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Calcium and Magnesium Levels in Children with Febrile Seizures Admitted in a Tertiary Care Hospital

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ABSTRACT

Objective: To determine the diagnostic accuracy of hypocalcaemia and hypomagnesaemia in paediatric patients suffering from febrile seizures.

Study Design: Cross-sectional validation study.

Place and Duration of Study: Department of Pediatrics, Pak-Emirates Military Hospital, Rawalpindi Pakistan, Jul 2021 to Feb 2022.

Methodology: We included 87 patients between the ages of 1-6 years with ongoing febrile illness who had a history of febrile seizures. Those with a history of febrile seizures within the last month, suffered from organic brain disease or were on drugs that altered serum calcium and magnesium levels were excluded. Patients were tested for serum magnesium and calcium on admission and remained admitted throughout the febrile period for observation of the development of seizures.

Results: The mean age ± standard deviation of our sample was 3.23±1.50 years, with 46(52.9%) males. The serum magnesium levels demonstrated that 46(52.9%) had hypomagnesaemia at a cut-off of 1.4 mEq/L, which had a sensitivity of 70.3%, a specificity of 55.0% and diagnostic accuracy of 59.8% in predicting the development of febrile seizures. Serum calcium levels at a cut-off of 8.8 mg/dL showed that 36(41.4%) had hypocalcaemia, which carried a sensitivity of 48.2%, a specificity of 61.7% and a diagnostic accuracy of 57.5%.

Conclusion: Both serum magnesium and calcium levels had comparable diagnostic accuracy in predicting whether a patient with a history of febrile seizures would go on to develop febrile seizures during the current illness. However, the individual diagnostic accuracy for this prediction could have been higher.

Keywords: Calcium, Febrile seizures, Magnesium.

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INTRODUCTION

Febrile seizures affect approximately 4% of the global population of children between 0.5 and 5 years and occur without any metabolic disorder or central nervous system infection, making them the most common seizure form in this age group.[1] The disorder occurs because of a complex interaction of cytokines in the setting of pyrexia, resulting in neuronal hyperexcitability.[2] Disturbance in levels of certain trace elements are also claimed to be associated with the propensity to develop febrile seizures, some of which include zinc, copper and selenium.[3,4] The mechanism by which the disturbance in the levels of these electrolytes is thought to cause increased susceptibility may not be associated with the properties of the element itself but with the disturbance in charge across the membrane of the neuron produced due to lack or excess.[5] Other less commonly implicated electrolytes include sodium, potassium, magnesium and calcium; however, the literature available needs to be more consistent, with different studies validating or refuting these elements' role in febrile seizures.[6] In addition, in most of the studies available, the serum electrolyte levels were measured proximal to the occurrence of febrile seizures, and it was unclear whether the electrolyte disturbances were present before seizure development or as a consequence of them.[7,8]

Febrile seizures remain a common malady globally. Efforts to reduce the occurrence of the disorder are aimed at identifying potentially identifiable patient factors that may be associated with the propensity for the development of the disorder.[9] Trace elements such as magnesium and calcium are two such factors, the disturbed levels of which may be associated with the development of febrile seizures.[10] The logic behind this thinking is that if the association between the development of febrile seizures and the altered serum levels of these elements is established, these can be targeted and managed to reduce the frequency of seizures in susceptible individuals. This study was conducted to determine whether low serum levels of calcium and magnesium were useful in predicting the development of seizures during febrile episodes,

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which would help guide future management and research.

METHODOLOGY

The cross-sectional validation study was conducted from Jul 2021 to Feb 2022 in the Department of Paediatrics, Pak-Emirates Military Hospital, Rawalpindi Pakistan. The WHO sample size calculator was used to calculate the sample size, keeping an expected sensitivity of 45.1%, an expected specificity of 92.6%, an expected prevalence of 42.9%.[11]

Inclusion Criteria: Patients of either gender, aged 1-6 years with a history of febrile seizures with ongoing febrile illness were included in the study.

Exclusion Criteria: Patients who suffered from febrile seizures within the past month, organic brain disease, non-febrile seizures, abnormal electroencephalography, developmental delays or who were on drugs that altered serum calcium or magnesium levels within the past month were excluded from the study. Patients who presented with a first episode of seizures were specifically excluded as febrile seizures are a diagnosis of exclusion; by the time a work-up is completed to rule out other causes, patients are usually no longer febrile due to treatment provided. Patients under one year of age were also excluded due to different laboratory values used to define hypomagnesemia and hypocalcaemia in this population.

All patients were thoroughly evaluated by history and clinical examination on enrollment in the study and the demographic data collection to ensure that they fulfilled the sample selection criteria. All patients underwent peripheral blood sampling by a trained paediatric phlebotomist with at least two years of experience on admission. All samples were tested on a control-tested and calibrated BS-9200 Chemistry Auto Analyzer and a PW-3000M Clinical Chemistry Analyzer for measuring serum magnesium and calcium levels, respectively. A serum magnesium level of less than 1.4 mEq/L and a serum level calcium level of less than 8.8 mg/dL were considered to be low.[12,13] Patients remained hospitalized throughout the febrile illness and were observed for the development of febrile seizures till discharge.

Statistical Package for Social Sciences (SPSS) version 25.0 was used for the data analysis. Quantitative variables were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Chi-square test was applied to explore the inferential statistics. The *p*-value of ≤0.05 was considered statistically significant. Diagnostic parameters were calculated using a 2x2 table. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy were determined by using the standard formulae.

