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Research Article

ASSOCIATION BETWEEN SERUM MAGNESIUM AND CALCIUM LEVELS AND FEBRILE SEIZURES: A RETROSPECTIVE CASE-CONTROL STUDY

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ABSTRACT

Background: Febrile Seizure (FS) is the most common neurological condition in pediatrics. In addition to genetic predisposition, age of onset, temperature, electrolyte imbalances, including serum magnesium and calcium levels, are also widely studied as contributing factors.

Methods: This retrospective case-control study, conducted from February 2020 to February 2021, involved data collection from 142 children with febrile seizures and 142 age- and gender-matched controls with fever but no seizures. Data analysis was performed using SPSS, applying independent t-tests and Chi-square tests.

Results: The mean serum magnesium levels were 0.88 ± 0.1361 mmol/L in the cases and 0.98 ± 0.0804 mmol/L in the controls, with a statistically significant difference ($p<0.001$). The mean serum calcium levels were 2.31 ± 0.1171 mmol/L in the cases and 2.27 ± 0.1009 mmol/L in the controls, also showing a significant difference ($p=0.002$). Hypomagnesemia was detected in a higher proportion of cases compared to controls ($p<0.001$). Conversely, hypocalcemia was found in only one child (0.7%) in both the case and control groups.

Conclusion: Serum magnesium levels were significantly lower in children with febrile seizures than those without. Hypomagnesemia was identified as a risk factor for the occurrence of febrile seizures. Serum calcium levels were significantly higher in the febrile seizure group than in the control group with no significant calcium deficiency in the both groups.

Keywords: febrile seizure, magnesium, calcium, risk factor

INTRODUCTION

Febrile seizure (FS), affecting 2% to 5% of children aged 6 months to 5 years (1), are most common in healthy children when body temperature rises above 38.0°C (100.4°F) without intracranial infections, afebrile seizure and metabolic disorders (2). The peak occurrence is between 12 and 18 months(3). The recurrence rate for febrile seizures is estimated to be between 25% and 30%, with significant risk factors including early age at onset, a family history of febrile seizures, and the height of the fever at the time of the first seizure (4–6) . Understanding the role of electrolyte disturbances alongside these risk factors could provide further insight into the mechanisms underlying febrile seizures and aid in developing more targeted prevention and management strategies.

The link between serum magnesium and calcium levels and the occurrence of FS has been widely studied in pediatric neurology. Research consistently shows that children who experience febrile seizures tend to have lower levels of these critical electrolytes compared to those who do not experience seizures. Magnesium deficiency is associated with neurological disorders such as epilepsy and febrile seizures. Ataei-Nakhaei et al. (2020) found that low serum magnesium levels could heighten seizure susceptibility (7). Magnesium plays a crucial role in inhibiting excitatory neurotransmitters like glutamate and enhancing inhibitory ones such as gamma-aminobutyric acid (GABA). A deficiency in magnesium disrupts this balance, increasing neuronal excitability and seizure risk (8). Furthermore, low magnesium levels may also stimulate the release of acetylcholine and serotonin, which can exacerbate seizure activity (9).

Calcium is crucial for neuronal excitability and seizure activity, as it is vital for neurotransmitter release and neuronal signaling. Changes in intracellular calcium levels can heighten neuronal excitability and synchronization, key characteristics of seizures. The study demonstrated that reduced extracellular calcium can exacerbate seizures in certain brain regions, emphasizing the importance of calcium balance (10). Another research noted that excitotoxic mechanisms involving calcium influx contribute to neuronal damage during seizures, underscoring the need for effective calcium regulation (11). Additionally, a study found significantly lower serum calcium levels in children with febrile seizures compared to controls, suggesting that hypocalcemia may play a role in seizure development (12). Similarly, a study has found lower serum levels of calcium, magnesium, and potassium in children with febrile seizures, suggesting a broader electrolyte imbalance that might increase seizure risk (13). In this study, we compared serum magnesium and calcium levels between children with febrile seizures and those with fever but no seizures to explore the potential link between these electrolytes and the occurrence of febrile seizures.

