



SERUM ZINC LEVELS IN CHILDREN WITH SIMPLE FEBRILE SEIZURES

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ABSTRACT

Background And Objective: Febrile convulsions are the most common type of seizures disorder in children. Febrile seizure is an event in infancy and early childhood usually occurring between 6 months and 5 years of age, associated with fever but without the evidence of intracranial infection or defined cause. The aim of the present prospective analytical case control study was to estimate the levels of serum zinc in children with febrile convulsions and to compare serum zinc levels between children with febrile seizures and febrile children without seizures

Materials And Methods: A comparative study was done on 100 children for one year period from August 2014 to July 2015, in Rajah Muthiah medical college & hospital, Chidambaram. Of these 50 children were diagnosed to have febrile convulsions. The other 50 were febrile children without seizures. Serum zinc levels were measured in all 100 subjects using calorimetric methods. Data was analyzed.

Results: Mean Serum zinc levels in children with febrile seizures were 68.4 micrograms/deciliter and mean serum zinc levels in control group was 94.1 micrograms/dl ($p=0.0001$).

Interpretation And Conclusion: These findings revealed that there is correlation between serum zinc and simple febrile seizures. Serum zinc level was significantly lower in children with simple febrile seizures in comparison with febrile children without seizure.

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INTRODUCTION

A seizure is a paroxysmal event caused by abnormal electrical discharge inside the brain [1]. Febrile seizure is one of the most common types of seizure occurring in children between 5 months and 6 years of age, accounting for 30% of all seizures in children [2, 3]. This is an age dependent response of the immature brain to fever in children [4], who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures [5]. Eighty to eighty five percent febrile seizures occur between 6 months and 3 years of age, with peak incidence at 18 months [6, 7]. A child with a simple febrile seizure has potential for recurrence and 2-7% of children may develop epilepsy by adolescence [8, 9]. Contrary to simple febrile seizure, complex febrile seizures are prolonged (>15 minutes), focal and occur more than once in 24 hours [10].

Zinc is an important micronutrient that plays a significant role in growth and development, immune system response, enzymatic activity of different organs, proteins and cellular metabolism, neurological functions, nerve impulse transmission and hormone release [11,12]. The possible role of zinc deficiency in provoking febrile seizures has been reported in different studies [13,14]. Zinc stimulates the activity of pyridoxal kinase, the enzyme that modulates GABA level, a major inhibitory neurotransmitter [15]. It also modifies the affinity of neurotransmitters and thus prevents the excitatory neuronal discharge [2]. In addition, zinc significantly reduces the severity of illness and the duration of fever in children with pneumonia and diarrhea by the activation of immune enhancing T-cells [11, 16].

Earlier no such study has been done in this region to see the association between low serum zinc level and febrile seizure. This study will provide a base line data and help

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in the formulation of guidelines for zinc supplementation as a part of management of febrile seizure.

METHODS AND MATERIALS

The study is a prospective Case control study done in Rajah Muthiah Medical College and Hospital. It is a 1200 bedded tertiary care centre serving the rural population. The study was done in a period of one year from April 2014 to March 2015. A total of 50 children admitted with simple febrile seizures (generalized tonic clonic seizures), aged between 6 months and 5 years were included in the study group. 50 age matched children with fever and without febrile seizure were included as the control group. The following children were excluded from the study: Children on zinc supplementation, Children with afebrile seizures, Children on any medications (antiepileptic drugs), Children with malnutrition (grade III and grade IV) according to I.A.P classification, Children with seizure disorders, Children with diarrheal disease, Children with central nervous system infections, Children known to have zinc deficiency and Children with simple febrile convulsions who are admitted for second time.

