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Study of Serum Zinc Levels in Typical Febrile Seizures

[1]Dr Syed Muneeb Mohammad*, [2]Dr Nisar Ahmad Ganie, [3]Dr Mohsin Rashid, [4]Dr Mohd Rafiq Lone [5]Dr Sheikh Mushtaq Ahmad [6]Dr Syed Saba Jehan

[1, 5] Department of Pediatrics and Neonatology Skims Soura
[2, 3, 4]Department of Pediatrics Skims MCH Bemina
[6]Department of Endodontics and Conservative Dentistry Govt Dental College Srinagar

***Corresponding Author:**
Dr Syed Muneeb Mohammad
Department of Pediatrics and Neonatology Skims Soura

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ABSTRACT

Introduction: A seizure is a paroxysmal event due to abnormal electrical discharge inside the brain. Febrile seizure is one of the most common neurological problems during childhood. Approximately affecting 2-5% of children before they are 5 years old. Zinc modulates the affinity of neurotransmitter's such as glutamate to their receptors and facilitates the inhibitory effect of calcium on NMDA receptors and thus prevents the excitatory neuronal discharge.

Materials and Methods: 100 children were enrolled in the study with half as cases and half as controls. Children presenting with typical febrile seizures aged between 6 and 60 months were evaluated for serum zinc levels. Similarly equal number of matched controls, presenting with fever but no seizures were evaluated for serum zinc levels.

Results: It was observed that serum zinc level was significantly low in cases of typical febrile seizures as compared to controls. Mean serum zinc level was 47.54µg/dl less in cases of typical febrile seizures as compared to controls and was highly significant with p value of <0.0001. By taking level of <65µg/dl as cutoff for hypozincemia as suggested by WHO results show that 42% of the cases and 10% of controls had bio-chemical hypozincemia and is statistically significant (P=0.0003).

Conclusion: Our study showed that serum zinc levels were low in children with typical febrile seizures in comparison with febrile children without seizures. In conclusion, low serum zinc level can be considered one of the predicting and contributing factors of febrile seizure.

Keywords: Typical febrile seizure, Zinc.

INTRODUCTION

A seizure is a paroxysmal event due to abnormal electrical discharge inside the brain [1].This is an age dependent response of the immature brain to fever in children, who do not have an intracranial infection, metabolic disturbance, or history of afebrile seizures.

Febrile seizure is one of the most common neurological problems during childhood [2]. Approximately 2-5% of children are estimated to experience at least one episode of seizure during a febrile illness before they are 5 years old. The incidence of febrile seizures varies between 2% to 4% in Western countries, whereas the incidence is 7% in Japan and higher in developing countries [3, 4].

Typical febrile seizure is a primary generalized, usually tonic–clonic attack associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period. Atypical febrile seizure is more prolonged (>15 min), is focal, and/or reoccurs within 24 hr. Febrile status epilepticus is a febrile seizure lasting longer than 30 min[5].

One major concern of parents of children with first FS is the risk of recurrence and the most important factor which increases febrile convulsion recurrence

rate is occurrence of first FS at an age of less than 1 year. Other major risk factors for recurrence of FS are duration of fever in less than 24 h and 38 to 39°C fever. Minor risk factors for recurrence of FS are positive family history of FS, family history of epilepsy, Complex FS, day care, male sex, and lower serum sodium [5].

Eighty to eighty five percent febrile seizures occur between 6 months and 3 years of age, with peak incidence at 18 months [6].Children with a typical febrile seizure have potential for recurrence and 2-7% of children may develop epilepsy by adolescence.

Typical febrile seizures do not have an increased risk of mortality even though they are, concerning to the parents when they first witness them. The exact cause of febrile seizures is not known. In some families, the disorder is inherited as an autosomal dominant trait, and multiple single genes that cause the disorder have been identified in such families. However, in most cases the disorder appears to be polygenic, and the genes predisposing to it remain to be identified. Identified single genes include *FEB 1, 2, 3, 4, 5, 6, 7, 8, 9,* and *10* genes. . Only the function of *FEB 2* is known: it is a sodium channel gene, *SCN1A* [5].

Several factors such as vitamin B6 deficiency, electrolyte disturbances, reduction in serum and cerebrospinal fluid (CSF) zinc levels, iron deficiency, iron deficiency anemia,reduction in inhibitory neurotransmitter and gamma-aminobutyric acid (GABA) levels are thought to play a role in the pathogenesis of febrile seizure [7,8,9,10,11].

