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Original Article

Association of Serum Calcium and Magnesium Level with Febrile Seizure

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Key words:
Febrile Seizure, S. Calcium, S. Magnesium

Abstract

Background: *Febrile seizures occur in 2 to 5% of all children with a recurrence rate of 30 to 40%. Calcium and magnesium is closely related to pathophysiology of seizures and aim of this study was to find out the association of serum calcium and magnesium level with febrile seizure.*

Methods: *A cross sectional analytical study was conducted among One hundred (100) subjects of both sexes with age range 6 months to 60 months in department of pediatrics from June 2019 to May 2020. The subjects were grouped into case (group A) and control (group B) by purposive sampling who were seeking fever with convulsion (group A) and fever without convulsion (group B). Statistical analyses were performed by Chi-square test and/or Fisher's exact test as applicable for comparing qualitative variables and for quantitative variables using unpaired t-test and/or Mann-Whitney U test for comparing between the groups. Pearson's Correlation Coefficient test was done to observe the correlation between low calcium and Magnesium level in febrile seizure. A p-value of <0.05 was considered as significant for all analytical tests.*

Results: *Hypocalcaemia were more in 25-36 months of age and hypomagnesaemia 37-48 months in febrile seizure Hypomagnesaemia were more in patients who had previous febrile seizure (1.89 ± 0.73 mg/dl, p- value 0.045). Association and positive correlation were found between serum calcium and serum magnesium with febrile seizure. Multivariate logistic regression showed hypocalcaemia and hypomagnesaemia are independent risk factor for febrile seizures where hypocalcaemia OR=2.144 and hypomagnesaemia OR 1.2.*

Conclusion: *Association and positive correlation were found between serum calcium and serum magnesium with febrile seizure and more in recurrent febrile seizure.*

Introduction:

Febrile seizures are the commonest cause of seizures in children, occurring in 2-5% of children which is very agonizing to the parent and child and can cause psychological trauma to both.

In the brain, hundreds of intracellular processes are known to depend on calcium influx. Studies have shown different results for an association between reduced serum electrolytes including low serum Calcium and Seizures. Excitatory post synaptic transmissions that occur with very low calcium state lead to uncontrolled epileptic-form discharges.

Calcium binds to the exterior surface of the Sodium channel protein molecule in the plasma membrane

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of nerve cells, increasing the permeability of neuronal membranes to sodium ions, causing a progressive depolarization thus increases the possibility of action potentials. When Calcium ions are absent, the voltage level required to open voltage gated Sodium channels is significantly altered (less excitation is required). With hypocalcemia, action potentials may be spontaneously generated causing contraction of peripheral skeletal muscles resulting in clinical seizures.

During any acute febrile disease, disturbances in water and electrolytes occur frequently. It has been suggested that change in serum calcium might enhance the susceptibility to seizures[1]. A common biochemical abnormality causing seizures is hypocalcaemia, which may manifest as muscle cramps, tetany, seizures and paresthesia[2].

Magnesium is the fourth most common cation in the body and the third most intra cellular cation [3]. The normal plasma magnesium levels are 1.5 to 2.3 mg/dl. Magnesium is essential for membrane stabilization and nerve conduction. Hypomagnesaemia is defined as serum magnesium levels below 1.5 mg/dl. Hypomagnesaemia causes secondary hypocalcaemia by impairing the release of PTH by the parathyroid gland. Hypomagnesaemia is characterized by hyper excitability of the central nervous system leading to convulsions [2].

Glutamate is a major excitatory neurotransmitter in the brain acting as an agonist at N-Methyl–D-aspartate (NMDA) receptors. Extracellular Mg2+ normally blocks NMDA receptors. Thus, hypomagnesaemia may release the inhibition of NMDA receptor. This leads to glutamate-mediated depolarization of the postsynaptic membrane and enhancement of epileptiform electrical activity.[4,5,6]

Several studied showed that there is association between serum calcium and magnesium with febrile seizure in serum and CSF[7,8,9,10]. Hence the study is undertaken to find out the association of serum Magnesium levels with febrile seizure.

To the best of my knowledge, very few studies were done on 'association of serum calcium and magnesium level with febrile seizure in Bangladesh'. If any association of S. calcium and magnesium with febrile seizure is found out, it will be beneficial for the patient as because, calcium and magnesium deficiency is correctable condition and it will also provide information to future investigators in this field

Methodology:

2.1 Objectives:

General objective:

To evaluate the association between serum calcium and magnesium level in children with febrile seizure, aged 6 to 60 months.