The study was approved by Institutional ethical committee. Informed Consent was obtained from the subject's parents or guardians. A detailed history was obtained including age, sex, socioeconomic status, duration of fever before onset of seizures, duration of seizures, consanguinity, family history of febrile seizures and consanguinity. Complete physical examination of the child was performed with weight, height, head circumference and mid arm circumference to emphasis that there is no evidence of malnutrition. All children were subjected to the following investigation: Hemoglobin and total leukocyte count which was done by auto analyzer and serum zinc done by calorimetric method. Normal range of serum zinc levels were taken as 70 to 150 micrograms/dl.

RESULTS AND ANALYSIS

The following results were made from the study. The study group consisted of 50 cases and 50 controls.

Descriptive Datas

Age

The cases and controls were age matched in our study

Table 1 Age distribution of cases

AGE Group Months	Cases		Controls	
	No.	%	No.	%
<12	21	42	21	42
13-24	22	44	22	44
25-36	5	10	5	10
37-48	2	4	2	4
Total	50	100	50	100

Majority of the cases were between 1 to 2 years (44%). Infants were 42%. Very few children were between 2 to 3 years (10%) and between 3 to 4 years (4%).

Gender

Table 2 Gender distribution of cases and controls

Gender	Cases		Controls	
	No.	%	No.	%
MALE	33	66	26	52
FEMALE	17	34	24	48
TOTAL	50	100	50	100

Socio Economic Status

Table 3: Socioeconomic status among cases and controls

Class	Cases		Controls	
	No.	%	No.	%
I	2	4	3	6
II	10	20	14	28
III	15	30	14	28
IV	16	32	13	26
V	7	14	6	12
TOTAL	50	100	50	100

We used kuppuswamy scale to divide our cases and controls into 5 classes each. out of 100 children 2 (4%) in cases and 3 (6%) in controls were among class I . 10 (20%) in cases and 14 (28%) in control group were in class II. 15 (30%) in cases and 14 (28%) in control group were in class III. 16 (32%) in cases and 13(26%) in control group were in class IV. 7(14%) in cases and 6 (12%) in control group were in class V. These statistics shows that most of the children fall in class III & IV.

Cause of fever

Table 4 cause of fever distribution among cases and controls

Cause of fever	Cases		Controls	
	No.	%	No.	%
URTI	37	74	38	78
UTI	4	8	4	8
VIRAL FEVER	5	10	4	8
AOM	4	8	3	6
TOTAL	50	100	50	100

In the present study out of 100 children 37(74%) in cases and 38(78%) in controls were having upper respiratory tract infection. 4 (8%) in cases and 4 (8%) in controls were having urinary tract infection. 5 (10%) in cases and 4 (8%) in controls were having viral fever without a focus. 4 (8%) in cases and 3 (6%) in controls were having acute otitis media. Most of the children in cases and control group had upper respiratory tract infection.

Duration of Seizures

Table 5 Duration of seizures among cases

Duration of seizures (in minutes)	Cases	
	No.	%
<5	14	28
5-10	22	44
10-15	14	28
Total	50	100

In the present study out of 50 children in cases group 14 (28%) of them had seizures lasting for less than 5 minutes, 28 (44%) of them had seizures ranging between 5 to 10 minutes, 14 (28%) of them had seizures ranging between 10 to 15 min. Nearly half of them had seizures lasting for 5 to 10 minutes which constituted majority of the case group. 72% of children had seizures less than 10 minutes.

Duration of Fever before the Onset of Seizures

Table 6 Distribution of duration of fever before the onset of seizures among cases

Duration of Fever before the onset of Seizures (In Hours)	Cases	
	No.	%
<24	37	74
>24	13	26
Total	50	100

In the present study out of 50 children in cases group 37 (74%) of them had seizures within 24 hours after onset of fever and 13 (26%) had seizures after 24 hours of onset of seizures. Most of the children had seizures within 24 hours of onset of fever.

Consanguinity

Table 7 Consanguinity distribution among cases and controls

Consanguinity	Cases		Controls	
	No.	%	No.	%
Yes	5	10	13	26
No	45	90	37	70
Total	50	100	50	100

In the present study out of 100 children 5(10%) in the case group and 13 (26%) in control group were born for consanguineous marriage. 45(90%) in case group and 37 (70%) in control group did not have any history of consanguinity.