Among these factors, low zinc levels in both the CSF and serum have attracted interest, and studies on the correlation between low serum zinc levels and febrile seizures are being currently conducted. Gammaaminobutyric acid (GABA) is an important inhibitory neurotransmitter. Zinc has a regulatory effect on glutamic acid decarboxylase and the synthesis of GABA [12,13].

Zinc is a trace element that has a critical role in cell division, protein synthesis, wound healing and immune function and it is estimated that 25% of the world population is at risk of zinc deficiency.

Millions of people throughout the world may have inadequate levels of zinc in the diet due to limited access to zinc-rich foods (animal products, oysters and shellfish) and the abundance of zinc inhibitors, such as phytates, common in plant-based diets [14]. Our understanding of the public health importance of inadequate zinc intakes has been hampered by lack of indicators of zinc status for identifying individuals with zinc deficiency [15].Zinc deficiency is largely related to inadequate intake or absorption of zinc from the diet, although excess losses of zinc during diarrhea may also contribute [16].

Breast milk is only an adequate source of zinc in the diets of infants aged less than six months, and zinc intakes from drinking water typically increase total zinc intakes by only 2% provided a usual water intake of 2 litre/day. The estimated global prevalence of zinc deficiency is 31%, and ranges from 4% to 73%.

It is also important to note that maternal or gestational zinc deficiency may affect immunological development in the newborn in ways that compromise immune function throughout the lifespan irrespective of zinc status [17].

Zinc modulates the affinity of neurotransmitter's such as glutamate to their receptors and facilitates the inhibitory effect of calcium on NMDA receptors and thus prevents the excitatory neuronal discharge [18].Zinc stimulates the activity of pyridoxal kinase, the enzyme that modulates GABA level, a major inhibitory neurotransmitter. 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.

MATERIALS AND METHODS:

This Prospective case control study was conducted over a period of two years in the Department of Pediatrics and Neonatology at a tertiary care institute in north india.

Patient population

Eligible participants included children aged 6 to 60 months, their weight and height were above the third percentile on WHO growth curves. A total of 100 children were enrolled in the study with 50 patients as cases and 50 patients as controls. Children presenting with typical febrile seizures aged between 6 months and 60 months were evaluated for serum zinc levels. Similarly equal number of matched controls, aged between 6 and 60 months presenting

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with fever but no seizures were evaluated for serum zinc levels.

Inclusion criteria

The inclusion criteria included:

1. Children between 6 months and 60 months of age.
2. Typical febrile convulsions.
3. Having normal growth and development.

Exclusion criteria

Exclusion criteria are as:

1. Being younger than 6 months or older than 5 years.
2. Having a history of previous afebrile convulsion.
3. Having history of recent zinc intake (within past 3 months).
4. Central nervous system infections.
5. Neurodevelopmental delay.
6. Chronic systemic diseases (endocrine, cardiac, renal, metabolic, malignancy, rheumatologic, etc.).
7. Protein energy malnutrition (PEM).
8. Acute Gastroenteritis.

The study was approved by the Institutional Ethics Committee. Informed consent was taken from the children's parents before 3cc of blood was obtained for laboratory measurement of serum zinc levels. The axillary temperature was recorded in all children for three minutes, followed by general examination and systemic examination in detail. Children in both groups were from same race/ethnicity and their dietary consumption of zinc-rich foods were similar. Serum zinc level was measured by colorimetric method.

RESULTS:

The following results were obtained from the study. The study group consisted of 50 cases and 50 controls. In the present study, 64% of cases were males and 36% were females. Among controls 56% were males and 44% of them were females, thus showing that males predominated in both the groups

Table 1: Distribution of sex among subjects

SEX	Group		Total n, (%)
	Case n, (%)	Control n, (%)	
Male	32 (64)	28 (56)	60 (60)
Female	18 (36)	22(44)	40 (40)
Total	50	50	100

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Figure 1 Represents age distribution among subjects

