Association of Serum Zinc Level with Febrile Seizure in Children

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Abstract

Background: *Febrile seizure is a common pediatric emergency. This is the most common type of seizure in children aged 6 months to 6 years constituting 30% of all seizure types. Despite the high clinical burden of febrile seizure, little advance has been made in understanding its etiology. This study was undertaken to find out whether low serum zinc level is a risk factor of febrile seizure in children.*

Methodology: *This case-control study was conducted in department of Pediatrics, Dhaka Medical College Hospital, Dhaka from March, 2021 to February, 2022. Sixty-nine children presenting with febrile seizure, fulfilling inclusion criteria were enrolled as cases, along with similar number (sixty-nine) of age and sex matched healthy controls. Venous blood samples were obtained and analyses of serum zinc levels were done.*

Results: *The results of cases and controls were compared. Data were analyzed through SPSS (version 26) software. Significance for the statistical tests (Chi Square test & unpaired t-test) were determined at a probability value of less than 0.05 ($p<0.05$). Mean age of the respondents was 21.53±11.52 months in case group and 24.33±16.80 months in control group. Majority (59 to 62%) patients were male in both groups and majority (95.65%) of cases were simple febrile seizure and mean duration of seizure was 10.46±5.60 minutes. The mean serum zinc was found 76.84±14.16 µg/dl in case group and 81.59±13.28 µg/dl in control group. The difference between the case and control group was significant (P value = 0.044). ROC curve showed OR= 2.21, cut off value =84.5 (<65 µg/dl), p = 0.045, 95% CI, sensitivity = 71.0%, Specificity = 50.0%.*

Conclusion: *Serum zinc was found to be significantly low in children with febrile seizure than that of febrile children without seizure. However further large-scale studies are needed to generalized the result of this study.*

Keywords: *Febrile seizure, children, serum zinc level.*

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Introduction

Febrile seizure is a very common emergency in paediatric ward and happens to be the most common type of seizure in the age group of 6 months to 60 months. It constitutes 30% of all seizure types.[1,2] Current definition is, Febrile seizures are seizures that occur between the ages of 6 and 60 months (peak 12-18 months) with a temperature of 38°C (100.4°F) or higher, that are not the result of CNS infection or any metabolic imbalance, and that occur in the absence of a history of prior afebrile seizures.[3]

Febrile seizure may present in different form. A simple febrile seizure is a primary generalized, usually tonic-clonic, attack associated with

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fever, lasting for a maximum of 15 minutes, and not recurrent within a 24 hours period. A complex febrile seizure is more prolonged (>15 minutes), and/or is focal, and/or recurs within 24 hours. Febrile status epilepticus is a febrile seizure that lasts longer than 30 minutes.[3] Various risk factors involved in development of febrile seizures like infections (Bacterial and viral), temperature susceptibility of immature brain, interleukins, circulating toxins association, micronutrient deficiency and iron deficiency.[4,5,6] Role of various micronutrients like copper, zinc, magnesium and selenium have been described in association with febrile seizures.[7,8]

Zinc is necessary for the activity of over 300 enzymes.[9,10,11,12,13] Zinc homeostasis in glutaminergic neuron-rich areas (such as, the hippocampus and amygdala) may be associated with the etiology and manifestation of epileptic seizures.[14]

Zinc homeostasis in the brain plays vital role for prevention of seizure development because it can act either as proconvulsan or anticonvulsant.[15,16] As Zinc stimulates the activity of pyridoxal kinase thereby it modulates the activity of glutamic acid decarboxylase and the synthesis of GABA.[17] After being formed within GABAergic axon terminals, GABA is released into the synapse, where it acts at one of two types of receptors: $GABA_A$, which controls chloride entry into the cell, and $GABA_B$, which increases potassium conductance, decreases calcium entry, and inhibits the presynaptic release of other transmitters.[18] Zinc deficiency is quite common among febrile seizure patients compared to other patients with febrile illness but without seizur.[20]

As zinc deficiency is fairly common, this study was undertaken to find out the serum zinc levels and its association with febrile seizures.

