Original Article

Simple febrile seizures in toddlers: Do they have low serum calcium levels?

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ABSTRACT

Objective: The objective of the study was to study the serum calcium levels at presentation in two subgroups of febrile toddlers; one with and the other without febrile seizures. **Materials and Methods:** This observational, cross-sectional study was conducted in a tertiary care center. The mean serum calcium level was compared at presentation between the two subgroups of febrile toddlers; one group with and the other without febrile seizures during the presentation for current illness. Based on a previous study of micronutrients in febrile seizures and a pilot study from our center, a sample size of 35 toddlers in each group was included in the study. Main outcome measure was to see the number of children with serum calcium less than 9 mg/dl in each group and compare the proportions for any significant difference. **Results:** Serum calcium levels of less than 9 mg% was seen in 13 (37.1%) toddlers who presented with febrile seizures compared to the group of febrile toddlers without seizures 7 (20%). The difference was statistically significant ($p<0.001$). **Conclusion:** Our study noted a significant proportion of low serum calcium levels of less than 9 mg/dl in patients presenting with febrile convulsions when compared to controls.

Key words: Febrile seizure, Febrile toddler, Serum calcium, Simple febrile seizure

Febrile seizures are the most common seizures encountered in childhood and are a major cause of concern to the parents and caregivers. Although very common, they remain one of the least understood disorders of childhood. Febrile seizures are prevalent in all ethnic groups; however, seen more commonly among Indian children a with prevalence of 5–10% [1]. The peak incidence of febrile seizures is between 12 and 18 months with a progressive decrease [2].

Febrile seizures occur between the age of 6 and 60 months with a temperature of 38°C (100.4°F) or higher, with no underlying central nervous system infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures [3]. A simple febrile seizure is a primary generalized, usually tonic–clonic, attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24 h period [3]. A complex febrile seizure is more prolonged (>15 min), is focal, and/or reoccurs within 24 h [3]. Febrile status epilepticus is a febrile seizure lasting longer than 30 min [3].

The disease has been studied extensively; however, the exact pathophysiology remains elusive. Association between febrile seizures and calcium is explored all over the world, results being conflicting. In one of the case control study from South India, a definite association was found between serum calcium levels and the occurrence of febrile seizures. Although serum calcium levels were not in the hypocalcemic range, they were decreased enough to cause a statistical significance in precipitating febrile seizures [4]. However, these studies have included all types of febrile seizures without the stratification of simple and complex febrile seizure. This study was aimed toward establishing any association between serum calcium levels with simple febrile seizures.

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MATERIALS AND METHODS

It is an observational study which was conducted at a tertiary care hospital in Western India over a period of 18 months after taking approval of Institutional Ethical Committee. Based on a study of micronutrients in febrile seizures [5] and a pilot study conducted at a tertiary health care center, mean serum calcium in the Group 1 (Febrile toddler with seizure) was taken as 9.0 mg/dL while in Group 2 (Febrile toddler without Seizure) was taken as 9.5 mg/dL. Based on the above, the sample size was calculated by two-tailed test and the sample size in each arm was found out to be 28 in each arm. Considering possible 25% chance of exclusion due to changed diagnosis (e.g., meningitis, electrolyte abnormalities, and encephalitis), a minimum of 35 toddlers in each arm were included in the study.

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All consecutive febrile toddlers presenting with fever more than 38°C (100.4 F), which was either recorded at arrival or was recorded by parents, were included in the study. Children with history of simple febrile seizure, first episode or recurrence, seen at outpatient department, day care or admitted in ward within 24 h of fever with seizures (majority of the children are brought within 2 h by the parents) were included in the study.

Those with identifiable cause such as meningitis, encephalitis, and cerebral malaria (changed diagnosis from febrile seizures), children with known metabolic disorders, concurrent detection of hypo/hypernatremia /hypocalcemia/ hypoglycemia in the same, timed sample, malnourished children (Wt <–2 Z score weight for age/sex), developmental delay, history of birth asphyxia, history of previous unprovoked seizure, cerebral palsy, or presence of any focal neurological deficit were excluded from the study.

This study was conducted after taking approval of Institutional Ethical Committee. Written informed consent was obtained from parents/guardians of all the participants. Febrile toddlers presenting with seizures and those presenting without seizures were clinically examined to rule out any other systemic illness or syndromes. Laboratory investigations (hematology and biochemistry) along with serum calcium levels were sent within 1st h of arrival. Sampling for serum calcium was timed with the routine investigations at arrival to avoid additional venupuncture.

Serum levels of calcium were measured using an autoanalyzer device – Siemens Dimension Xpand plus which worked on the principle of spectrophotometry. Since, serum albumin levels are known to affect the measured serum calcium values, corrected serum calcium was used for statistical analysis. The corrected serum calcium levels were calculated based on the following formula: Calcium (corrected) = Calcium (measured) + {0.8 x (4 – Serum Albumin)}. Comparison of means between two independent samples for serum calcium was calculated by student's t-test. Proportion of toddlers presenting with low serum calcium levels was compared using Fisher's exact test.