Specific objective:

1. To analyze Serum calcium and magnesium level in children, 6 months to 60 months of age with febrile seizure.
2. To estimate Serum calcium and magnesium level in age matched children, with fever without convulsion.
3. To compare Serum calcium and magnesium level between two groups.
4. To find out the association of calcium and magnesium level with febrile seizure patients.

2.2 Participant selection and evaluation of febrile seizure:

On the basis of inclusion and exclusion criteria, all the patients with febrile seizure admitted in Department of Pediatrics, SSMC & MH during the specified period of time were considered as case and age matched children who were admitted with fever due to any disease without any history of seizure, participated in the study as the control.

The subjects were allocated into two groups, 50 patients in each group:

Group A: patients with fever and seizure

Group B: patients with fever and without seizure

2.3 Inclusion criteria

1. Age range: 6 months to 60 months.
2. All admitted child with febrile seizure.
3. Age matc hed control group was selected from admitted patient who had fever without any episode of seizure.
4. Willing to give informed consent.

2.4 Exclusion criteria

1. Clinically suspected meningitis or encephalitis.
2. Known case of epilepsy with fever.
3. Any neuro-developmental co-morbidity.
4. Very sick children

2.5 Data collection

Data were collected by interview of the patients and their guardians, clinical examination and laboratory investigations using the research instrument.

All patients admitted in the Department of Pediatrics, SSMC& MH, fulfilling the inclusion and exclusion criteria were considered as case for the study. Age matched child who were admitted with fever due to any cause but had no history of seizure were considered as control in this study. Sample size was 50 in case group and 50 in control group.

Informed written consent was taken from each parent or guardian of each subject before enrollment. Meticulous history was taken and detailed clinical examination was done and recorded in predesigned structured schedule.

Demographic data like age, sex, occupation of parents, housing status were taken. The question was asked and scrutinized with how many times seizure occurred for the last 24 hours before admission in hospital, how long seizure persisted, any family member suffering from same disease and any previous diagnosis rather than febrile seizure. Serum calcium and magnesium were measured by photometric method. Updates of study, problems or any issues regarding this study were consulted time to time with honorable guide.

2.6 laboratory testing

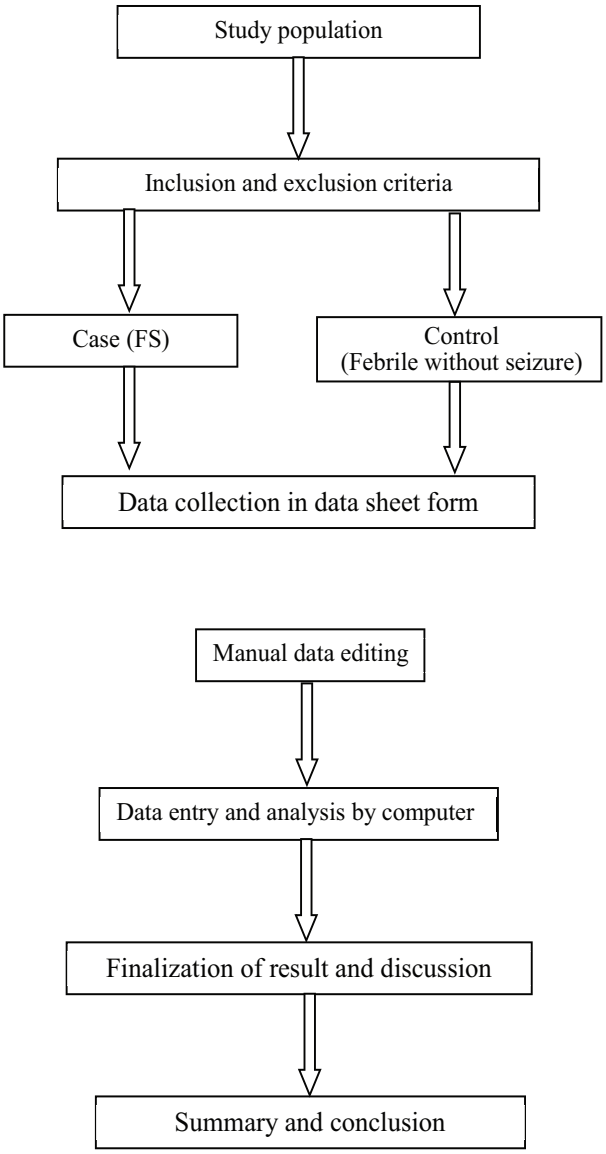
5 ml venous blood was drawn under aseptic precaution in both group and S. calcium and magnesium levels were measured using electrolyte analyzer (SIEMENS DIMENSION EXL, GERMANY, VITROS- 250 JHONSHON and JHONSHON USA) in biochemical laboratory where analyzer facilities available. Serum calcium and magnesium were measured by photometric method

2.7 Statistical Analysis

Data was analyzed by the software statistical program for social sciences (SPSS 25.0 Inc).