Family history of febrile seizures

Table 8 Family history of febrile seizure distribution among cases and controls

Family history Of febrile Seizures	Cases		Controls	
	No.	%	No.	%
Present	11	22	7	14
Absent	39	78	43	86
Total	50	100	50	100

In the present study out of 100 children 11(22%) in cases group and 7(14%) in control group had family history of febrile seizures, 39(78%) in cases group and 43(86%) in control group did not have family history of febrile seizures.

Hemoglobin

Table 9 Hemoglobin distribution among cases and controls

Hemoglobin	Cases		Controls	
	No.	%	No.	%
<11gms%	37	74	27	54
>11gms%	13	26	23	46
Total	50	100	50	100

In the present study out of 100 children 37(74%) children in cases group and 27(54%) in control group had hemoglobin less than 11gms %, 13(26%) children in cases group and 23(46%) in control group had hemoglobin more than 11gms%. The normal hemoglobin limits were taken as 11 grams% according to W.H.O definition of anemia.

Serum Zinc

Table 10 Serum zinc levels among cases and controls

Serum zinc	Cases		Controls	
	No.	%	No.	%
Normal	19	38	45	90
Low	31	62	5	10
Total	50	100	50	100

$p=0.000$ degree of freedom (df) = 1

In our study 31(62%) of the children in cases group had low serum zinc levels and only 5(10%) of children in control group had low serum zinc levels. On other hand only 19(38%) of children in case group and 45(90%) of children in control group had normal serum zinc levels. When the cases were compared with age matched controls the comparison was highly significant.

Analysis of Serum Zinc Status with Other Variables

Serum zinc levels were significantly low in children with febrile seizures when compared with age matched children with fever but without seizures. It was statistically highly significant with a p value of 0.000

Socio economic status was statistically significant in the children with febrile seizures when compared with age and sex matched controls. Serum zinc levels were low in low socioeconomic status people and it was highly significant with a p value of 0.000

In our study all subjects had seizures duration of less than 15 minutes. Our study also shows that lower the serum zinc levels, longer the duration of seizures. It is statistically highly significant with a p value of 0.000.

DISCUSSION

Febrile seizure is one of the most common types of seizures in pediatric age group. The incidence of febrile seizures is 2% to 5% worldwide. It is generally believed that, febrile seizure is an age dependent response of the immature brain to fever. This postulation is supported by the fact that most (80-85%) febrile seizures occur between 6 months and 3 years of age, with the peak incidence at 18 months^(17,18,19) Although the mechanism of this increased

Table 11 Analysis of Serum Zinc Status with Other Variables

Variables	Serum Zinc Cases				Serum Zinc Controls		p value <0.05 is significant
	Normal	Low	Normal	Low			
AGE in months	<12	6	15	19	2	1.442	
	13-24	10	12	20	2		
	25-36	2	3	5	0		
	37-48	1	1	1	1		
Gender	Male	12	21	22	4	0.74	
	Female	7	10	23	1		
Socio Economic status	I	2	0	2	1	0	
	II	10	0	14	0		
	III	4	11	14	0		
	IV	1	15	12	1		
	V	2	5	3	3		
Duration of Seizures (In Minutes)	<5	13	1	-	-	0	
	05-Oct	4	18	-	-		
	Oct-15	2	12	-	-		
Duration of Fever (in hours)	<24	16	21	-	-	0.198	
	>24	3	10	-	-		
Family history of Febrile seizures	Yes	4	7	7	0	0.899	
	No	15	24	38	5		
Haemoglobin	Normal	5	8	20	3	0.968	
	Low	14	23	25	2		

susceptibility is unclear, animal models suggest that there is enhanced neuronal excitability during the normal brain maturation.⁽²⁰⁾

The exact cause of febrile seizures is still a mystery. However a variety of cause are proposed to be involved in the pathogenesis of febrile seizures such as genetic factor, environmental factors, iron deficiency, immunological disorders and zinc deficiency. Though the association of serum zinc deficiency in febrile seizures is existent and well described in literature, the epidemiological data available regarding the same is less in India. Limited numbers of studies were conducted in Indian population in febrile seizures with probable hypozincemia as a risk factor for febrile seizures.

