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Original Article

Paediatrics Section

Serum Zinc and Magnesium Levels in Children with Febrile Seizure: A Hospital Based Cross-Sectional Study

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ABSTRACT

Introduction: Febrile Seizure (FS) is one of the most common forms of seizures in children. Precise aetiology of FS is still not known. Studies have shown that micronutrients like zinc, magnesium, iron, selenium, and copper are highly effective in preventing FS.

Aim: To assess serum zinc and magnesium levels in children with FS and to compare them with that of febrile children without seizure, in order to find out whether serum zinc and magnesium levels have any relationship with occurrence of FS.

Materials and Methods: This was a hospital based comparative cross-sectional study done in the Paediatrics department of Assam Medical College, Dibrugarh, Assam (India). One hundred and thirty children between 6-60 months, with first episode of FS, admitted in the department of paediatrics from June 2016 to May 2017 were taken as cases and 130 age and sex matched febrile children without seizure were taken as controls. After recording history, examination findings and investigations on pre-designed proforma, serum zinc and magnesium levels were estimated using colorimetric and modified methylthymol blue method respectively and comparison was made between cases and controls, and also among simple and complex FS. Data were analysed by Microsoft Excel 2010 and SPSS (Statistical Package for the Social Sciences) program version 16.0 and $p<0.05$ was taken as significant.

Results: Mean serum zinc levels in cases and controls were (79.68±21.7 µg/dL) and (120.93±29.00 µg/dL), respectively. Hypozincaemia was present in 14 (10.77%) cases and 1 (0.77%) control ($p<0.001$). Mean serum magnesium levels in cases and controls were 2.02±0.21 mg/dL) and (2.22±0.22 mg/dL), respectively. Hypomagnesemia was present in 8 (6.15%) cases while none of the controls had hypomagnesemia ($p=0.006$). Mean serum zinc levels in cases with simple and complex FS were (85.55±24.13 µg/dL) and (71.92±14.97 µg/dL), respectively ($p<0.001$). Mean serum magnesium levels in simple and complex FS were (2.11±0.21 mg/dL) and (1.90±0.14 mg/dL), respectively ($p<0.001$).

Conclusion: Children with FS had low serum zinc and magnesium levels in comparison to febrile children without seizure and both the levels were lower in children with complex

Keywords: Convulsion, Essential minerals in blood, Fever, Paediatric

INTRODUCTION

A seizure is a transient occurrence of signs and/or symptoms resulting from abnormal excessive or synchronous neuronal activity in the brain. FS is the most common forms of seizure in children. It occurs in 2-5% of children aged between 6-60 months with a temperature of 38°C (100.4°F) or higher. FS are of two types: (a) Simple FS- it is primarily generalised, usually tonic-clonic, lasting for a maximum of 15 minutes and not recurrent within a 24 hour period; (b) Complex FS- it is more prolonged (>15 minutes), is focal and/or reoccurs within 24 hours [1]. American academy of Paediatrics (2008) defined FS as a "seizure occurring in febrile children between the ages of 6 and 60 months who do not have an intracranial infection, metabolic disturbance or history of FS" [2,3]. Direct cause of FS is not yet known. Cigarette smoking and alcohol consumption by the mother during pregnancy may increase the risk of FS [4]. Recent vaccination specially MMR may also increase the risk [5]. Prematurity, complications during childbirth, perinatal asphyxia are some risk factors for the occurrence of FS [6]. Although prognosis of FS–is usually good, they are of serious concern to the parents witnessing them [7] and about 2-7% of children having it, may proceed to develop epilepsy in future [1]. Studies have shown that zinc, magnesium, iron, selenium and copper are highly effective in preventing FS [8].

Zinc regulates the activity of glutamic acid and the rate limiting enzyme in the synthesis of gamma-aminobutyric acid, an inhibitory neurotransmitter [9]. It also facilitates the inhibitory effect of calcium on N-Methyl-D-Aspartate (NMDA) receptors and thereby, prevents the stimulation of neuronal discharge [10]. Magnesium inhibits the facilitatory effects of calcium on synaptic transmission and also exerts a voltage dependent blockage of NMDA receptor channel [11].

In this study, the serum zinc and magnesium levels of children with FS and fever without seizure were compared in order to find out whether serum zinc and magnesium level have any relationship with FS.