Categorical variables were presented as frequency & percentage and continuous variables were shown as mean ± SD. Statistical analyses were performed by Chi-square test and/or Fisher's exact test as applicable for comparing qualitative variables and for quantitative variables using unpaired *t*-test and/or Mann-Whitney U test for comparing between the groups. Pearson's Correlation Coefficient test was done to observe the correlation between low calcium and magnesium level in febrile seizure. A p-value of <0.05 was considered as significant for all analytical tests. The summarized data was presented in the form of tables.

Study Flow Chart



2.8 Operational definition

Febrile Seizures (FS): Seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and

not meeting the criteria for other acute symptomatic seizures.

Febrile seizure plus: Recurrence of febrile seizure within 24 hours

Complex febrile seizure: Prolonged duration of convulsion (more than 15 minutes), focal, and / or recurs within 24 hours.

Recurrent febrile seizure: Has history of previous febrile seizure.

Febrile status epilepticus: Febrile seizure lasting longer than 30 minutes.

Serum calcium level: The normal level of calcium in 8.5 -10.8 mg/dl.

Hypocalcaemia is defined as serum calcium levels below 8.5 mg/dl.[2]

Serum magnesium level: The normal plasma magnesium levels are 1.5 to 2.3 mg/dl. Hypomagnesaemia is defined as serum magnesium levels below 1.5 mg/dl [2]

Results:

Among one hundred participants including cases and control male children were predominant 72% and female 28%, in control group 60% were male and 40 % were female. P value was 0.205 which was non-significant. In case group mean age was 28.82±15.39 months and 23.44±13.58 months in control group. P value was 0.067 which was not significant. (Table I)

Table-I

Age and gender distribution of the study subject (N=100)

Variables	Group A (Case) (n=50) No. (%)	Group B (Control) (n=50) No. (%)	p-value
Age (months)			
6-12	4 (8.0)	13 (26.0)	
13-24	25 (50.0)	23 (46.0)	
25-36	5 (10.0)	10 (20.0)	
37-48	9 (18.0)	0 (0.0)	
49-60	7 (14.0)	4 (8.0)	
Total	50 (100.0)	50 (100.0)	
Mean±SD	28.82±15.39	23.44±13.58	0.067^{ns}
Gender			
Male	36 (72.0)	30 (60.0)	0.205^{ns}
Female	14 (28.0)	20 (40.0)	

Unpaired t-test was done for quantitative variables and Chi-square test was done qualitative variable, ns= not significant

Among the cases of febrile seizures most common type of seizure was simple in type thirty one among total fifty and it occurred mostly between 13-24 months. And recurrent febrile seizure was not so rare among the febrile convulsive children, which was 42%. (Table II)

Table-II

Distribution of study subjects by type of febrile seizure (n=50)

Age group (months)	Simple FS (n=31) No. (%)	Complex FS (n=17) No. (%)	FS epilepticus (n=2) No. (%)
6-12	4 (12.9)	0 (0.0)	0 (0.0)
13-24	8 (25.8)	15 (88.2)	2 (100.0)
25-36	5 (16.1)	0 (0.0)	0 (0.0)
37-48	8 (25.8)	1 (5.9)	0 (0.0)
49-60	6 (19.4)	1 (5.9)	0 (0.0)
Total	31 (100.0)	17 (100.0)	2 (100.0)

Table-III

Distribution of the patients by recurrent febrile seizure (n=50)

Recurrent febrile seizure	Frequency	Percentage (%)
Present	21	42.0
Absent	29	58.0
Total	50	100.0

Table-IV shows 62% patient's duration of seizure was <15 minutes, 66% patients had generalized seizure.

