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Serum Zinc Levels In Simple Febrile Seizures – A Case Control Study

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ABSTRACT

Background: Febrile seizures are the most common type of seizures in childhood. Various theories have been put forward regarding the role of micro nutrients as risk factors for febrile seizures. The aim of the present study was to find out the association between serum zinc levels and simple febrile seizures in children aged between 6 months to 5 years.

Materials And Methods: This Hospital based case control study was conducted during June 2019 to June 2020 at Institute of child health & Research centre, Government Rajaji hospital, Madurai medical college, Madurai. The study population includes 70 children with simple febrile seizures and 70 children with fever without seizures as control. Serum zinc levels were measured in two groups by colorimetric method.

Results: Serum zinc level was low in 60 % (n=42) of children with simple febrile seizures and 24.28 % (n=17) of children with fever without seizures though there was no statistical significant difference in distribution of age, sex, temperature, consanguinity & nutritional status (according to IAP grading) between two groups. Mean serum zinc was 57.96 mcg/dl among cases and 84.86 mcg/dl among controls. Hence serum zinc levels were significantly low in Children with simple febrile seizures compared to fever without seizures ($p < 0.001$) in our study. Also, Majority of children with prolonged febrile seizures had low serum zinc levels.

Conclusion: This study establishes a significant relationship between low serum zinc levels and simple febrile seizures thereby substantiating Hypozincemia was one of the predisposing factors in simple febrile seizures.

Keywords: *Febrile seizures, Serum zinc levels, Epileptics, Hypozincemia, Neuronal activity.*

1. INTRODUCTION

A seizure is a transient occurrence of signs and / or symptoms resulting from abnormal excessive neuronal discharge in the brain. Epilepsy[(1)] is a disorder of brain characterized by enduring predisposition to generate seizures and by cognitive, psychologic, biological and social consequences of this condition. The lifetime incidence of epilepsy is 3 % and more than 50% of these cases starts in childhood. Infants and children are more prone to have seizures than adult. It is due to imbalance between excitatory glutamate and inhibitory GABA system resulting in greater neuronal activity in this age group. Febrile

seizures are the most common type of seizures in child hood. 19th century. Lennox is the first clinician to study the background and risk factors for febrile seizure and risk of progression to epilepsy. International League against Epilepsy developed a consensus regarding treatment of child with simple febrile seizure. Between 2 - 5 % of neurologically normal children experience atleast one simple febrile seizure. The lifetime prevalence of simple febrile seizure is 2 – 6%. The incidence of febrile seizure in India varies between 3-4 %. The peak incidence of febrile seizure occurs in the second year of life.

Although 15 % of children with epilepsy had history of febrile seizures in the past, only 2- 7 % of children with febrile seizures are prone to develop epilepsy later in life. The risk for epilepsy in simple febrile seizure is 1%and complex febrile seizure is 6%. But the risk of epilepsy in those children who experienced first a febrile seizure is 30 % and it decreases to 20 % if neurological examination, EEG and neuro imaging are normal. There are no long term adverse effects of having one or more simple febrile seizures. Children with simple febrile seizure do not experience abnormality in behavior, scholastic performance, cognition or attention when compared to age matched controls.

National institute of health in 1980[(2)] defined Febrile seizure as "Abnormal, excessive neuronal activity, occurring in age group between 3 months to 5 years, associated with fever, but without evidence of intracranial infection or defined cause" International league against epilepsy[(3)] defined febrile seizure as "epileptic seizure occurring in childhood after 1 month of age associated with fever, but without evidence of intracranial infection or defined cause. Febrile seizure in children who experienced a previous a febrile seizure are excluded from this definition (ILAE 1993).

Most recently AAP[(4)] (American academy of pediatrics) 2011 defined febrile seizure as "seizure occurring in febrile children between 6 months to 5 years who do not have a intracranial infection, metabolic disturbances or past history of a febrile seizures. Various factors have been described in the etiology of febrile seizures like genetic factors, bacterial and viral infections, circulating toxins, interleukins and temperature susceptibility of growing brain, micronutrient and iron deficiency. Of all these, genetic factors contribute strongly to the pathogenesis of febrile seizures.

Many trace elements like zinc, copper, magnesium and selenium have been described in association with febrile seizures because of their influence on lig and and voltage gated ion channels, turnover of some neurotransmitters and effect on membrane lipid peroxidation. Zinc, the second most prevalent trace element in the body. It is important for the growth, development and normal brain function. In CNS, zinc is present in synaptic vesicles in glutaminergic neurons in hippocampus and amygdala. It is released by electrical stimulation and modulate responses at both excitatory receptor (NMDA) and inhibitory receptor (GABA).