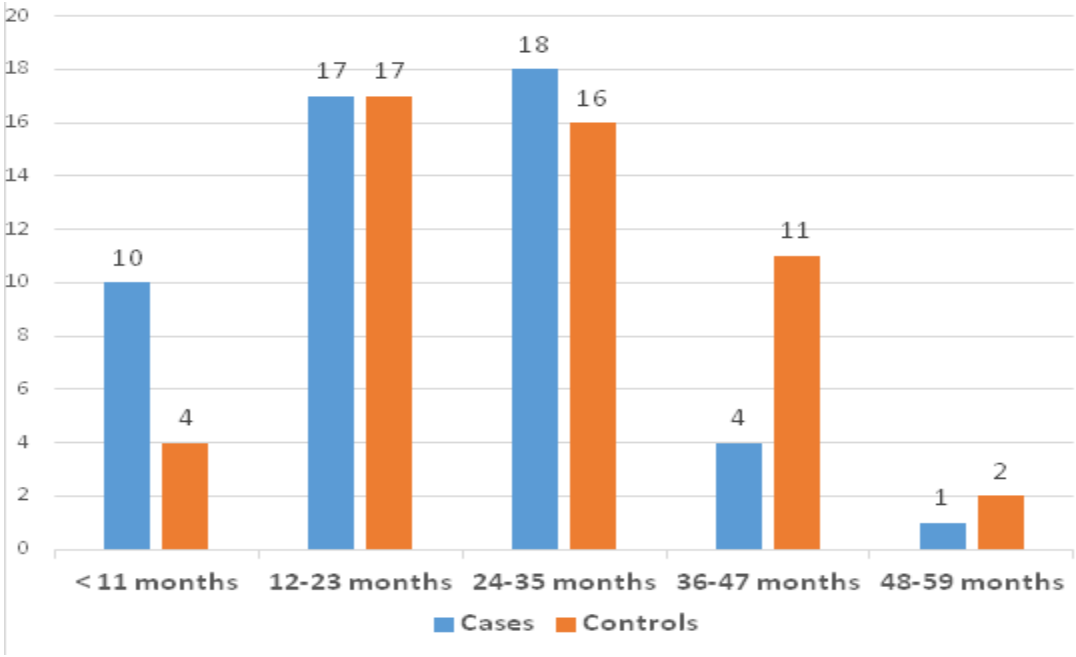

Table 2: Distribution of age among subjects

Age(months)	Group		Total n (%)
	Case n (%)	Control n (%)	
<= 11	10 (20)	4 (8)	14 (14)
12 - 23	17 (34)	17 (34)	34 (34)
24 - 35	18 (36)	16 (32)	34 (34)
36 - 47	4 (8)	11 (22)	15 (15)
48 - 59	1(2)	2 (4)	3 (3)
Total	50	50	100

Majority of the cases were between 2 to 3 years (36%) with infants (20%) and 1 to 2 years (34%), very few children were between 3 to 4 years (8%) and 4 to 5 years (2%).

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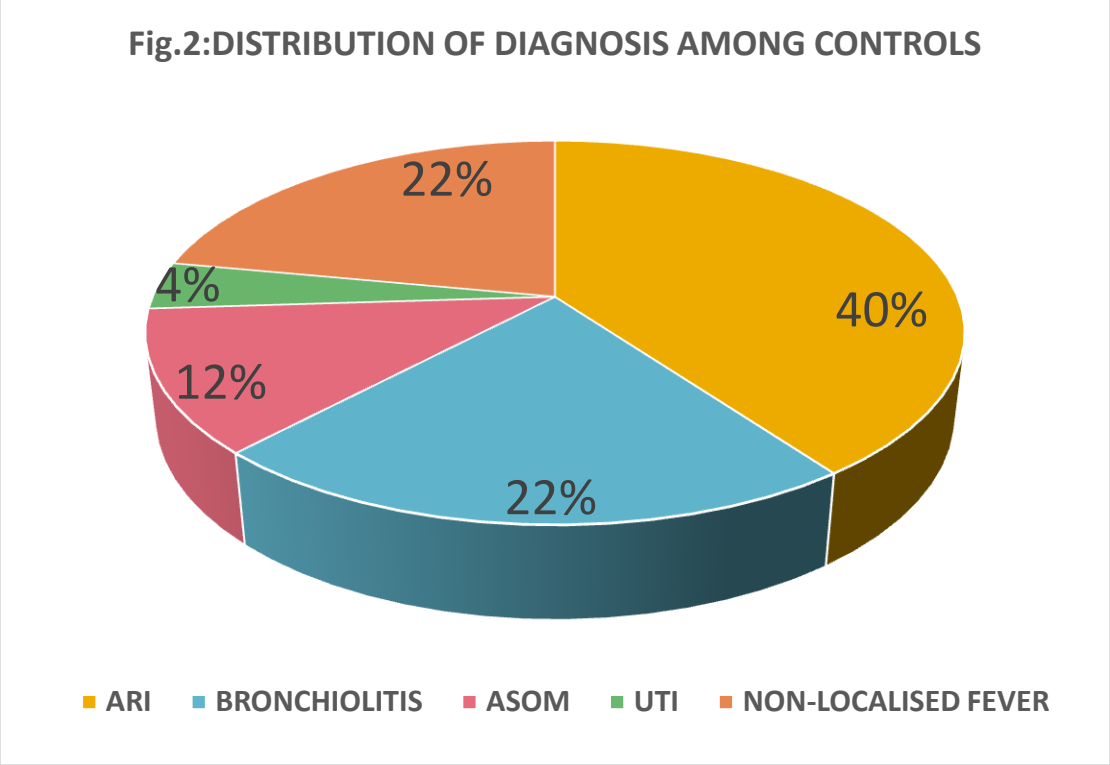