MATERIALS AND METHODS

This retrospective case-control study was carried out in the Department of Pediatrics at Zhongnan Hospital, Wuhan University, China, spanning from February 2020 to February 2021, following approval from the hospital's Research Ethics Committee. Data were collected from 142 children with febrile seizures and an equal number of age- and gender-matched controls who had fever but no seizures. The study targeted

children aged 6 to 60 months with normal developmental histories. Exclusion criteria included children with congenital defects, central nervous system (CNS) infections, and metabolic disorders.

Data Collection and Laboratory Findings:

We collected data on key patient information such as age at onset, sex, temperature, history of FS, family history of seizures, underlying cause of fever, as well as serum magnesium and calcium levels. Electrolyte levels were measured within 12 hours post-seizure, with abnormal values defined as those falling outside the reference ranges established by our hospital's laboratory: serum magnesium (0.85–1.15 mmol/L) and serum calcium (2.11–2.52 mmol/L)(14).

Data Analysis:

Continuous variables were expressed as mean ± SD, while categorical variables were represented by frequency and percentages. Data coding was performed using SPSS-27 software, with an initial assessment for normal distribution. Group means were compared using the independent t-test, depending on the data distribution. A p-value of <0.05 was considered to indicate statistical significance.

RESULTS

The summary of demographic characteristics for the 284 children (142 cases and 142 controls) enrolled in the study reveals several key findings. The mean age of the cases was significantly lower (30.89 ± 14.5 months) compared to the controls (36.8 ± 16.5 months), with this difference being statistically significant ($p < 0.05$). Gender distribution showed no significant differences, with males being the most prevalent in both groups. The mean temperature in cases was slightly lower (39.1 ± 0.7°C) than in controls (39.5 ± 0.9°C), and this difference was also statistically significant ($p < 0.05$). A history of febrile seizures was notably more common among cases (36.5%) compared to controls (3.5%), and a family history of febrile seizures was exclusively observed in the cases (33.9% vs. 0%). Respiratory tract infections were the predominant cause of fever in both cases and controls, accounting for 99.1% and 100%, respectively, while 0.7% of cases had acute gastroenteritis. Detailed description is shown in Table 1.

The independent t-test analysis showed a significant difference in serum magnesium levels between the two groups. The mean serum magnesium level was significantly lower in the case group (0.88 ± 0.1361 mmol/L) compared to the control group (0.98 ± 0.0804 mmol/L), with a p-value less than 0.05. Furthermore, 40.1% of the cases had hypomagnesemia, defined as serum magnesium levels below 0.85 mmol/L, while only 4.2% of the controls fell into this category. In contrast, serum calcium levels differed significantly between the groups as well. The case group had a higher mean serum calcium level (2.31 ± 0.1171 mmol/L) compared to the control group (2.27 ± 0.1009 mmol/L), with a p-value less than 0.05. However, the prevalence of hypocalcemia, defined as serum calcium levels below 2.11 mmol/L, was similarly low in both groups, at 0.7%. Detailed description is shown in Table 2 and 3.

Variables		Cases (n=142)	Controls (n=142)	P-value
Age (months)		30.9 ± 14.5	36.8 ±16.5	0.003*
Gender	Male	91 (64.1%)	81 (57%)	0.225
	Female	51 (35.9%)	61 (43%)	
Temperature (℃)		39.1 ± 0.7	39.5 ± 0.9	<0.001*
History of FS	Yes	46 (32.4%)	11 (7.7%)	<0.001*
	No	96 (67.6%)	131 (92.3%)	
Family History of FS	Yes	31 (21.8%)	0 (0%)	<0.001*
	No	111 (78.2%)	142 (100%)	
Cause of fever	RTI	141(99.3%)	142 (100%)	0.316
	AGE	1 (0.7%)	0 (0%)	

*p value is significant, if <0.05

Table 1: Comparison of risk factor between cases and controls

Variables	Cases (n=142)	Controls (n=142)	P-value
Magnesium, mmol/L	0.88 ± 0.1361	0.98 ± 0.0804	<0.001*
Calcium, mmol/L	2.31 ± 0.1171	2.27 ± 0.1009	0.002*