During fever [(6)], there is a acute phase response mediated bycytokines which reduces serum zinc levels. Hypozincemia[(7)] down regulate the activity of glutamic acid decarboxylase (rate limiting step in synthesis of GABA) and stimulates NMDA receptors which leads to hyperexcitability of neurons causing seizures. Our study aims to find out the association between serum zinc levels and simple febrile seizuresin children aged 6 months to 5 years.

2. MATERIALS AND METHODS

This case control Study was done over 12 months (June 2019 – June 2020) at the Institute of child health and research centre, Government Rajaji hospital, Madurai medical college. Ethical clearance was obtained from the Institutional Ethical committee, Madurai medical college. Study participants include febrile children aged between6 months to 5 years, with or without simple febrile seizures. An informed written consent obtained from Parents / Guardians of all children aged between 6month to 5 years after fully explaining the study procedure.

INCLUSION CRITERIA:

1. Cases: Children with simple febrile seizures

2. Children aged 6 months to 5 years with fever without seizures serves as control.

EXCLUSION CRITERIA:

1. Developmental delay
2. Known epileptics
3. Neurological disorders
4. Dysmorphic and Syndromic features
5. Children on zinc supplementation

A detailed history obtained including age, sex, duration of seizure, type of seizure, type of infection, family history of febrile seizure, temperature at admission were recorded. Anthropometry – weight, height, head circumference & mid arm circumference were measured. Protein energy malnutrition by IAP classification 1972 (weight for age) were graded. Vitals monitoring and systemic examination was done in all children included in our study. With all aseptic precautions, 2 ml of

blood from vein puncture were taken from both case and control group at admission. These samples were immediately sent to biochemistry laboratory. The sample was centrifuged for 3 to 4 minutes at 3000-4000 rpm. The serum thus obtained was analysed for zinc levels by colorimetric method [25].Zinc in an alkaline medium reacts with Nitro PAPS[2-(5-nitro-2-pyridylazo)-5-(N-propyl-N-sulfopropylamino) phenol, disodium salt, dehydrate to form a purple coloured complex. Intensity of the formed complex is proportional to the amount of zinc present in the sample. The normal reference[5]range for serum zinc level was 70 – 150 microgram / dl. WHO recommended cut off level for hypozincemia was < 65 microgram/dl.

STATISTICAL ANALYSIS:

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer by using SPSS 16 software. Using this software, 'p' values were calculated through One way ANOVA for raw data and chi square test for consolidated data to test the significance of difference between variables. A 'p' value less than 0.05 is taken to denote significant relationship. The linear correlation between two variables were measured by Pearson correlation coefficient (r).r is always a number between -1 and +1

$r > 0$ indicates positive correlation

$r < 0$ indicates negative correlation

$r < 0.3$ = None or Very weak correlation

$0.3 < r < 0.5$ = Weak correlation

$0.5 < r < 0.7$ = Moderate correlation

$r > 0.7$ = Strong correlation

3. RESULTS

This is a case control study conducted over a period of one year (June 2019- June 2020) which include 70 children with Simple febrile seizures (cases) and 70 children with fever without seizures (controls).In the simple febrile seizure group, 21.4 % of children were below 1year, 25.7 % between 1-2 years, 21.4 % between 2-3 years, 18.5 %between 3-4 years and 12.8 % between 4-5 years. In the fever group, 18.5 % of children were below 1 year, 28.5 %between 1-2 years, 17.1 % between 2-3 years, 22.8 % between 3-4years and 12.8 % between 4-5 years. There was no statistically significant difference in age distribution between the 2 groups **(p value 0.926).** In simple febrile seizure group, 57.14 % were males and in fever group, 64.28 % were males. Samples were gender matched with **p value (0.489).**

Table 1: correlation between temperature and mean serum zinc level

Temperature(F)	Mean serum zinc level (mcg/dl)	
	Mean	SD
100 - 100.9	72.30	30.53
101 - 101.9	73.90	33.90
> 102	64.05	36.67
P value	0.407 Not Significant	