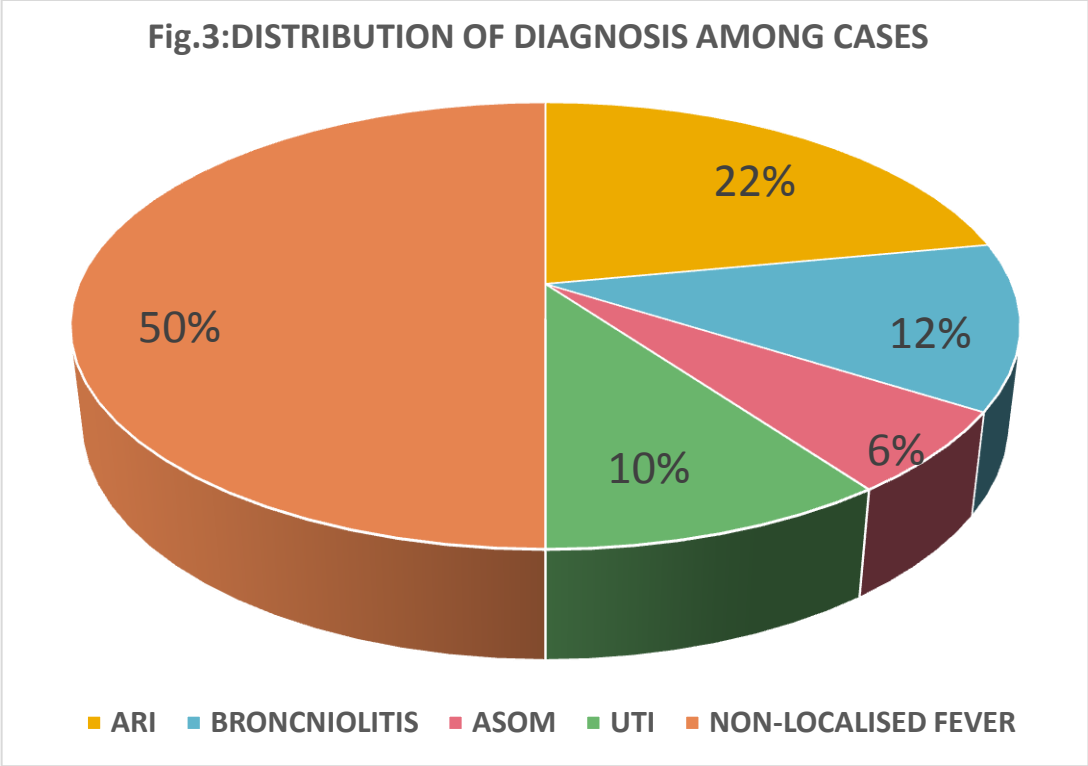

The distribution of diagnosis among cases and controls shows that non-localized fever (viral fever) predominated the cause of fever in cases and ARI predominated the causer of fever in controls.

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Table 3: Comparison of mean serum zinc levels in both the groups

Group	SERUM ZINC LEVELS (µg/dl)			p-value
	Mean±Sd	Mean Difference	95% CI of the Difference	
Case (n=50)	70.28 ±18.895	-47.54	-60.68 to -34.39	<0.0001
Control (n=50)	117.82 ±42.856			

Mean serum zinc level was 47.54µg/dl less in cases of typical febrile seizures as compared to controls and was highly significant with p value of <0.0001.