Table-IV

Distribution of the study subjects by duration and frequency of convulsion in the present episode in Group A (n=50)

Variables	Frequency	Percentage
Duration of seizure (minutes)		
<15	31	62.0
15-30	17	34.0
> 30	2	4.0
Total	50	100.0
Type of seizure		
Generalized	33	66.0
Focal	17	37.0
Total	50	100.0
Frequency of convulsion		
One episode/24 hours	33	66.0
Two or more/ 24 hours	17	34.0
Total	50	100.0

Serum calcium among the cases was significantly lower than control group. Mean calcium of case and control were 8.28±1.09 and 9.07±0.82 respectively; P value was <0.001. Mean magnesium of case and control group were 2.11±0.68 and 2.40±0.67 respectively. P-value was 0.036 which was significant. Table

Table-6 shows hypocalcaemia in case and control group (<8.5mg/dl) was 58% and 28 % respectively. P-value was 0.002 which was significant. Hypomagnesaemia in both groups. In Group A Hypomagnesaemia was present 20% and there was 2% hypomagnesaemia in control group. P-value was 0.004 which was significant.

Table-V

Comparison of Serum Calcium and Serum Magnesium between two groups (N=100)

Variable	Group A (Case) (n=50) Mean±SD	Group B (Control) (n=50) Mean±SD	p-value
S. Calcium (mg/dl)	8.28±1.09	9.07±0.82	<0.001[s]
S. Magnesium (mg/dl)	2.11±0.68	2.40±0.67	0.036[s]

Unpaired t-test was done, s= significant

Table-VI

Distribution of Hypocalcaemia and Hypomagnesaemia in study subject (N=100)

Variables	Group A (Case) (n=50) No. (%)	Group B (control) (n=50) No. (%)	p-value
Hypocalcaemia (<8.5mg/dl)	29 (58.0)	14 (28.0)	0.002[s]
Normal (>8.5 mg/dl)	21 (42.0)	36 (72.0)	
Total	50 (100.0)	50 (100.0)	
Hypomagnesaemia (<1.5g/dl)	10 (20.0)	1 (2.0)	0.004[s]
Normal (>1.5 mg/dl)	40 (80.0)	49 (98.0)	
Total	50 (100.0)	50 (100.0)	

Chi-square test was done, s= significant

Table-VII

Serum calcium and magnesium among different age group in Subjects with febrile seizure (n=50)

Age groups (months)	N	Mean±SD Minimum	Range Maximum	p-value		
S. calcium (mg/dl)	6-12	4	8.40±0.36	8.10	8.90	0.537[ns]
13-24	25	8.52±1.08	5.80	10.00		
25-36	5	7.74±0.98	6.80	9.20		
37-48	9	8.01±1.15	6.20	9.80		
49-60	7	8.09±1.39	5.50	10.00		
Total	50	8.28±1.09	5.50	10.00		
S. Magnesium (mg/dl)	6-12	4	2.25±0.10	2.20	2.40	0.743[ns]
13-24	25	2.18±0.71	1.10	3.90		
25-36	5	1.78±0.37	1.30	2.20		
37-48	9	1.98±0.70	1.10	3.20		
49-60	7	2.19±0.96	1.20	3.90		
Total	50	2.11±0.68	1.10	3.90		

ANOVA test, ns= not significant

Table-VII shows the mean and range of serum calcium and S. magnesium among different age group in group A. p –value is not significant.

Table VIII shows in group A hypocalcaemia, hypomagnesaemia was found in 46 % and 8%. Combined hypocalcaemia and hypomagnesaemia was present in group A 12%. In group B hypocalcaemia, hypomagnesaemia was found in 28% and 2%. Combined hypocalcaemia and hypomagnesaemia was present in group B 0%. P - value was 0.001 which was significant.

Table IX shows there was no significant change of serum calcium and serum magnesium level in different types of seizure is case group.

Table X shows the mean of serum calcium was insignificant in first febrile seizure and recurrent febrile seizure. But the result of serum magnesium was significant in first and recurrent febrile seizure, which had previous history of febrile seizure had low magnesium than first febrile seizure.