In simple febrile seizure group, 32 had 100 -100.9 F, 24 had101-101.9 F, 14 had > 102 F which accounts to 45.71%, 34.28%and 20%.In fever without seizure group, 26 had 100-100.9F, 32 had 101-101.9 F and 12 had >102F which accounts to 37.14, 45.71% and17.14 %.Temperature distribution is statistically similar in two groups with **p value = 0.383.**There was no significant difference in relationship between temperature and mean serum zinc level (p value 0.407) [Table 1].35 children had seizures of duration 0 – 5 min of which 18 had low serum zinc levels. 22 had seizures of duration 5 – 10 min of which 13 had low serum zinc levels. 13 had seizures of duration 11 – 15 min of which 11 had low serum zinc levels. Thus majority of children with prolonged seizures had low serum zinc levels. The duration of seizures inversely correlates with serum zinc level. The children with lower zinc levels had prolonged seizures and vice versa [Table2].

Table 2: correlation between duration of seizure and mean serum zinc level.

Duration of seizures (minutes)	Mean serum zinc (mcg/dl)	SD
0 – 5	63.76	27.68
6 – 10	58.09	24.33
11 – 15	42.89	18.82
p value	**0.045 significant**	

Among children with simple febrile seizures, URI is seen in 33 cases (47%) which is the major triggering illness. Viral fever is seen in 14cases (20%). LRI is seen in 10 cases (14%). The percentage of Diarrhoea, Dengue and UTI among simple febrile seizures are 7%, 5% and 5% respectively. Among children with fever without seizures, LRI is seen in 16 cases (22.85%), Dengue is seen in 13 cases (18.57%). Enteric fever is seen in 11 cases(15.71%), URI and Diarrhoea is seen in 10 cases (14%), UTI is seen in 8 cases (11.42%) and Viral fever is seen in 2 cases(2.8 %)[Table 3].There was no relationship between focus of infection and mean serum zinc levels (p value 0.783).

Table 3: correlation between focus of infection and mean serum zinc level

Focus of infection	Mean serum zinc (mcg/dl)	SD
Diarrhoea	67.76	32.86
Dengue	82.6	31.15
LRI	61.9	30.7
URI	65.2	36.71
UTI	83.58	28.67
Viral fever	63.6	29.5
Enteric fever	94.34	27.87
p value	0.783 Not significant	

As the severity of protein energy malnutrition increases, mean serum zinc level decreases which was statistically significant **(P<0.001)**[Table4]

Table 4 : correlation between PEM Grading and mean serum zinc level:

Grading of PEM (IAP)	Mean	SD
Normal	100.19	28.18
Grade 1	78.11	24.46
Grade 2	52.38	17.24
Grade 3	46.34	16.30
Grade 4	28.57	11.49
p value	**< 0.001 Significant**	

Serum zinc levels were low in 42 children with simple febrile seizures which accounts for 60%.Serum zinc levels were low in only 17 children with fever without seizures which accounts for 24.28%.Mean serum zinc level among cases and controls were 57.96 mcg/dl and 84.86 mcg/dl. There is a statistically significant difference in the serum zinc levels between two groups **(P<0.001) [Table 5]**

Table5: Distribution of mean serum zinc level:

Serum zinc level (mcg/dl)	Simple febrile seizure		Fever without seizure	
	No	%	No	%
<65 mcg/dl	42	60 %	17	24.28 %
>65 mcg/dl	28	40 %	53	75 %
Total	70		70	
Mean	57.96		84.86	
SD	26.25		33.82	
P value	**< 0.001 ** (Highly Significant)**			

4. DISCUSSION

In this study, the mean age of simple febrile seizure was 25 months and age distribution was statistically similar in both cases and controls (p value 0.926). Ganesh R et al[8], Heydarian et al[9], Margaretha L et al[10], Talebian et al [11]& Gunduz et al[12]also reported a mean age of simple febrile seizures within the range of 21-27 months and did not show statistically significant difference in age distribution between cases and controls. This study shows a peak incidence of simple febrile seizures among children around 2 years of age. Male children out numbered the female children in the incidence of simple febrile seizures in our study. Out of 70 cases of simple febrile seizures, 57 % (n=40) were males and 42.85 % (n=30) were females. Male: Female ratio was 1.3: 1. This was similar to the gender ratio ranging from 1.3 – 1.7: 1 as reported by Ganesh R et al[8], Heydarian et al[9], Margaretha L et al[10], Talebian et al[11]& Gunduz et al[12].

