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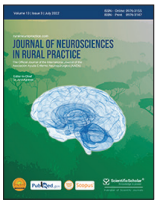

Original Article

Serum magnesium level in febrile children with or without simple febrile seizures from 6 months to 5 years of age: A case-control study

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ABSTRACT

Objectives: Febrile seizure is the most common type of seizure (2–4%) in children. Imbalance in electrolytes, especially hypocalcemia and hypomagnesemia predispose to all seizures, including febrile seizures. The objective of this study was to compare the serum electrolytes, especially magnesium levels in febrile children presenting with and without episodes of simple febrile seizure.

Materials and Methods: An institution-based age- and sex-matched case-control study done between May and October of 2022, involved 60 children aged 6 months to 5 years, divided into 30 cases (febrile children with seizure) and 30 controls (febrile children without seizure). Detailed history including past, birth, and family history was obtained, and serum magnesium, sodium, potassium, and calcium level estimations were done for each participant.

Results: The mean serum magnesium of the febrile seizure group was 1.6 ± 0.8 mg/dL, while that for the control group was 2.2 ± 0.3 mg/dL. Similarly, the mean serum calcium levels of the study participants recruited to the febrile seizure group was 8.4 ± 1.1 mg/dL, while that for the participants recruited to the control group was 9.4 ± 0.5 mg/dL. On analysis, it was seen that the serum magnesium and calcium levels were significantly lower among cases than controls ($P < 0.001$). However, participants did not differ significantly between the two groups with respect to serum sodium and potassium levels.

Conclusion: Mean serum magnesium and calcium levels of children suffering from simple febrile seizures were significantly lower than that of the control children, therefore maintaining optimum serum magnesium and calcium levels should be prioritized in febrile children to prevent the development of simple febrile children among them febrile seizure.

Keywords: Calcium, Child, Magnesium, Febrile, Seizure

INTRODUCTION

The term "febrile seizure" refers to the occurrence of seizures in children aged 6–60 months with fever (temperature 38°C or higher), that is not the result of any central nervous system (CNS) infection or metabolic imbalance and occur in the absence of a history of prior afebrile seizures.[1] Febrile seizures occur in around 2–4% of all healthy children, making them the most commonly encountered childhood type of seizure in daily pediatric practice.[2] Furthermore, there is a risk of recurrence in about one-third of children with febrile seizures. This makes febrile seizure an important clinical condition from the perspective of prevention to ensure better health of the children.[3]

It has been observed that children with febrile seizures often have certain imbalances with respect to their blood levels of elemental ions such as sodium (Na+), potassium (K+), calcium (Ca2+), and magnesium (Mg2+). Any change in the gradient of these ions across the cellular membranes of the CNS can result in a direct or indirect impact on the electric potential in the neurons. This can lead to inappropriate firing of the neurons, leading to the development of convulsion-like situations.[4]

Magnesium acts as a chemical gatekeeper, reducing acetylcholine release at the neuromuscular junction by antagonizing calcium ions at the presynaptic junction. This reduces the excitability of the nervous tissue, so it acts as a potent anticonvulsant. Therefore, a deficiency of magnesium within the body can cause a hyper-influx of calcium ions into the nerve tissues, rendering them excitable, which might lead to the development of seizures.[5] Furthermore, the extracellular magnesium produces a voltage-dependent block after binding to the N-methyl-D-aspartate (NMDA) receptor, resulting in decreased glutamate synaptic transmission and preventing neuronal hypersensitivity.[6]

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India, the second most populous country in the world has a significant burden of febrile seizures. Added to this are the widespread superstitions among rural Indians regarding seizures in general, which further complicate the cases for pediatricians. Therefore, prevention of febrile seizures is the best management, especially in the Indian scenario.[7] However, there is a significant scarcity of data regarding the imbalances of different trace elements, especially magnesium in the children affected with febrile seizures in India. However, this study was intended to compare the serum electrolyte levels, particularly magnesium among febrile children presenting with and without an episode of simple febrile seizure.

