might be indicated in selected patients. However, serum potassium levels in different studies showed no statistically significant differences.^{7,8} Studies have shown different (often inconclusive) results for an association between reduced serum calcium and febrile seizure. Excitatory post synaptic transmissions that occur with very low calcium levels lead to uncontrolled epileptiform discharges on electroencephalogram. In the brain, hundreds of intracellular processes are known to depend on serum calcium.⁹ Hence this study was conducted with an objective to study the association between serum electrolytes and febrile seizures.

A number of trace elements are said to play a role in febrile convulsions by their coenzyme activity or ability to influence ion channels and receptors. Zinc acts as a co-factor of glutamic acid decarboxylase, an enzyme which maintains the production of gamma amino butyric acid (GABA) in central nervous system and decrease level of Zinc in Cerebro Spinal Fluid (CSF) has also been observed in febrile seizures. In CNS, Zinc acts as a neuro-secretory product. Zinc is highly concentrated in the synaptic vesicles of a specific contingent of neurons called "zinc containing neurons". Recent evidences indicate that deficiency of zinc can play significant role in febrile seizures.¹⁰ Therefore with regard to importance of febrile seizure and its possible contributing factors including serum zinc level, this study was conducted to compare the serum Zinc levels in children with febrile seizures in comparison with febrile children without seizures.

Objectives

This present study has been undertaken with the following objectives:

- To study the association between levels of serum sodium, calcium, potassium, glucose, zinc and febrile seizures.

Material and Methods

This is a hospital based case control study carried out among patients of febrile seizures and age-sex matched controls attending the Department of Pediatrics of a tertiary care teaching Hospital of Central Odisha. It was carried out from March 2019 to October 2019. Sample size was calculated basing on the hospital based prevalence of febrile seizures every month. Data was collected on every alternate day from patients admitted to the wards of Department of Pediatrics with febrile seizures. Nearly 10-12 cases/controls could be investigated each week and a face-to-face interview was conducted using pre-tested, pre-designed semi-structured questionnaire. So, in a five months' time of data collection we could obtain a total of 104 cases and 101 controls and the final analysis was done using 100 cases and 100 controls. Children aged between 6 months and 60 months of either sex presenting with fever with seizure to OPD and Casualty of Department of Pediatrics were regarded as cases and children with fever of any etiology without seizures were regarded as controls. Cases with the following conditions were excluded from the study such as:

- Gastrointestinal diseases leading to electrolyte imbalance
- CNS infections like meningitis and encephalitis
- Neurological or structural abnormalities in the brain or skull
- Protein Energy Malnutrition
- Children on Zinc Supplements

Informed consent of parents of both groups of children was obtained in the vernacular language. Institutional ethical committee certificate was obtained prior to the study.

Prior to inclusion of the children in the study, a detailed history of presenting complaints was recorded including duration of fever, time of onset of seizures, type of seizures, duration of seizures, past history of febrile convulsion, family history of febrile convulsion, awareness about febrile convulsion and about intermittent prophylaxis. In addition to this, history suggestive of any triggering factors for febrile episode like cough, cold, nasal discharge, ear discharge, burning micturition or

crying during micturition were also recorded.

Vital signs such as heart rate, respiratory rate, oxygen saturation, blood pressure were measured and recorded. The axillary temperature was recorded in all children with digital thermometer placed in axilla for three minutes.

Four milliliters of whole blood was collected by venipuncture under strict aseptic precautions and sent to biochemistry laboratory of our hospital for assessment of serum electrolytes (sodium, potassium and calcium) and serum zinc.

Random blood sugar (RBS) was measured by glucometer by capillary method taking blood from tip of middle and 4th finger. Hypoglycemia was considered if RBS <54mg/dL.

Socio-economic status of the family of both cases and controls was determined by Modified Kuppuswamy scale updated for 2017.¹¹

Statistical Analysis

Data were entered using Microsoft excel 2010 and analyzed using statistical package for Social Sciences version 21. Descriptive statistics were used and results were expressed as mean (standard deviation) or frequencies and percentages. Categorical variables were compared using Pearson's chi-square test. Comparison of means

was done using independent T-test and P-value <0.05 was taken as significant.

Results

The mean age of cases was 22.39 (± 13.94) months and the mean age of controls was 23.29 (± 23.29 months). The male:female ratio was similar in both groups i.e. 2.125:1 (cases) and 2.03:1 (controls). The mean duration of fever in the study among the cases was 1.99 (± 1.068) days and among the controls was 2.16 (± 1.080) days. 64% of them presented with first episode of febrile seizure whereas 36% of the children had previous episodes of febrile seizure. Only 8% of them had family history of seizure. 64% of parents were previously unaware regarding the febrile seizure and its prevention. Among children with previous history of febrile seizure, 95% of them were not taking intermittent prophylaxis for febrile seizures.

Table 1 shows the differences between cases and controls with respect to various investigations carried out in them. Mean Serum Sodium, Serum Potassium and Serum Zinc was found to be lower among cases which was statistically significant. No significant difference could be found between the two groups with respect to mean Random blood sugar and mean serum Calcium.