MATERIALS AND METHODS

This was a hospital based comparative cross-sectional study which was conducted in the Department of Paediatrics of Assam Medical College, Dibrugarh, Assam, India, after obtaining approval from the Institutional Ethics Committee (H) (Regn No. ECR/636/Inst/AS/2014). It was conducted over a period of one year from June 2016 to May 2017.

Study population was febrile children, aged 6 to 60 months, admitted into the department with or without seizure. Febrile children were defined as children with a history of fever by the attendant and/or temperature more than 38°C.

Inclusion criteria: i) admitted children with first episode of FS; and ii) ages between 6 to 60 months; for the controls- age and sex matched admitted febrile children without seizure were included.

Exclusion criteria: Children having acute infections of brain, neurocysticercosis, neurotuberculosis, CNS tumours, any structural brain damage, any developmental delay, any previous history of afebrile seizure, electrolyte imbalance, children taking zinc and magnesium supplementation and parents not giving consent consent were excluded.

For sample size calculation, it was decided that all consecutive FS cases coming to the department during the study period, fulfilling the inclusion and exclusion criteria will be taken as cases. A total of 325 febrile children between 6-60 months, were admitted during the study period. Out of that, 136 children were enrolled as cases after fulfilling the exclusion criteria. But serum samples could not be collected from six children because of short time period between admission and discharge (against medical advice). So, ultimately 130 children were included as cases. One hundred and thirty febrile children without seizure, who were age and sex matched with cases, were enrolled as controls after fulfilling the exclusion criteria. (So, sample size was 260, 130 cases and 130 controls).

Informed and written consent were taken from parents/guardian of both cases and controls. Detailed history about type of convulsion, focal or generalised, duration, loss of consciousness, family history, number of convulsions during the febrile episode, history of previous attacks and other associated complaints like coryza, cough, loose motions, ear discharge were taken. Clinical examination about presence of fever, degree of fever, consciousness level and systemic examination of all the systems with nervous system in particular were done. History and examination findings were recorded in pre-designed proforma. Routine blood examination, serum zinc estimation, serum magnesium estimation were done in all the children. Chest X-ray, neuroimaging of brain, lumber puncture, serum electrolytes estimation, Mantoux test etc., were done as and when required. Serum zinc levels were estimated by Nitro-PAPS method. It is a colorimetric (kits by Tulip diagnostics) method. Normal serum zinc levels were taken as (60-120) µg/dL [12]. Serum magnesium levels were estimated using modified methylthymol blue method and normal serum magnesium levels were taken as (1.8-2.4) mg/dL [13]. Both tests were done in the Department of Biochemistry.

STATISTICAL ANALYSIS

Data were analysed by Microsoft Excel 2010 and Statistical Package for the Social Sciences (SPSS) program version 16.0. General characteristics of the patients were presented in terms of percentages, mean and standard deviation. The t-test and Fisher's exact test were used to compare the mean serum zinc and magnesium levels between cases and controls. Chi-square test was used to compare hypozincaemia and hypomagnesemia in between the groups. Pearson's correlation coefficient (r) was used to find out the correlation between serum zinc and magnesium level and with duration of seizure. The p<0.05 was taken as statistically significant.

RESULTS

Out of the 130 FS cases, majority of the children i.e., 53 (40.77 %) were in the age group of 13-24 months with a mean age of (18.18±10.97) months. Out of 130 controls, majority of children i.e., 50(38.46%) belonged to the age group of 13-24 months with a mean age of (18.28±11.23) months. A total of 79 (60.77%) children were males among cases and 81 (62.31%) were males among controls. The male female ratio of FS cases was 1.5:1 [Table/Fig-1]. Most of the cases i.e., 103(79.23%) were from upper middle class and 100 (76.92%) controls were from lower middle socio-economic class (assessed by Modified Kuppuswamy scale) [14].

According to World Health Organization (WHO) growth chart [15], 93 (71.54%) children were nutritionally normal and 37 (28.46%) were moderately malnourished. According to World Health Organization (WHO), growth chart [15]; 79 (60.77%) children were nutritionally normal and 51(39.23%) were moderately malnourished in controls. Out of the 130 cases, 12 (9.23%) children had family history of FS and out of the 130 controls, only 3 (2.31%) had family history of FS (p=0.016). While finding out the causes of fever in FS cases, Respiratory Tract Infection (RTI) was seen in majority of children i.e., 55 (42.31%) [Table/Fig-1].