MATERIALS AND METHODS

An institution-based age- and sex-matched case-control study done between May and October of 2022, involved 60 children aged 6 months to 5 years, divided into 30 cases (febrile children with seizure) and 30 controls (febrile children without seizure), at the department of pediatrics, at the tertiary care center of western, Rajasthan. Detailed history including past, birth, and family history was taken, and serum magnesium, sodium, potassium, and calcium level estimations were done for each participant.

The sample size was calculated at alpha error 0.05 and study power 90% using the formula for hypothesis testing for two population mean -

$n = [2 \times (Z1\text{-}\alpha/2 + Z1\text{-}\beta)\ 2 \times \sigma 2]/(\mu 1 - \mu 2)2$

Where, n = sample size for each group.

$Z1\text{-}\alpha/2$ = Standard normal deviation for alpha error (taken as 1.96 for alpha error 0.05).

$Z1\text{-}\beta$ = Standard normal deviation for beta error (taken as 1.28 for 90% study power).

$\sigma 2$ = pooled variance of two samples. Calculated as: $\sigma 2 = (s12 + s22)/2$.

Where, s1 = standard deviation (SD) of serum magnesium levels of group 1 and s2 = SD of serum magnesium levels of group 2.

$\mu 1 - \mu 2$ is the difference in serum magnesium level between the two groups.

Using the results reported by Goutham *et al.*, s1 was taken as 0.24, and s2 was taken as 0.20. Considering a difference in means of 0.22, at a study power of 90%, the calculated sample size for each group was 21. This was rounded off to 30, making the total sample for the present study 60 infants.[8]

The study was conducted after receiving clearance from the Institutional Ethics Committee.

Children with any signs of CNS infections, neurodevelopmental delays, liver, renal, or endocrine disorders, and children with visible signs of nutritional deficiencies or signs of micronutrient deficiencies were excluded from the study. Febrile children with or without an episode of simple febrile seizure presenting to the institute during the study duration were considered for the analysis. Of those meeting the inclusion and exclusion criteria, 30 children with febrile seizures were included in the febrile seizure group (group S), and 30 children matched for age and sex were recruited to be controls for the study (group C). On admission, sociodemographic characteristics and a detailed history were recorded for each of the participants which included duration of fever, time of onset, type and duration of seizures, and past history and family history of seizures. All patients then underwent laboratory testing including serum magnesium levels and other ions Na, K, and Ca. The Absorption spectrometry method was used in the assessment of all the electrolytes with the help of BECKMAN COULTER Auto-Analyzer.

Statistical analysis

The collected data were entered into a Microsoft Excel data sheet and analyzed with the statistical program IBM Statistical Package for the Social Sciences, version 22. The data were categorized and expressed in proportions. The continuous data were expressed as mean ± SD. For analytical statistics, $P < 0.05$ was considered to be statistically significant.

RESULTS

The present study was conducted in the Department of Pediatrics, at a tertiary care center in Western Rajasthan over 7 months (from June 2022 to December 2022). During this period, a total of 30 children with simple febrile seizures (group S) and 30 age-matched febrile children without having seizures serving as controls (group C) were included in the study. In our study, the mean age of the participants of the febrile seizure group was 22.6 ± 13.1 months, and that of the control group was 19.8 ± 9.1 months ($P = 0.345$). The sociodemographic distribution of both groups is presented in Table 1. Both groups were statistically comparable for gender ($P = 1.00$), rural-urban distribution ($P = 0.426$), and socioeconomic status ($P = 0.205$).

In our study, the mean duration of fever in the febrile seizure group was 5.0 ± 2.1 days, while was 4.1 ± 2.1 days in the control group (t-value 1.690; $P = 0.096$). About 16.7% of the participants of the febrile seizure groups reported a family history of seizure disorders while none in the control group had such a history ($P < 0.007$). About 66.7% of the participants of the febrile seizure groups had pallor at the time of their presentation, as compared to 16.7% of the control group ($P < 0.001$). Clinical features of both the study and control group are presented in Table 2.

In our study, the mean serum magnesium levels of the study participants recruited to the febrile seizure group were 1.6 ± 0.8 mg/dL, while that for the participants recruited to the control group was 2.2 ± 0.3 mg/dL (*t*-value -4.067; $P < 0.001$). The mean serum calcium levels of the study participants recruited to the febrile seizure group were 8.4 ± 1.1 mg/dL, while that for the participants recruited to the control group was 9.4 ± 0.5 mg/dL (*t* value −4.639; $P < 0.001$). Table 3 shows a comparison of mean serum electrolyte levels in both groups.