In this study we have tried to compare serum zinc status with socioeconomic status, duration of seizures, duration of fever before onset of seizures, family history of febrile seizures, hemoglobin, and febrile children with and without seizures to find out any association with serum zinc status.

Demographics

Study population was divided in two groups; 50 children with febrile convulsions (cases) and 50 febrile children without seizures (controls).

Demographic parameters like age, sex were comparable in both the groups.

Gender

In cases majority were males (66%) and remaining were females (34%). This shows a clear cut male

preponderance. M: F ratio=1.9:1. In controls 52% are male and remaining were females (48%). The results in other Indian studies done by Ganesh *et al* study⁽²¹⁾ and Leelakumari *et al*⁽²³⁾ did not show significant male preponderance; while Lestari *et al*⁽²²⁾ found that simple febrile seizures most commonly occurred in males (M:F=1.3:1). Our results are compared with other studies also which are as follows

Age

Hartfield *et al* ⁽²⁴⁾ reported that maximum children with febrile seizures were in the age group less than 24 months and mean age was 17.9 months. The mean age of children with febrile seizures in our study is also 17.9 months. This is because the febrile seizures incidence peaks at 18 months according to the literature ^(17, 18, and 19). In a study done by LeelaKumari *et al* ⁽²³⁾, the found the 55.8% of cases and 56.5% of controls were in the age group less than 17 months. Alberto Romero Guzman *et al* ⁽²⁵⁾ found that 55% of children with febrile seizures were among 6 months to 24 months. Which are mostly similar to our study were 44% of children in 12-24 months and 82% of children were in 6 to 24 months age group. This is because the febrile seizures incidence peaks around 18 months.(17,18,19)

Cause of Fever

In our study, both cases and controls have comparable diagnosis. Upper respiratory infection dominated the tables in both the groups. 74% of children with febrile convulsions group and 78% of febrile children without seizures had upper respiratory tract infection. This is because the cause of fever in children with febrile convulsion is mostly viral in origin. Other causes being

viral fever without a focus, urinary tract infection, and acute otitis media. Tomoum *et al*⁽²⁶⁾ says infections causing febrile seizures were mostly viral in origin (60%) which is similar to our study.

Family History of Febrile Seizures

In the present study, 11(22%) cases had family history of febrile seizure. Offringa *et al*⁽²⁷⁾ in 1994 studied that, of children with febrile seizures 24% had family history of febrile seizures which is similar to our study.

Socioeconomic Status

India being a developing country has largest number of people living under poor socioeconomic class. In present study, 62% of children belonged to class III and IV socioeconomic status among cases and 54% among controls.

In our study as the socioeconomic status decreases (According to kuppuswamy scale), serum zinc levels also decreases. There are no major studies proving this entity in India.

Duration of Seizures

In our study we found out that lower the serum zinc levels longer the duration of seizures

Study	<5min	5 to 10 min	10 to 15 min
Present study	28%	44%	28%
Mean serum zinc levels	77.9 micgr/dl	64.8 micgr/dl	61.2micgr/dl
Margaretha <i>et al</i> (2009)(125)	12%	72%	16%

Sadlier⁽²⁸⁾ *et al* found out that 87% of the children in their study had seizures <10 min, while 9% had seizures lasted for 15 min which is mostly similar to our study where children with seizures < 10 min were 72%.

Berg *et al*⁽²⁹⁾ in 1996 also found out that 87% of children had febrile seizures for < 10 minutes and only 9 % of children had seizure for more than 15 minutes.

Febrile Seizures and Serum Zinc Levels

The results of this study detected that Serum zinc levels was significantly low in children who had simple febrile seizures in comparison with children who had fever without febrile seizures.