Table-VIII

Distribution of hypocalcaemia, hypomagnesaemia and combined in study subject (N=100)

Variables	Group A (Case) (n=50) No. (%)	Group B (Control) (n=50) No. (%)	p-value
Hypocalcaemia alone (<8.5mg/dl)	23 (46.0)	14 (28.0)	0.001[s]
Hypomagnesaemia alone (<1.5g/dl)	4 (8.0)	1 (2.0)	
Combined hypocalcaemia and hypomagnesaemia	6 (12.0)	0 (0.0)	
Normal	17 (34.0)	35 (70.0)	
Total	50 (100.0)	50 (100.0)	

Chi-square test was done, s= significant

Table-IX

Comparison of serum calcium and serum magnesium among different type of seizure (n=50)

		N	Mean±SD	p-value
Serum calcium (mg/dl)	Simple	31	8.11±1.12	0.204[ns]
	Complex	17	8.47±1.00	
	Febrile seizure epilepticus	2	9.35±0.92	
	Total	50	8.28±1.09	
S. Magnesium (mg/dl)	Simple	31	2.03±0.61	0.227[ns]
	Complex	17	2.18±0.76	
	Febrile seizure epilepticus	2	2.85±1.06	
	Total	50	2.11±0.68	

ANOVA test, ns= not significant

Table-X

Comparison of serum calcium and serum magnesium in recurrent febrile seizure (n = 50)

Variable	With recurrent febrile seizure (n=21) Mean±SD	Without recurrent febrile seizure (n=29) Mean±SD	p-value
S. Calcium (mg/dl)	7.99±1.10	8.49±1.05	0.114[ns]
S. Magnesium (mg/dl)	1.89±0.73	2.28±0.62	0.045[s]

Unpaired t-test was done, s= significant r=+.380, p=< 0.01

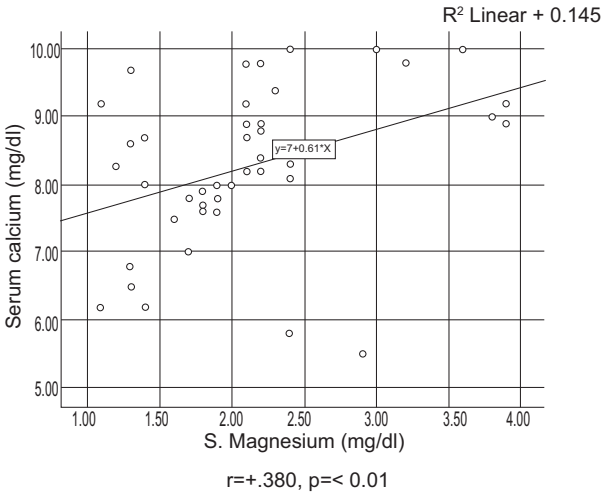


Fig.-1: *Scatter diagram showing the correlation of S. Magnesium with S. calcium in febrile seizure.*

Discussion

About 58% children experienced febrile seizures have lower calcium level than control group. Mean calcium of case and control were 8.28±1.09 and 9.07±0.82 respectively and which is highly significant; P value was <0.001. The findings suggest that children having febrile seizures suffer from calcium deficiency. In a study Sharma, et al. (2018) found mean ionized calcium level was 4.62±0.26mg/dl and 4.88±0.27 mg/dl in study and control groups respectively and this difference was found statistically highly significant (p<0.001).

In a study by Akbayram, et al. (2012) where 48 children with febrile seizures were compared with age matched controls and found low serum calcium (P=0.001)[11]. Similar result was found by in their studies by Chiarelli, et al. (1985) where Serum levels of sodium and calcium were significantly lower in children with FS [12]. In a hospital based case control study in Jaipur India Sharawat, et al. (2016) found mean calcium of case and control group 8.2 ± 0.6 and 9.0 ± 0.6 mg/dl and p value was < .001 which was significant [13]. Definite association was found between serum calcium levels and the occurrence of febrile seizures in their study although calcium levels were not in the hypocalcemic range, they were decreased enough to cause a statistical significance in precipitating febrile seizures [14]. On the other hand Rutter and Smales, (1976) & Sayedzadeh and Hemati, (2007) failed to show any association between low Serum calcium and FS in studies by [15,16].

In current study mean magnesium of case and control group were 2.11±0.68 and 2.40±0.67 respectively. P-value of the mean was significant.

Iyshwarya, et al. (2013) found hypomagnesaemia act as a precipitating factor in febrile seizure in their study[17]. Papierkowski, et al. (1999) also reported similar findings in their studies [18]. But there is no significant changes observed among the other two groups.