Methodology

This case-control study was conducted in department of Pediatrics, Dhaka Medical College Hospital, Dhaka from March, 2021 to February.Children from 6 to 60 months of age with febrile seizure admitted to Paediatric department of Dhaka Medical College Hospital, Dhaka who met the inclusion criteria were enrolled as cases and similar number of febrile children without seizure were taken as controls. Children who have history of afebrile seizure, history of neonatal seizures, suspected CNS infections, suspected neurometabolic disorders, severe acute malnutrition, receiving zinc supplementation were excluded. Sixty nine children with febrile seizure were enrolled as cases and sixty nine febrile children without seizure were enrolled as controls. Data was collected through predesigned questionnaire. After selection of the patients; aims, objectives and procedures of the study was explained with understandable language to the parents. Risks and benefits were also made clear to the parents of the patients. Then they were encouraged for voluntary participation and were allowed being free to withdraw themselves from the study. Then, informed written consent was taken for each patient. With all aseptic precaution Two (2) ml of blood sample was collected in plain (Red) tube and sent to Department of Biochemistry, BSMMU for serum zinc level estimation. After centrifuging serum zinc level estimation was done by Thermo scientific Indiko Plus automated, random access benchtop analyzer by colorimetric method. Complete blood count (CBC) was done in SYSMEX XE-5000 analyzer. With all aseptic precaution 3 ml of blood was collected in an EDTA tube and was sent to Haematology department of DMCH for CBC estimation. Serum electrolytes, serum calcium and RBS estimation was done by Dimension EXL-200 analyzer. With all aseptic precaution 3 ml of blood was collected in a plain (Red) tube and was sent to Laboratory medicine department of DMCH for estimation. Data were processed, compiled and analysis was done with Statistical Package for Social Science (SPSS) version 26.0 for Windows.

Results

Patient selection:

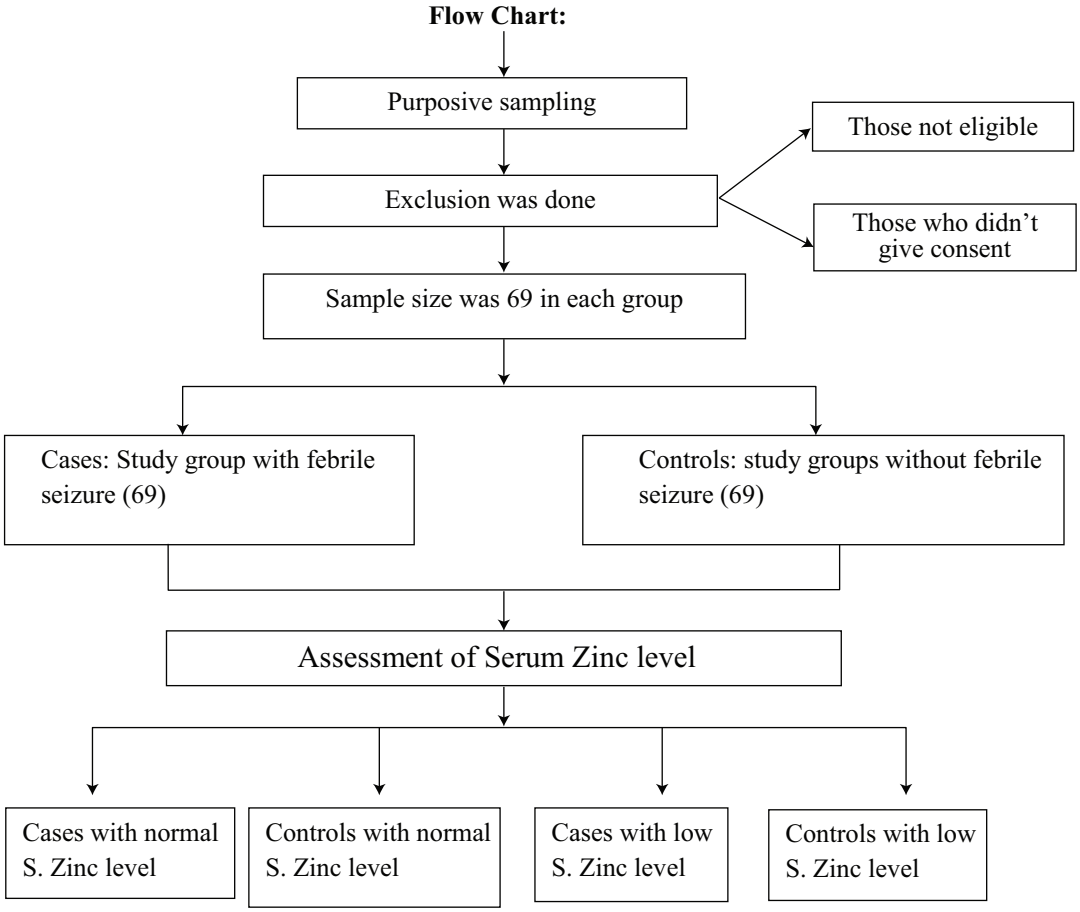

Table I- shows that almost 50% patients belonged to age 12 to <24 months in case group and 29% in control group. In age group <12 months and 12 to <24 months, P value between case and control group was statistically significant. The mean age was found 21.53±11.52 months in case group and 24.33±16.80 months in control group. The difference was not statistically significant (P>0.05) between two groups. Majority (59 to 62%) patients were male in both groups. Male and female ratio was 1.6:1 in case and 1.4:1 in control group. The difference was not statistically significant (P>0.05) between two groups.

Table I

Distribution of the study population by age and sex (n=138)

Age (months)	Case (n=69)		Control (n=69)		P value
	n	%	n	%	
<12	8	11.59	18	26.08	0.029
12 to <24	35	50.72	20	28.98	0.009
24 to <36	15	21.73	15	21.73	1.000
36 to <48	6	8.69	4	5.79	0.511
48 to 60	5	7.24	12	17.39	0.069
Mean±SD	21.53±11.52		24.33±16.80		0.25^{ns}
Male	43	62.32	41	59.42	0.727^{ns}
Female	26	37.68	28	40.58	

Table II shows in majority (95.65%) of cases are simple febrile seizure. Mean duration of seizure was 10.46±5.60 minutes and range was 5 to 30 minutes. Most of the cases suffered from respiratory tract infection (42.03%). Others were gastroenteritis (11.59%) and urinary tract infection (7.24%). A vast portion of cases were suspected viral infections (39.13%).

Table II

Characteristics and etiology of seizure in cases (n=69)

Duration of seizure (Minutes)	No. of Cases (n=69)	Percentage %
≤15	66	95.65
≥30	3	4.35
Types of febrile seizure		
Simple febrile seizure	66	95.65
Febrile status epilepticus	3	4.35
Etiology of fever		
Respiratory Tract Infection	29	42.03
Gastroenteritis	08	11.59
Urinary Tract Infection	05	07.24
Suspected viral infection	27	39.13

Table III- shows that the mean blood glucose was found 5.90±1.23 mmol/L in case group and 6.03±1.06 mmol/L in control group. The difference was statistically not significant (P>0.05) between two groups. The mean serum sodium was found 136.71±3.30 mmol/L in case group and 137.63±3.13 mmol/L in control group. The difference of mean was statistically not significant (P>0.05) between two groups. The mean serum calcium was found 9.25±0.63 in case group and 9.44±0.63 in control group. The difference of mean was statistically not significant (P>0.05) between two groups.

Table IV- shows that 19 (27.54%) patients were found with hypozincaemia (<65 µg/dl) in case group and 10 (14.49%) in control group. The mean serum zinc was found 76.84±14.16 µg/dl in case group and 81.59±13.28 µg/dl in control group. The difference between means was significant (P= 0.045, OR= 2.24) between two groups.