RESULTS

The study population consisted of 28 males and seven females in Group 1 and 24 males and 11 females in Group 2 (p=0.205). The mean age, height, head circumference, weight, and maximum temperature of febrile toddlers in both the groups were comparable (Table 1).

In Group 1, no focus was found in 17 (48.57%) while in 15 cases (42.85%) focus of infection was an upper respiratory tract infection. In Group 2, upper respiratory tract infection was the focus of infection in 12 cases (34.28%). There was history of NICU stay in 3 (8.6%), prior history of febrile seizures in 5 (14.3%) toddlers and family history of febrile seizures was present in 2 (5.6%) toddlers. The mean serum corrected calcium in Group 1 was 9.09±0.43 mg/dL while it was 9.14±0.40 mg/dL in Group 2 (p=0.627) (Table 2). The serum calcium in febrile toddlers with seizures was <9 mg/dL in 13 (37.14 %) as compared to febrile toddlers without seizures in which serum calcium was <9 mg/dL in 7 (20%) (p=0.001).

Table 1: Baseline characteristics of the study population

Characteristics, Mean (SD)	Group 1 (n=35)	Group 2 (n=35)	p-value
Age (months)	22.49 (8.66)	24.06 (8.54)	0.447
Height (cm)	85.47 (9.13)	83.33 (10.55)	0.366
Weight (kg)	11.29 (2.04)	10.70 (2.29)	0.251
Head circumference (cm)	47.13 (1.98)	47.26 (2.12)	0.794
Maximum temperature (°F)	101.77 (0.71)	101.99 (0.95)	0.278

Table 2: Mean serum calcium, albumin, and hemoglobin levels

Lab Parameters, Mean±SD	With seizure	Without seizure	p-value
Serum calcium (mg/dL)	9.09±0.43	9.14±0.40	0.627
Serum ALBUMIN (g/dL)	3.9±0.3	3.6±0.5	0.656
Hemoglobin (g %)	10.7±1.7	10.5±1.7	0.179
Serum sodium (mEq/dL)	137.9±3.1	139.7±4.9	0.452

DISCUSSION

Our study evaluated the serum calcium in two subgroups of febrile toddlers aged between 1 and 3 years of age with or without seizures at presentation. Baseline characteristics were comparable in both the groups. Patients presenting with febrile seizures were checked for the antecedent cause of fever. It was noted that 15 patients amounting to 42.85% of the febrile seizure group were affected with upper respiratory infection. Other identified causes included gastroenteritis and urinary tract infection. Multiple etiologies have been noted in causation of febrile convulsions in the literature.

In our study, the proportions of children with serum calcium values <9 mg% were significantly higher in febrile seizure group as compared to the other group (p<0.001). However, serum calcium levels were never in the hypocalcemic range to be labeled as hypocalcemic seizures. Although the mean serum calcium levels were lower in the febrile seizure group, it was statistically not significant. Akbayram *et al*. [6] noted that serum calcium, magnesium, and potassium concentrations in children with febrile seizure were lower than those without any febrile seizure. Sharawat *et al*. [7] also noted lower levels of calcium in patients presenting with febrile convulsions when compared to the controls.

Association between febrile seizures and calcium is explored all over the world, results being conflicting. In one of the case control study from South India, a definite association was found between serum calcium levels and the occurrence of febrile seizures. The serum calcium levels were not in the hypocalcemic range; however, they were reduced enough to cause a statistical significance in precipitating febrile seizures [4]. In another study from Maharashtra, no correlation was found between low serum calcium levels and febrile seizures [8]. Another Indian study has reported a significantly low ionized calcium levels in children

with febrile seizures [9]. Similar studies have also been conducted in other parts of the world and a similar association between low serum calcium levels and febrile seizures was found [5].

The possible mechanisms such as role of L-type voltage-gated calcium channels which may modulate firing rates of pyramidal neurons in a temperature-dependent manner, suggesting that these channels may contribute to a state of hyperexcitability during febrile episodes [10].

This study adds to the evidence toward ensuring Vitamin D and calcium adequacy which might have a role in reducing the incidence of febrile seizures. The ionized serum calcium and Vitamin D levels were not included in this study as many peripheral hospitals are only equipped with limited resources. However, calcium and Vitamin D can be supplemented orally following an episode of simple febrile seizures at such centers. The study has its limitation due to a small sample size and non-inclusion of ionized calcium and Vitamin D levels which could have further added to the evidence and thus warrants for further studies.

CONCLUSION

Our study noted a significant incidence of low serum calcium levels of less than 9 mg/dl in patients presenting with febrile convulsions when compared to controls. However, the mean serum calcium levels were lower (9.09 mg/dL) in the febrile seizure group; it was statistically not significant. The external validity of this study is limited in view of small sample size, lack of follow-up and study not going to the domain of effect of calcium supplementation. However, further studies should be conducted in this regard.

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