Normal serum zinc levels 70 to 150 milligrams/deciliter Similar results were seen in other studies which are as follows

Papierkowski *et al*⁽³⁰⁾ from Poland in 1999, has done a study with 33 children aged 8 months to 60 months including 18 children with febrile seizures and 15 healthy children in control group, zinc and magnesium were evaluated in serum and CSF compared it to control group. They observed that serum and CSF zinc levels were significantly low in children with febrile seizures when compared with healthy children in control group.

Gunduz *et al*⁽³¹⁾ from turkey in 1996 did a study to determine the serum and CSF zinc levels in children with febrile convulsions. They observed that serum and CSF zinc levels was decreased in children with infectious diseases and this decrease was more significant in patients with febrile convulsions. Serum Zn levels of groups A, B, C and D had a mean of 0.70 +/- 0.10 mg/dL, 1.07 +/- 0.08 mg/dL, 1.26 +/- 0.32 mg/dL and 1.17 +/- 0.21 mg/dL, respectively, and the values of group A were lower than those of the other three groups

Kumar *et al*⁽³²⁾ in a prospective analytical case control study in 2011 found out that mean serum zinc levels were significantly lower in in children with febrile seizures as compared to controls

Ehsanipour *et al*⁽³³⁾ (2003 to 2005) did a study on 92 patients aged 6 months to 5 years 3 group of patients(34 patients who had febrile seizures, 40 patients who had fever without seizures, 18 patients with non febrile seizures). It was observed that children with simple febrile seizures had lower serum zinc levels compared to other groups.

In a study done by Amiri *et al*⁽³⁴⁾ (2010) in 60 patients , there were 30 children in febrile seizures group and 30 children in control group. Serum zinc selenium and copper levels were evaluated. The mean serum zinc levels were 66.13 micrograms/dl which is similar to our study .he concluded that serum zinc and selenium levels were significantly lower in children with febrile convulsions.

Ganesh *et al*⁽²¹⁾ did a prospective case-control study in a major tertiary care hospital for children during June 2005 to May 2006 on children aged between 3 months and 5 years to compare serum zinc levels in 38 cases of simple febrile seizure and 38 age-matched controls. The mean serum zinc levels in cases and controls were 32.17 and 87.6 micrograms/ deciliter and they conclude that Indian children with febrile seizure had low serum zinc levels

Mahayar *et al*⁽³⁵⁾ (2013) did a case-control study, 52 children with febrile seizure compared with 52 healthy children based on serum zinc level. The age range of children was 9 months to 5 years. The mean zinc level in case group was 62.84 ± 18.40 and in control group 85.70 ± 16.76 (P < 0.05). This study revealed that the serum zinc level in children afflicted with their first febrile seizure is lower than in healthy children and the difference is statistically significant. This study is very similar to our study.

Zinc, as a major element of some enzymes, has an important role in some tissues like central nervous system and can affect some inhibitory mechanisms of CNS⁽³⁵⁾. It has an important role in Gamma Amino Butyric Acid (GABA) synthesis through glutamic acid decarboxylase synthesis. So, a low serum zinc level can cause decrease GABA concentration^(36, 37) Also, zinc can suppress some excitatory mechanisms in CNS. It may directly raise the threshold of the seizure level through inhibiting N methylD-aspartate (NMDA) receptors or via improving calcium inhibitory function.

CONCLUSION

- In our study serum zinc levels were low in children with simple febrile seizures in comparison with febrile children without seizures. So children with low serum zinc levels are more prone to get febrile seizures than children with normal serum zinc levels.
- In our study we also found out that children in low socio economic status group have low serum zinc levels than in high socio economic status group.
- In our study we found out that lower the serum zinc levels longer the duration of seizures. So Serum zinc levels also have an effect on Duration of seizures.
- However further multicenter studies with large number of cases are required to establish the correlation between serum zinc and febrile convulsion.

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