Table III

Blood glucose, Serum sodium and Serum calcium level of the study population (n=138)

Blood glucose (mmol/dl)	Case (n=69)	Control (n=69)	P value
Mean±SD (mmol/L)	5.90±1.23	6.03±1.06	0.505^{ns}
Range (min-max)	3.40-8.35	4.10-8.60	
Serum sodium (mmol/L)	Case(n=69)	Control(n=69)	P value
Mean±SD (mmol/L)	136.71±3.30	137.63±3.13	0.093^{ns}
Range (min-max)	131-145	130-143	
Serum calcium (mg/dl)	Case (n=69)	Control (n=69)	P value
Mean±SD (mg/dl)	9.25±0.63	9.44±0.63	0.087^{ns}
Range (min-max)	7.90-10.90	8.20-11.20	

Table IV

Serum zinc level of the study population (n=138)

Serum zinc (mg/dl)	Case(n=69)		Control(n=69)		Odds ratio	P value
	n	%	n	%	(OR)	
Hypozincaemia (<65 µg/dl)	19	27.54	10	14.49	2.24	0.045^{s}
Normal	50	72.46	59	85.51		
Mean±SD (µg/dl)	76.84±14.16		81.59±13.28			
Median	78.0		84.0			
Range (min-max)	54-102		54-105			

p value obtained by Mann Whitney U test,

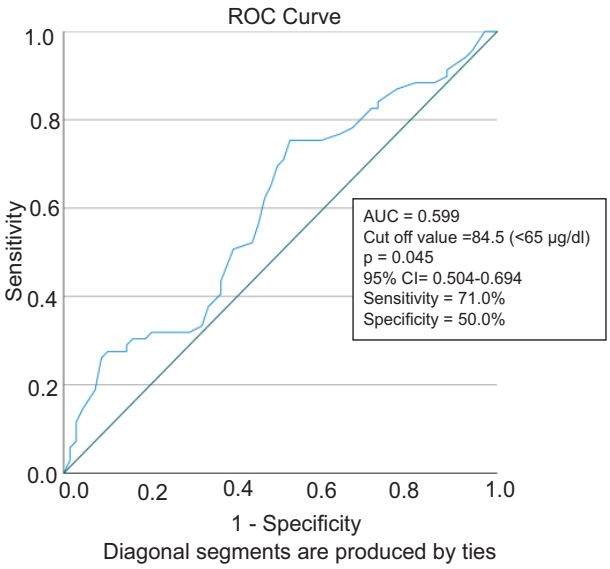

Fig.-1: *ROC analysis was performed to evaluate the predictive ability of serum zinc levels for febrile seizures.*

Figure-1 showed that statistically significant association between serum zinc levels and febrile seizures in children (p=0.045). The area under the curve (AUC) analysis showed a moderate predictive ability (AUC = 0.599), suggesting that serum zinc levels may have some potential as a predictor for febrile seizures. The sensitivity of the test was 71.0%, indicating a relatively high probability of a positive result in children with febrile seizures, while the specificity was 50.0%, indicating a 50% chance of obtaining a negative result in children without febrile seizures.

Discussion:

This study was conducted to determine the role of serum zinc level in children with febrile seizure which was compared to febrile children without convulsion. These two groups of children were compared with respect to their age, sex, characteristics of seizure, serum zinc etc.

In this study, majority of cases were between 12 to 24 months of age which corresponds to the age of peak incidence (12-18 months) of febrile seizure.[3] This is almost similar to a study by Allam et al.[26] The mean age in cases is similar to another study (Mollah et al. 2008) conducted in Bangladesh.[21] In this study, the mean age of febrile seizure was above the peak incidence age (18 months) due to inclusion of some recurrent febrile seizure cases. Some studies showed that mean age of febrile seizure happen in children between 24 and 30 months of age.[22,23] Though febrile seizure occurs in both male and female children without any significant gender predominance but in this study majority of the cases were male but the difference was not statistically significant. Mollah et al. (2008) in Bangladesh also revealed that male children were more prone to develop febrile seizure than female children.[21] Another study in Bangladesh by Begum et al. (2019) also found male predominance in febrile seizure.[28] Other studies also showed male predominance.[1,26] This may be due to the fact that, males are found to be more susceptible to temporal lobe like seizures because of higher levels of testosterone than female.[34]