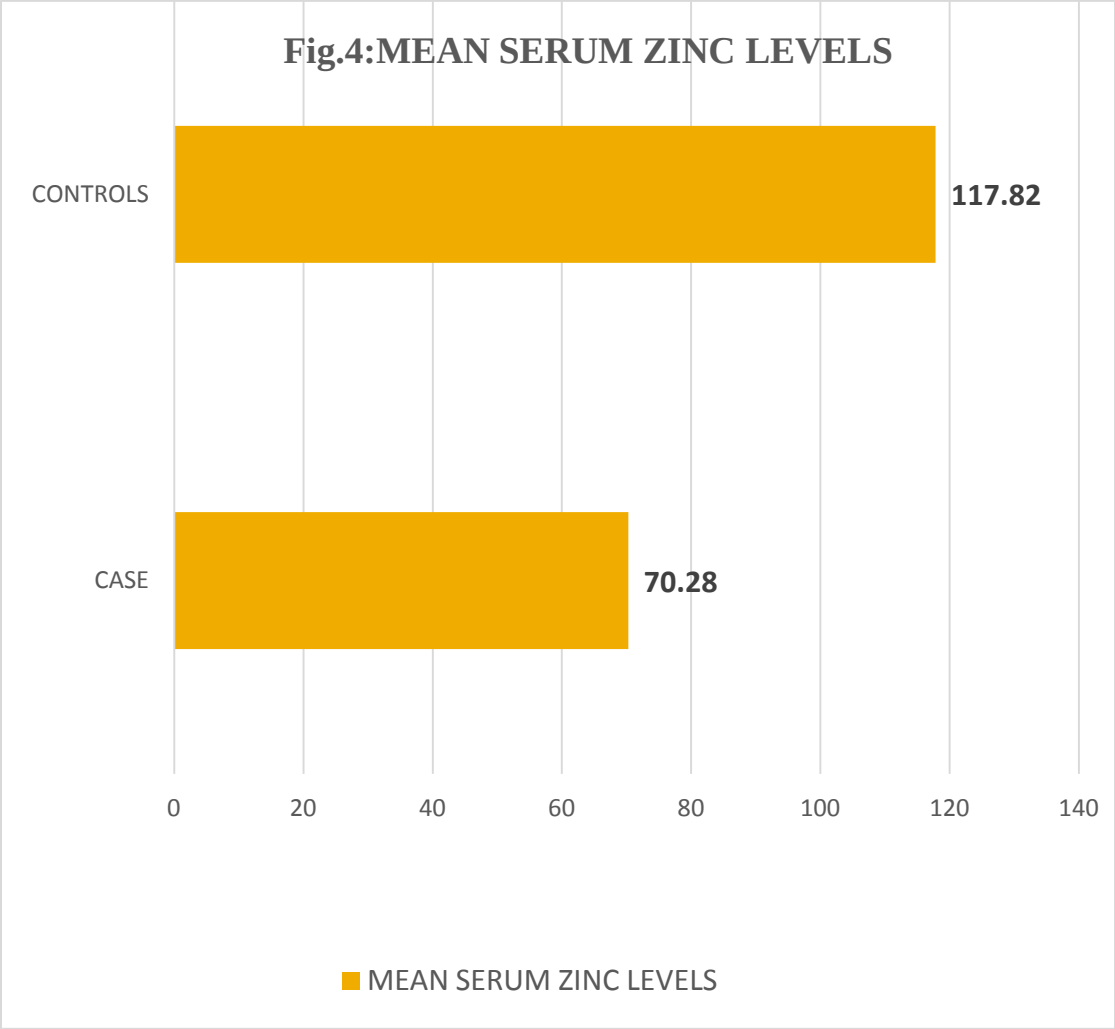

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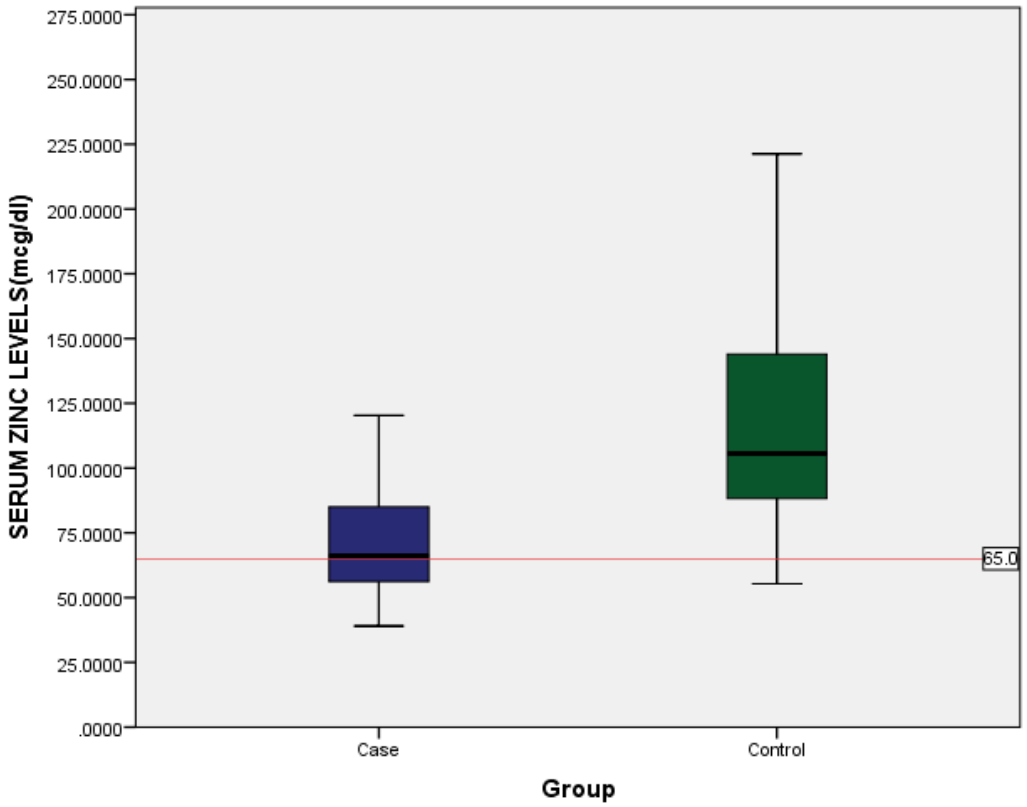
Table 4: Represents the number of patients having hypozincemia in subject population by taking level of <65µg/dl as cutoff for hypozincemia as suggested by WHO

Serum zinc levels (µg/dl)	Group		p-value*
	Cases n (%)	Control n (%)	
<65	21(42)	5(10)	0.0003
>65	29(58)	45(90)	
Total	50	50	

Results show that 42% of the cases and 10% of controls had bio-chemical hypozincemia and is statistically significant (P=0.0003)

Fig.5: Serum zinc level in study population by taking WHO cutoff into consideration



Box plot representation showing the number of patients having hypozincemia in subject population by taking level of <65µgm/dl as cutoff for hypozincemia.

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DISCUSSION

Febrile convulsion is the most common type of seizure in children; approximately 2-5% of children are estimated to experience at least one episode of seizure during a febrile illness before they are 5 years old. The incidence of febrile seizures varies between 2% to 4% in Western countries, whereas the incidence is 7% in Japan and higher in developing countries [3, 4].The etiology and pathogenesis of febrile seizure remain unknown. However change in trace elements level might be a contributing factor for pathogenesis of FS [19, 20]. Some studies showed iron deficiency and iron deficiency anemia were more frequent in children with FS [21,22] and in other research, serum and cerebrospinal fluid zinc levels of children with FS were significantly lower than in children with febrile illness and afebrile seizure [23,26,27,25,11,24].