Parameters	Cases n=130	Controls n=130	p-value
Age (months) (Mean±SD)	18.18±10.97	18.28±11.23	0.946
Sex n (%)			
Male	79 (60.77)	81 (62.31)	0.798
Female	51 (39.23)	49 (37.69)	
Nutritional status (WHO) n (%)			
Normal	93 (71.54)	79 (60.77)	0.066
Moderate malnutrition	37 (28.46)	51 (39.23)	
Family history of febrile seizure n (%)			
Present	12 (9.23)	3 (2.31)	0.016
Absent	118 (90.77)	127 (97.69)	
Aetiology of fever n (%)			
RTI	55 (42.31)	56 (43.08)	0.508
UTI	6 (4.62)	10 (7.69)	
ASOM	3 (2.31)	3 (2.31)	
Acute gastroenteritis	17 (13.08)	23 (17.69)	
Non localised fever	49 (37.69)	38 (29.23)	

[Table/Fig-1]: Baseline parameters of cases and controls.
p<0.05 was taken as significant; For age (months), student's t-test and for family history of FS, Fisher's-exact test, and for sex, nutritional status and aetiology, Chi square test were used; RTI: Respiratory tract infection; UTI: Urinary tract infection; ASOM: Acute secretory otitis media; SD: Standard deviation

Mean serum zinc and magnesium levels were significantly reduced in cases as compared to controls [Table/Fig-2]. Hypozincaemia and hypomagnesemia were seen to be significantly more in cases in comparison to controls [Table/Fig-3]. On comparing the serum zinc and magnesium levels among simple and complex FS, both the levels were significantly (p<0.001) lower in children with complex FS than in children with simple FS [Table/Fig-4].

Groups	Serum zinc level (Mean±SD) (µg/dL)	p-value	t-value
Cases	79.68±21.7	<0.001	12.99
Controls	120.93±29.00		
	Serum magnesium level (Mean±SD) (mg/dL)		
Cases	2.02±0.21	<0.001	7.64
Controls	2.22±0.22		

[Table/Fig-2]: Mean serum zinc and magnesium levels in cases and controls.
p<0.05 was taken as significant. Test used was student's t-test; SD: Standard deviation

The FS cases with duration of seizure of <5 minutes, 5-10 minutes, >10-15 minutes and >15 minutes had mean serum zinc levels as (92.42±21.47) µg/dL, (68.61±10.98) µg/dL, (67.94±17.27) µg/dL, (61.83±22.46) µg/dL, respectively and mean serum magnesium levels as (2.07±0.22) mg/dL, (1.99±0.19) mg/dL, (1.92±0.11) mg/dL, (1.85±0.14) mg/dL, respectively. There were significant negative correlations between duration of seizure with serum zinc level (r= -0.495, p <0.001) and serum magnesium level (r =-0.328, p<0.001).

DISCUSSION

This study was conducted to find out whether serum zinc and magnesium levels have any relationship with FS in children. The present study saw a male preponderance in FS with a male female ratio of 1.5:1. Srinivasa S and Manjunath MN, showed male female ratio as 1.4:1 [8]. Majority of children with FS belonged to the age group of 13-24 months with a peak incidence at 18 months. Srinivasa S and Manjunath MN, stated that 56% of children with FS were below two years of age [8].

In present study, more than 3/4th children from both cases and controls were from middle socio-economic class. On the other hand, in cases, 71.54% children were nutritionally normal and in controls, 60.77% children were nutritionally normal. Hence, it can be stated that nutritional status has no role in the occurrence of FS. Out of 130 FS cases, 74 (56.92%) cases had simple FS and 56 (43.07%) cases had complex FS.

Groups	Hypozincaemia (<60 µg/dL)					Hypomagnesemia (<1.8 mg/dL)				
	Present n (%)	Absent n (%)	p-value	Odd's ratio	95% CI	Present n (%)	Absent n (%)	p-value	Odd's ratio	95% CI
Cases (n=130)	14 (10.77)	116 (89.23)	<0.001	15.57	(2.02, 120.24)	8 (6.15)	122 (93.85)	0.006	18.11	(1.03, 317.12)
Controls (n=130)	1 (0.77)	129 (99.23)				0 (0)	130 (100)			

[Table/Fig-3]: Hypozincaemia and hypomagnesemia in cases and controls.
p<0.05 was taken as significant; Test used was Fisher's-exact test; CI: Confidence interval

Type of seizure (n)	Serum zinc level (Mean±SD) (µg/dL)	p-value	Serum magnesium level (Mean±SD) (mg/dL)	p-value
Simple (74)	85.55±24.13	<0.001	2.11±0.21	<0.001
Complex (56)	71.92±14.97		1.90±0.14	