In this study, duration of seizure was d”15 minutes in most of cases. This is similar to some studies where majority of cases had <15 minutes seizure duration.[24,28,29]

In this study, respiratory tract infection was the most common cause of fever in children with febrile seizure followed by gastroenteritis and urinary tract infection. In some cases cause of fever was undetermined. Study done by Absar et al. (2020) with 100 febrile seizure cases revealed majority of children presented with acute respiratory tract infection as the cause of fever followed by acute gastroenteritis and urinary tract infection.[24] In some other studies conducted in Bangladesh also showed majority cases presented with respiratory tract infection which is similar to present study.[28,29]

In present study, hyponatraemia was seen in 17.39% cases. This is similar to the study done by Baek et al. (2018) where 21.1% cases had hyponatremia[27]. In this study mean serum sodium was 136±3.30 mmol/L which is similar to the study done by Namakin et al. (216) where it was 136.2±3.3 mmol/L.[22]

Current study shows 14.49% cases had hypocalcaemia. This is similar to a study by Al-Hakeim, Al-Hillawi & Al-Kindi (2015) which revealed that 21.7% cases were hypocalcaemic[25]. In this study mean serum calcium level in cases were 9.25±0.63 mg/dl

which is similar to mean 9.45±0.57 mg/dl found by Amouian et al. (2011)[35]. In this study no statistically significant difference was found between case and control group. Although Al-Hakeim, Al-Hillawi & Al-Kindi (2015) found no significant difference, but Namakin et al. (2016) found that calcium level was significantly low in children with febrile seizure.[25,22]

All (100%) patients were normoglycemic in both case and control group. The mean blood glucose was found 5.90±1.23 mmol/L in case group and 6.03±1.06 mmol/L in control group. Higher mean blood glucose may be related to the fact that there is stress hyperglycaemia.[33] CSF study was done in 11 cases (8 cases below 12 months of age and 3 cases of febrile status epilepticus), which revealed no abnormality.

In the current study, serum zinc level was found significantly low in cases than the controls. Hypozincaemia was noticed in 27.54% children with febrile seizure. On the other hand, 14.49% of the controls were with low serum zinc level. Vidyasagar, Venugopal and Darshan (2015) found higher percentage of cases (60%) and controls (33.8%) were affected with hypozincaemia, which is contradictory to present study.[20] In the present study mean serum zinc level difference between two groups is statistically significant (P value <0.05). In Pakistan Qudrat et al. (2020) found the frequency of hypozincemia in febrile seizures among children presenting at tertiary care hospitals was 54.48% and mean serum zinc levels were calculated as 64.28±12.13 µg/dl.[36] Whereas Reddy and Solomon (2019) found the mean serum zinc levels were 64.92 µg/dl, 81.03 µg/dl respectively in febrile seizure and febrile children without seizure[37]. Several studies showed that serum zinc level was significantly lower in febrile seizure patients compared to febrile children without seizure.[8,20,21,22] Rahman et al. (2016) conducted a cross sectional nationwide survey, which showed about 44.6% of pre-school age children (6-59 months) had zinc deficiency.[19] That doesn't match with the current study.

Reddy and Solomon (2019) found in a study that decreased serum zinc level is a significant predisposing factor for febrile convulsions[37]. Same conclusion was done by Allam et al. (2018)[26]. This study showed no correlation of serum zinc with age and sex in febrile seizure.

Conclusion:

It can be concluded that serum zinc is significantly low among the children with febrile seizure compared to febrile children without seizure. So, hypozincaemia might be regarded as a risk factor of febrile seizure in children.

Recommendations:

Routine assessment of serum zinc level can be recommended in children with febrile seizure but further large-scale studies are needed to generalize the result of this study. Other studies can be carried out whether zinc supplementation could prevent the recurrence of febrile seizure in children.

Limitations of the study:

This study has been conducted in a single centre with small sample size. This study was conducted in a single tertiary care hospital; therefore, the findings may not represent the whole population of our country. Other risk factors of febrile seizure were not assessed in this study.

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