RESULTS

We based our study on a total sample of 87 patients with a mean age of 3.23±1.50 years. A total of 46 (52.9%) patients were male. The mean duration of onset of febrile seizures to time to presentation was 15.70±8.94 months. A total of 28(32.2%) patients had a history of febrile seizures in a first-degree relative. The mean serum magnesium and calcium levels of the sample were 1.34±0.45 mg/dL and 9.07±1.21 mg/dL, respectively. 46(52.9%) had hypomagnesaemia, while 36(41.4%) had hypocalcaemia. 27(3.0%) developed febrile seizures during current admission (Table-I). Table II shows calculation the various test parameters, such as sensitivity and specificity of hypomagnesemia in predicting the development of febrile seizures. Similarly, statistics for hypocalcaemia in predicting the development of febrile seizures is displayed in Table-III.

Table-I: Study Characteristics according to Gender (n=87)

Variables	Male	Female	*p*-value
Gender	46(52.9%)	41(47.1%)	-
Age (years)	3.30±1.49	3.15±1.53	0.627
Duration of Complaints (months)	16.07±8.95	15.29±9.02	0.690
Number of Episodes	3.54±2.62	4.85±2.95	0.031
Family History of Febrile Seizures	11(31.4%)	17(41.5%)	0.080
Serum Magnesium Levels (mg/dL)	1.39±0.43	1.30±0.47	0.369
Hypomagnesaemia	22(47.8%)	24(58.5%)	0.318
Serum Calcium Levels (mg/dL)	9.10±1.10	9.04±1.33	0.837
Hypocalcaemia	18(39.1%)	18(43.9%)	0.652
Febrile Seizures Developed	13(28.3%)	14(34.1%)	0.554

Table-II: Contingency Table for Hypomagnesemia (n=87)

		Development of Febrile Seizures Clinically	
		Yes	No
Prediction of Febrile Seizures according to Hypomagnesemia	Yes	True Positive: 19(21.8%)	False Positive: 27(31.1%)
	No	False Negative: 8(9.2%)	True Negative: 33(37.9%)

Serum magnesium levels at a cut-off of less than 1.4 mg/dL as an indicator of hypomagnesaemia in children had a sensitivity of 70.3%, a specificity of 55.0% and a diagnostic accuracy of 59.8%. Serum calcium levels at a cut-off of less than 8.8 mg/dL as an

indicator of hypocalcaemia in children had a sensitivity of 48.2%, a specificity of 61.7% and a similar diagnostic accuracy of 57.5%. The results for the various characteristics of the tests are shown in Table-IV.

Table-IV: Diagnostic Parameters (n=87)

Tests	Sensitivity	Specificity	Positive Predictive value	Negative Predictive Value	Diagnostic Accuracy
Serum Magnesium	70.3%	55.0%	41.3%	80.5%	59.8%
Serum Calcium	48.2%	61.7%	36.1%	72.5%	57.5%

DISCUSSION

In this study, we looked at the diagnostic accuracy of low serum magnesium and calcium in predicting the development of febrile seizures in patients with a history of the disorder during ongoing febrile illness. The cut-off serum values indicating the presence of hypomagnesaemia and hypocalcaemia were less than 1.4 mEq/L and 8.8 mg/dL, respectively, in the search for a cheap and readily available marker for predicting whether seizures would develop in febrile patients who had a history of the disorder.[13,14]

Our study sample comprised a majority of males, 46(52.9%). This is in keeping with findings in literature where existing studies such as Mahyar *et al.* and Ashrafzade *et al.* noted that males have an increased propensity to develop the disorder.[14,15] This susceptibility may be attributable to high circulating testosterone levels, which have been demonstrated to be associated with the development of temporal lobe-like seizures in animal models.[16]

However, our study noted that females had more episodes per patient than males. While no data is available on the subject, we believe this outcome is due to a reporting bias due to females presenting to healthcare late, which has been reported in older females but not studied in young female children in Pakistan.[17] The Mean±SD age of our sample was 3.23±1.50 years, and while febrile seizures have a peak age of onset of 12-18 months, we studied a population who were already diagnosed with the disorder, and the age of onset of the disease was not recorded.[18] A family history of febrile seizures was present in 28(32.2%) of patients in our study sample, which falls in the range reported by Veisani *et al.* i.e., 25-40% of all patients of febrile seizures had a first degree relative with a history of febrile seizures.[19]

We found that low serum magnesium levels predicted the development of febrile seizures with a sensitivity of 70.3%, a specificity of 55.0% and a diagnostic accuracy of 59.8%. Baek *et al.* reported that patients with febrile seizures had significantly low serum magnesium levels compared to normal controls with hypomagnesaemia present in 42.9% versus 6.9%, respectively, in febrile children (p<0.001).20 Our study demonstrated that the use of serum magnesium and calcium levels in isolation has a limited ability to predict the development of febrile seizures.

LIMITATIONS OF STUDY

Hypocalcaemia due to vitamin D deficiency is a common phenomenon in Pakistan, and we did not account for its presence in producing confounding effects in our results. Additionally, most modern diets are deficient in magnesium. Thus, both deficiencies may have been present in the affected individuals incidentally and may have had no relation to the development of seizures. Moreover, the cut-off levels for each element tested may not have been optimal in predicting the development of febrile seizures. This study was limited by its sample size and was conducted in a specific population drawn out from families of the armed forces. It may be different from the general population.

CONCLUSION

Serum magnesium and calcium levels have limited diagnostic accuracies in predicting the development of febrile seizures in susceptible individuals. While the deficiency of both elements is implicated in the development of febrile seizures, and correcting low levels may result in a lower chance of developing seizures, using their serum levels to predict if a child will develop seizures during a febrile episode does not appear to be reliable. Thus, routine testing and correction may be useful, but the diagnostic and predictive utility is limited.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

ANA: & FI: Conception, study design, drafting the manuscript, approval of the final version to be published.

SZ: & SHN: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

SH: & HS: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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