The mean serum sodium levels of the study participants recruited to the febrile seizure group was 137.7 ± 6.5 meq/L, while that for the control group was 137.9 ± 2.3 meq/L ($P = 0.855$). The mean serum potassium level of the study participants of the febrile seizure group was 4.4 ± 0.9 meq/L, while that for the control group was 4.1 ± 0.3 mg/dL ($P = 0.293$). However, on analysis, the difference between the mean serum sodium and potassium levels of the participants of the two study groups was statistically not significant.

DISCUSSION

As the ages of the patients were matched, the children of the two study groups were comparable with respect to their age (mean age 22.6 ± 13.1 months for group S and 19.8 ± 9.1 months for group C, with $P = 0.345$). The age at presentation with febrile seizures as was observed in the present study was similar to that reported by Baek *et al.* in their study.[9] The age distribution was, although lower, much like that reported by Mishra *et al.*[10] Regarding the sex distribution, *t* 53.3% of the study participants were male. It has been well established that febrile seizures have a slight male predisposition and similar findings have been reported elsewhere in India as well as globally.[9,10]

When the fever characteristics of the patients in both groups were assessed, it was observed that the mean duration of fever in the febrile seizure group was slightly higher (5.0 ± 2.1 days) than in the control group (4.1 ± 2.1 days) ($P = 0.096$). In a similar case-control study, Kannachamkandy *et al.* also reported similar observations in his study.[11] As evident from the selection of the two groups, the control group patients did not have any episodes of seizure at the time of presentation. However, an important observation made in the present study presence of a family history of seizure in the febrile seizure group (16.7% in Group S vs. 0% in Group C, $P = 0.016$). The assertion that a positive family history of seizure predisposes children to develop febrile seizures subsequently has been made by numerous studies.[11] This phenomenon can be explained by means of the theories of genetic linkage of seizure genes. Twin studies have observed that epilepsy might be genetically linked and hereditary, leading to more children developing seizures, both febrile as well as afebrile when their immediate relatives have had a past history of seizure or epilepsy.[12] Some authors, such as Sawires *et al.*, have opined that the two conditions are related, with a positive family history of epilepsy being associated with 25–40% of children developing an episode of febrile seizure and generalized epilepsy with febrile seizure plus being a familial disorder presenting as febrile seizures in a significant proportion of these patients.[13]

There was a significant difference in clinical pallor in both groups (66.7% in Group S vs. 16.7% in Group C, $P < 0.001$) Kumari *et al.* in their study among children suffering from simple febrile seizures provide evidence to support this assertion, reporting findings that are akin to this study.[14]

A comparison of the serum electrolyte values of the patients of the two study groups revealed significant differences between the two. It was observed that the mean serum magnesium

Table 1: Sociodemographic.

Age (months)	Group S	Group C	*P*-value
Mean	22.6	19.8	0.345
SD	13.1	9.1	
Residence			
Rural	17 (56.7)	20 (66.7)	0.426
Urban	13 (43.3)	10 (33.3)	

SD: Standard deviation, Group S: Children with simple febrile seizures, Group C: Age-matched febrile children without having seizures serving as controls.

Table 2: Clinical features.

Fever duration (days)	Group S	Group C	*P*-value
Mean	5.0	4.1	0.096
SD	2.1	2.1	
Family h/o seizure			
Yes	5 (16.7)	0 (0)	**<0.007**
No	25 (83.3)	30 (100)	
Pallor			
Yes	20 (66.7)	5 (16.7)	**<0.001**
No	10 (33.3)	25 (83.3)	

SD: Standard deviation, Group S: Children with simple febrile seizures, Group C: Age-matched febrile children without having seizures serving as controls. Bold values significant for <0.05.

Table 3: Mean serum electrolyte levels.