Table 1: Comparison of Various Parameters of Investigations Among Cases and Controls (n=200).

| Investigations | Cases (Mean ± SD) | Controls (Mean ± SD) | P Value (Independent T Test) |
|--------------------|-------------------|----------------------|------------------------------|
| Random Blood Sugar | 108.83 ± 19.31 | 111.45 ± 16.64 | 0.30 |
| Serum Sodium | 137.29 ± 5.02 | 140.02 ± 3.79 | <0.001 |
| Serum Potassium | 4.78 ± 0.10 | 4.94 ± 0.21 | <0.001 |
| Serum Calcium | 1.03 ± 0.10 | 1.02 ± 0.10 | 0.25 |
| Serum Zinc | 57.13 ± 20.46 | 77.25 ± 18.74 | <0.001 |

Table 2 shows the association of different socio-demographic variables. 83% of cases belonged to low SES which was significantly different than the controls among which only 71% belonged to low SES (p=0.04, OR 1.99, 95% CI 1.01-3.92). Parent who were just literate i.e. 46% were found to have significantly higher proportion of children with febrile seizures than compared to those who

were more educated (P=<0.001, OR 1.92 95% CI 1.92-6.85). It was also seen that parents who were unaware regarding the disease, its management and prevention were less educated compared to those who were more educated. Only 13.6% of parents who were aware regarding the disease and its prevention strategies gave the intermittent prophylaxis for prevention of seizures.

Table 2: Association Between Clinical and Social Factors Among Cases and Controls (n=200)

| | Low Ses | Other Ses | P -Value | OR (CI) |
|----------|---------------|-----------|----------|------------------|
| Cases | 83 (83) | 17 (17) | 0.04 | 1.99 (1.01-3.92) |
| Controls | 71 (71) | 29 (29) | | |
| | Just Literate | Others | P-Value | Or (CI) |
| Cases | 46 (46) | 54 (54) | <0.001 | 3.63(1.92-6.85) |
| Controls | 19 (19) | 81 (81) | | |

| | | | | |
|------------------------|------------------------------------|--------------------------------|----------------|------------------|
| Awareness absent | 24 (37.5) | 40 (62.5%) | 0.02 | 0.38 (0.16-0.88) |
| Awareness present | 22 (61.1%) | 14 (38.9%) | – | – |
| Not taking Prophylaxis | 43 (45.3%) | 52 (54.7%) | 0.51 | 0.55 (0.08-3.45) |
| Taking Prophylaxis | 3 (60%) | 2 (40%) | | |
| Characteristics | Not Taking Prophylaxis N(%) | Taking Prophylaxis N(%) | P-Value | OR(CI) |
| Awareness absent | 64(100) | 0(0) | 0.002 | 1.16 (1.01-1.32) |
| Awareness Present | 31(86.1) | 5(13.9) | | |
| Male | 66 (97.1) | 2(2.9) | 0.16 | 3.4 (0.54-21.5) |
| Female | 29(90.6) | 3(9.4) | | |

Table 3: Comparison of Parameters of Various Investigations Done with History of Previous Convulsion Among Cases (n=100).

| Investigations | Recurrent of Episode Febrile Seizure | First Episode of Febrile Seizure | P-value (Independent T-test) |
|-----------------|--------------------------------------|----------------------------------|------------------------------|
| Serum Sodium | 135.21 4.92 | 138.47 4.72 | 0.02 |
| Serum Potassium | 4.71 0.52 | 4.810.41 | 0.29 |
| Serum Calcium | 0.97 0.09 | 1.07 0.09 | < 0.001 |
| Serum Zinc | 56.73 19.22 | 57.36 21.28 | 0.88 |

We found mean serum sodium among the cases who presented with first episode of febrile convulsion was 138.47 (4.72) mEq/L which was significantly higher ($p=0.02$) than those who had recurrent episodes of febrile seizures. Similarly, serum calcium was significantly higher in those cases who presented with first episode of febrile seizure than those who had repeated episodes. The difference in serum values of Potassium and Zinc between patients with first episode and recurrent episodes of febrile seizures was not found to be statistically significant.

Discussion

The mean age of cases was 22.39 months and that of controls was 23.29 months which was similar to the findings in other studies.¹² We found only 8% with family history of febrile seizures contrary to the findings of other studies where 57% of cases had a positive family history of febrile seizures. Only 3 out of 10 parents were aware of febrile seizure, its management and prevention. Lack of awareness regarding febrile seizures among parents led to providing intermittent prophylaxis in only 5% cases.

The mean of serum sodium among cases was found to be 137.29 with a significant difference when compared to controls which was similar to other studies.^{12,13} On the contrary, some other studies did not find any significant difference in the levels of Serum sodium between cases and controls.^{14,15} Our study found a significant difference in levels of potassium between cases and controls similar to other studies. We did not find a significant difference in serum levels of potassium

among cases and controls similar to some other studies.^{16,17} Different studies carried out in different parts of the world have showed a similar result of serum zinc being significantly different between cases and controls.¹⁸⁻²⁴

We found a relative hyponatremia in cases of recurrent febrile seizures when compared to those who had first episode of febrile seizures similar to other studies.^{14,25} Serum calcium was found to be significantly low among cases with previous episode of febrile seizure which has also been seen with other studies.¹⁷

The limitations of the present study are

- A larger sample size and involvement of multiple centres could have increased the external validity of the study.

Conclusions

This study shows that, among children with febrile seizures, serum Sodium, serum Potassium and serum Zinc levels are significantly lower in comparison to children with fever and without convulsion, indicating that deficiency of Sodium, Potassium and Zinc play significant role in the pathogenesis of febrile seizures. The role of zinc in febrile convulsions should be investigated by further studies and if the results are reproducible, zinc supplementation can be given for prophylaxis of febrile seizures. This study also shows that there is significant lack of awareness regarding febrile seizure and intermittent prophylaxis of febrile convulsion among the parents. It is also concluded from this study that, serum sodium level and serum calcium level are predictors of recurrence of febrile seizure.

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Conflicts of Interest: None

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