*p value is significant, if <0.05

Table 2: Comparison of electrolyte levels between cases and controls

Variables		Cases (n=142)	Controls (n=142)	P-value
Magnesium	Deficiency	57 (40.1%)	6 (4.2%)	<0.001*
	Normal	85 (59.9%)	136 (95.8%)	
Total		**142 (100%)**	**142 (100%)**	
Calcium	Deficiency	1 (0.7%)	1 (0.7%)	1.000
	Normal	141 (99.3%)	141 (99.3%)	
Total		**142 (100%)**	**142 (100%)**	

*p value is significant, if <0.05

Table 3: Comparison of electrolyte deficiencies between cases and controls

DISCUSSION

By demographics, the mean age in cases and controls were 30.9 ± 14.5 months and 36.8 ±16.5 months respectively. Mean age of FS in this study which is similar to another study where mean age of FS was 30.17 ± 14.5 months (15).64.1% was male and 35.9% were female, males were more affected by the febrile seizure which aligns with the study which reported a male-to-female ratio of 1.5:1 among pediatric patients experiencing recurrent febrile seizures (16). In this study, the mean body temperature recorded for the cases and controls were 39.1 ± 0.7°C and 39.5 ± 0.9°C respectively with significant difference (p=<0.001). a study also showed that the mean temperature was lower in the FS group than in the controls (17). For instance, a study has identified that a temperature of less than 40°C during a febrile seizure was linked to a higher risk of recurrence (18).

A study reported that 25-40% of children with febrile seizures have a family history of similar events, indicating a strong genetic predisposition (19). Younger age at the onset of the first febrile seizure and a positive family history of febrile seizures or epilepsy significantly correlated with FS recurrence (18). In the present study, a positive family history of febrile seizures was found in 21.8% of cases, compared to none in the controls, with a significant difference (p<0.001). Additionally, positive past history of febrile seizures was more common in the case group (32.4%) than in the control group (7.7%), also showing a significant difference (p<0.001). Respiratory tract infections emerged as the leading cause of fever, present in 99.3% of cases and 100% of controls, underscoring their role as a common etiological factor (20).

Our study found that serum magnesium levels were significantly lower in children with febrile seizures compared to those with fever but without seizures (p<0.001). Hypomagnesemia was present in 40.1% of the febrile seizure group, compared to just 4.2% in the control group, suggesting a strong

association between magnesium deficiency and febrile seizures in young children. This finding supports the idea that magnesium deficiency may contribute to the pathogenesis of these seizures, consistent with other studies (15)(21) . Research on magnesium sulfate as a treatment has shown promise, with some studies documenting its effectiveness in managing febrile illness-related epilepsy syndrome (22). However, other research found no significant link between serum magnesium levels and febrile convulsions, indicating that routine magnesium supplementation may not be necessary for all cases (23).

Our study found that serum calcium levels were significantly higher in the febrile seizure group compared to the control group (p=0.002), though only one child (0.7%) in each group exhibited calcium deficiency. While many studies suggest that low serum calcium levels are linked to febrile seizures (24), some research has found no significant association, highlighting the need for further investigation into this relationship (25). Additionally, one study reported elevated serum calcium levels in the seizure group compared to controls, but without significant differences (26). The interplay between calcium and other electrolytes has also been explored, with some research indicating that changes in cerebrospinal fluid (CSF) calcium levels may correlate with serum calcium levels, emphasizing the importance of calcium homeostasis in both the serum and the central nervous system (27). This is particularly relevant for febrile seizures, as disruptions in calcium balance could contribute to excitotoxicity and potential neuronal damage.

The nature of the study, including its small sample size and single-center design, limits the generalizability of the findings. To confirm these results, future research with larger and more diverse populations is necessary. This underscores the importance of conducting more extensive, prospective studies to clarify the relationship between electrolyte levels and febrile seizures and to develop standardized clinical guidelines.

CONCLUSION

In summary, this study found that serum magnesium levels were significantly lower in children with febrile seizures compared to those without, with hypomagnesemia being strongly associated with the occurrence of febrile seizures. Additionally, serum calcium levels were higher in the seizure group than in controls, though not to the extent of indicating calcium deficiency. Therefore, larger cohort studies are needed to further investigate this association and establish proper management guidelines for these children.

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