During any acute febrile disease, disturbances in water and electrolytes occur frequently. It has been suggested that change in serum calcium might enhance the susceptibility to seizures. Action of magnesium level on nervous system multidimensional, it reduces the release of acetyl choline at the neuromuscular junction by antagonizing calcium ions at presynaptic junction, reduced excitability of nerves, and acts as anticonvulsants, reverses cerebral vasospasm. It is suggested that alteration in magnesium concentration in plasma and intracellular matrix give rise to functional impairment of the cell membranes, which might trigger seizures. Recent evidences indicate that the deficiency of magnesium play a significant role in febrile convulsion. Magnesium plays an important role in establishing electrical potential across cell membrane. It also affects calcium metabolism as the production of cyclic adenosine monophosphate is magnesium dependent which in turn controls release of parathyroid hormone[19,20,21]. In clinical practice, hypomagnesemia is underdiagnosed or incorrectly measured in patients with febrile seizure. People with modern diets are more likely to have low magnesium stores in their body, and magnesium can modulate seizures. For these reasons, it could be beneficial to, measure magnesium levels in patients with febrile seizure.

In this study the mean age was 28.82±15.39 months and 23.44±13.58 months were in case and control group. Cases were more in male 72% and female 28%, in control group 60% were male and 40 % were female. Naseer and Patra, (2015) found mean age of case was 21.74 ± 14.24 months and that of controls is 31.72 ± 20.99 and 62% of cases were males whereas 39% were females with male preponderance in their study[27].

Mollah, et al. (2002) showed in their study that male children are more prone to developed febrile seizure.[22]

Goutham, Dhingra and Shankar, (2017) found Mean age of cases with febrile convulsion and febrile patients without seizures were 1.97years ± 1.33 years and 2.01years ± 1.02 years respectively [3]. There were 24 male and 21 female babies in group-I and 23 male and 22 females in group-II. The mean age and sex were similar in both groups. Mean level of magnesium were 1.97±0.24 and 2.19 ± 0.20 in cases with febrile convulsion and febrile patients without seizures respectively and there was significant difference (p=0.001). They got a positive co relation between levels of serum magnesium and febrile convulsion.

Similarly recent study done in 2013 in Ain Shams University and National Research Centre, Egypt to assess blood levels of trace elements in familial febrile convulsion concluded that serum selenium and magnesium levels were significant low and logistic regression model in their study showed that selenium and magnesium have protective effect in children with febrile convulsion (Salah et al., 2014). [23]

In our study there was the significant positive correlation of S. Magnesium with S. calcium in febrile seizure. Multivariate logistic regression showed hypocalcaemia and hypomagnesaemia are independent risk factor for febrile seizures. In hypocalcaemia OR=2.144 and hypomagnesaemia (OR 1.2).

Namakin, et al. (2016) found that serum Zn, Na, Ca, and Mg levels were significantly lower in children with simple febrile seizure in comparison with febrile children without seizure [24].

Baek, et al. (2018) concluded in their study hypomagnesaemia was more common and serum iMg2+ level was lower in patients with febrile seizures than in controls [25]. They concluded further evidence is needed for the causal relationship between low magnesium and febrile convulsions. Nemichandra, et al. (2017) found mean serum magnesium levels in cases and controls were 2.13± 0.46 mg/dl and 2.61± 0.54 respectively [26]. They concluded that deficiency of trace elements may be significantly related to the risk of febrile seizures in children.

Conclusion

Hypocalcaemia were more in 25-36 months of age and hypomagnesaemia 37-48 months among febrile seizure cases. Hypomagnesaemia were more in patients who had previous febrile seizure (1.89 ± 0.73 mg/dl, p- value 0.045). Association and positive correlation were found between serum calcium and serum magnesium with febrile seizure and more in recurrent febrile seizure.

Recommendations

It may be considered that all children 6 months to 60 months of age with risk of febrile seizure should be screened for hypocalcaemia and hypomagnesaemia in order to reduce the risk of recurrence of febrile seizure. Further larger scale prospective follow up study is needed to draw a more significant inference.

Limitations of the study

Although result of the study in respect to clinical outcome revealed statistically significant and support the hypothesis there were some major limiting factors which might have affect results.

1) Number of study population was limited.
2) It was a single center study.
3) The study had time limitation.

Ethical consideration:

1. Keeping compliance with Helsinki Declaration of Medical Research Involving Human Subjects 1964, all patients were informed verbally about the study design and the purpose of the study.
2. Participants had the right to withdraw themselves from the project, at any time, for any reasons.
3. Written informed consent was taken from the respondents.
4. No data will be disclosed without the permission of the respondents.
5. No forceful attempt was made to interview any unwilling respondent.
6. Permission was taken from the academic and institutional Ethics Review Committee (ERC) of Sir Salimullah Medical College & Mitford Hospital (SSMC&MH), Dhaka for conducting the study.
7. Permission for the study was taken from the concerned departments of the institute.

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