[Table/Fig-4]: Comparison of mean serum zinc and magnesium levels with type of seizure.
p<0.05 was taken as significant; Test used was student's t-test; SD: Standard deviation

The present study documented that the mean serum zinc level was significantly low in children with FS as compared to febrile children without seizure. Salehiomran MR and Mahzari M, Srinivasa S and Manjunath MN, also showed similar results [4,8]. Kumar L et al., and Gattoo I et al., had earlier showed similar results with serum zinc when compared between children with febrile convulsion and febrile children without convulsion [9,16]. Mahyar A, also showed serum zinc levels to be significantly lower in children with FS as compared to healthy children [17]. Serum magnesium level was also low in FS cases in comparison to febrile children without seizure in present study. In a study done by Namakin K et al., serum magnesium levels were shown to be significantly lower in children with FS than in children with fever without seizure [18]. In another study, conducted by Baek SJ et al., mean serum magnesium level in children with febrile convulsion was significantly lower as compared to healthy children [19].

In our study, hypozincaemia and hypomagnesemia were also found to be present in significantly greater number of cases as compared to controls. In a study conducted by Gayathri D et al., hypozincaemia was found in significantly greater number of children with FS than in children having fever without seizure [20]. Sherlin and Ramu B, in their study found that 68% of children with FS had hypomagnesemia while it was normal in all the controls [21]. These studies were similar to the present study.

This study also found that, among the cases, the children with complex FS had significantly lower serum zinc and magnesium levels as compared to children with simple FS. Bharathi S and Chiranjeevi K, showed that statistically significant association was found between hypomagnesemia and 'Typical Febrile convulsions,' but not with Atypical Febrile convulsions [22]. Sampathkumar P and Kannan KS, also stated that there was no significant difference between serum zinc level of simple FS and complex FS [23].

In this study, positive family history was present in significantly greater number of cases than controls. Yahyaoui S et al., also identified family history of febrile convulsion as one of the risk factors for FS occurrence [24]. There was a significant negative correlation between duration of seizure and serum zinc level and serum magnesium level. Saqib N and Qavi M, also stated that prolonged seizures were observed in children with lower serum zinc levels [25].

Abuekteish F et al., showed upper RTI as the commonest (53%) triggering factor for FS [6]. Srinivasa S and Manjunath MN, found that upper RTI was the most frequent cause of fever apparent in 70% children, followed by dengue fever 11%, acute gastroenteritis 6%, urinary tract infection and otitis media in 8% children each and viral fever in 5% children [8]. Gattoo I et al., stated that the clinical presentation comprised of mainly non-localised fevers, majority of which had clinical evidence to suggest viral aetiology (60%), followed by ARI (20%), ASOM (10%), UTI (5%) and Bronchiolitis (5%) [16]. According to Delpisheh A et al., the important viral or bacterial causes of FS were recent upper respiratory infection (42.3%), gastroenteritis (21.5%) and otitis media infections (15.2%) [26]. In this present study also, RTI was the most common infectious cause (42.31%) followed by non-localised fever (37.69%), acute gastroenteritis (13.08%), urinary tract infection (4.62%) and acute otitis media (2.31%).

Since, undernutrition is not directly associated with FS occurrence, serum zinc and magnesium levels can be considered as two independent risk factors irrespective of the nutritional status of the child. Hence, serum zinc and magnesium estimation in a child with FS may help in the prevention of recurrence of FS. Supplementation of zinc will also prevent episodes of RTI and diarrhoea, the commonest two causes of FS.

Limitation(s)

Since, sample size was not large in our study, studies with larger sample size are needed to strongly comment on the role of serum zinc and magnesium level in the causation of FS in children.

CONCLUSION(S)

From this study, it can be concluded that low serum zinc and magnesium levels are associated with FS and children with lower levels of serum zinc and magnesium have more complex FS than simple FS. Hence, low serum zinc and magnesium levels can be considered as risk factors for development of FS in children. Duration of fever also increases at low serum zinc level in simple FS. By supplementing zinc and magnesium to those children-with high risk like, presence of history of seizure disorder and/or febrile convulsion in the family, febrile convulsion may be prevented. Recurrence can also be prevented by supplementing zinc and magnesium. But, further studies are necessary to prove these statements.

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Contributors: PD: collected, compiled, analysed the data drafted the initial manuscript and designed the study. AB: conceptualized and designed the research plan, supervised and finalized the manuscript.

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