In our study, 20 %(n=14) of cases and 4 % (n=3) of controls had family history of febrile seizures. There was statistically significant difference in its distribution between two groups(p=0.010). Similiar findings were reported by Saidulhaque et al[13] (20 %), Kumari P et al[14] (21.2 %), karthiekeyan P et al[15](22%), Offringa et al[16](24%).The mean age of cases with family history of febrile seizures was 20 months which is less compared to 25 months as a whole. Plochl et al[17]also reported the mean age of cases with family history of febrile seizures was 16 months compared to 20 months as a whole. Thus, cases with family history of febrile seizures experience simple febrile seizure at an earlier age. In our study, Temperature distribution shows that there was no statistically significant difference in the mean temperature between two groups (P =0.383). but vidhya sagar et al[18]reported a mean temperature was slightly higher in cases compared to controls and the difference was not statistically significant (P= 0.282).Also, there was weak negative correlation between the rise in temperature and mean serum zinc level (r value = - 0.2783) through pearson correlation coefficient analysis.

In our study, 81.4 % (n=57) of cases had seizures $\leq$ 10 minutes while 18.5 %(n=13) had seizures > 10 minutes. Sadlier et al[19] and Berg et al[20] also reported that 87 % of cases had seizures < 10 minutes which was similar to our study. Among cases, 81.4% (n=57) children had seizures $\leq$ 10 min of which 44% (n=31) had low serum zinc levels, 18.5% (n=13) had seizures > 10 min of which 15.6 % (n=11) had low serum zinc levels. Thus majority of children with prolonged febrile seizures had low serum zinc levels in our study. Mean serum

Zinc levels were also low in children who had seizures of prolonged duration which was statistically significant (P= 0.045). Karthikeyan Pet al[15]and Margaretha et al[10]also reported that mean serum zinc was significantly low(P=0.0001) in those with prolonged febrile seizures. There was moderate negative correlation (r value = -0.4983) between duration of seizures and mean serum zinc levels through Pearson correlation coefficient analysis.

In our study, Upper respiratory tract infection was found to be the major triggering illness in 47 % (n=33) of children with simple febrile seizures. Viral fever accounts for 20 %(n=14), Lower respiratory tract infection accounts for 14 %(n=10) and Diarrhoea accounts for 7 %(n=5). Dengue and Urinary tract infection accounts for 5 % (n=4) each. Margaretha et al[10], Gunduz et al[12] and Sampath kumar etal[21]also reported upper respiratory tract infections was themost common triggering illness in children with simple febrile seizures. All other studies reported viral fever was major triggering illness among simple febrile seizures. There was no relationship between focus of infection and mean serum zinc levels (P= 0.783).

In our study, there was no statistically significant difference in PEM grading distribution between two groups (P=0.462). As the severity of malnutrition increases, mean serum zinc levels decreases which was statistically significant (P< 0.001). There was strong negative correlation between severity of protein energy malnutrition and mean serum zinc levels (r=-0.75)by pearson correlation coefficient analysis. As per WHO recommendation,

Hypozincemia cut off was taken as 65 mcg/dl. Based on this cut off, serum zinc level was low in 60 %(n=42) of cases and 24.28 % (n=17) of controls. Serum zinc level was low in majority of children (60%) with simple febrile seizures, though there was no statistical significant difference in distribution of age, sex, consanguinity, temperature& nutritional status (according to IAP grading) between two groups. Mean serum zinc was 57.96 mcg/dl among cases and 84.86mcg/dl among controls. The mean difference was 27.10 mcg/dl. Hence serum zinc levels were signifcantly low(P<0.001) in children with simple febrile seizures compared to fever without seizures in our study.Okposio et al[22], Gattooet al[23], Mahyar et al[7]& Burhangnoglu et al[24] also reported mean serum zinc levels (58.70 mcg/dl, 61.53 mcg/dl, 62.84 mcg/dl and 66 mcg/dl) were significantly low (p<0.05) in simple febrile seizures compared to fever without seizures.

5. CONCLUSIONS

Serum zinc levels were significantly low in children with simple febrile seizures compared to febrile children without seizures. Also, Majority of children with prolonged febrile seizures had low serum zinc levels. Thus Hypozincemia was found to be one of the predisposing factors for simple febrile seizures. Considering the fact that zinc has multiple beneficial role in our body with extensive safety profile, its supplementation may serve as a cost effective measure for preventing simple febrile seizures in the susceptible age group. Future research should be directed towards the therapeutic trial of zinc supplementation for the prevention of febrile seizures.

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