Mean serum electrolyte	Group S	Group C	*P*-value
Magnesium (mg/dL)	1.6±0.8	2.2±0.3	**<0.001**
Sodium (mEq/L)	137.7±6.5	137.9±2.3	0.855
Potassium (meq/L)	4.4±0.9	4.1±0.3	0.293
Calcium (mg/dL)	8.4±1.1	9.4±0.5	**<0.001**

Group S: Children with simple febrile seizures, Group C: Age-matched febrile children without having seizures serving as controls. Bold values significant for <0.05

level of the participants recruited to the febrile seizure group was 1.6 ± 0.8 mg/dL, while that for the participants recruited to the control group was 2.2 ± 0.3 mg/dL. The difference between the mean serum magnesium levels of the two groups was found to be statistically significant ($P < 0.001$). Similar to our study, significantly lower serum magnesium levels among children suffering from simple febrile seizures as compared to their normal counterparts were observed by Mishra *et al*. and Talebian *et al*.[10,15] However, Prasad *et al*. (2009) did not observe a significant association between serum magnesium levels and the development of seizures among children in their study, Derakhshan *et al*. found that 25% of children presenting with febrile seizures had laboratory-confirmed hypomagnesemia in comparison to only 3% in the control group.[16,17] More recent research done among Indian children in 2020 and 2022 by Kannachamkandy *et al*. and Sarker *et al*., respectively, reported that a relative deficit of magnesium positively correlated with febrile seizures and those children and children who had lower serum levels of magnesium had a higher risk of developing a seizure episode.[11,18]

Regarding the other serum electrolytes assessed in the present study, while it was seen that the patients suffering from febrile seizures had lower serum sodium and higher serum potassium levels, there was found no statistically significant associations between them and the development of febrile seizures among the assessed children. A comparatively lower serum sodium among babies with simple febrile seizures has been reported by studies such as those conducted by Namakin *et al*. and Pabani and Khanna.[19,20] Similar to that of the serum sodium levels, the serum potassium levels among the participants of the two study groups were found to be statistically comparable. This implies that serum potassium might not have a substantial role to play in the pathophysiology of simple febrile seizures, an assertion that has been supported by the findings of Namakin *et al*.[19]

The role that calcium plays in the development and maintenance of seizure status is well-established. Increased entry of calcium inside the nerve cells leads to the development of seizures by means of lowering the excitation threshold. However, contrary to this, it has been observed that there exists an inverse relationship between neuronal excitability and the level of serum calcium in the body. Called the calcium paradox, this phenomenon is explained by the interplay between the extracellular and intracellular calcium content of the human body. As the different molecular mechanisms and calcium channels of the body are compromised during a stressful event such as the febrile state, there is an influx of calcium from the extracellular space into the intracellular space. This leads to a drop in the levels of extracellular calcium, which presents as relative hypocalcemia. On the other hand, the influx of calcium into the intracellular space of the tissues, especially the nervous tissues leads to the lowering of the action potential, and in turn leads to an excitable state, which predisposes the child toward developing a febrile seizure episode. Evidence toward this assertion has been provided in the present study, where it was seen that the mean serum calcium levels of the patients suffering from febrile seizures were statistically significantly lower than that of the control group patients ($P < 0.001$). Observations regarding relative hypocalcemia and the development of febrile seizures among children have also been made by Sarker *et al*. in their study.[18]

Therefore, the findings of the present study reiterate the importance of lower serum levels of magnesium in the predisposition of children toward the development of febrile seizures. Based on the observations made in the present assessment, it can therefore be said that maintaining optimal serum magnesium and calcium levels should be prioritized in any child suffering from an episode of fever so as to prevent the development of simple febrile seizures among them.

Limitations

The primary limitation of the present study was the small sample size of cases assessed, which limits the generalizability of the study. Another important limitation is that the present study was conducted in only one tertiary care institution due to limited time and resources. A multi-centric study exploring simple febrile seizures would lead to a more representative result.

CONCLUSION

It was observed that the mean serum magnesium and calcium levels of children suffering from simple febrile seizures were significantly lower than that of febrile children without seizures, therefore maintaining optimum serum magnesium and calcium levels in febrile children can prevent the development of simple febrile children among them.

Ethical approval

The research/study approved by the Institutional Review Board at Dr. S. N. Medical College Ethics Committee, number SNMC/IEC/2022/Plan/576, dated 08/06/2022.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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