Decreased levels of zinc can reduce GABA brain level and seizure threshold. Most research compares serum zinc level of children with FS and febrile children, and concludes that serum zinc levels in children with FS is significantly lower than in febrile children in the same age group. Zinc levels can be regarded as one of the predicting and contributing factors of febrile convulsion [28]. The present study was under taken in this context to study the correlation of serum zinc level with typical febrile seizures.

In the present study there was male preponderance. Out of 50 cases 32 (64 %) were male and 18 (36%) were female. Male to female ratio was 1.77:1. Regardless of the era of the study or particulars of the design; boys have consistently emerged with higher frequency of febrile seizures. Incidence ratios of boys: girls have ranged from 1.1:1 to 2:1as reported by Margaretha et al [1] Heydarian F et al [29] Talebian A [12] and others [27,30,31,32,33].Whether there is a biological basis for the gender-specific differences in febrile seizure susceptibility, or whether boys just contract more fevers and therefore are at greater risk, is currently not established.

More than two third of the patients were below 3 years with mean age of 21.74 and 26.18 months in cases and controls respectively. Mean age in cases falls within the range of mean age of (21-27 months) as reported by Margaretha et al [1] Heydarian F et al [29] Talebian A [12] Mahyar A [31] and others[33,29,32].

Non-localized fevers, majority of which had clinical evidence to suggest viral etiology (50%), was the commonest trigger of febrile seizure in the present study. However the etiology of febrile convulsion varies from country to country due to different infection profile. Zinc as an adjunct therapy in severe pneumonia has shown reduction in mortality, given these results; zinc could have additional benefit of preventing febrile seizures.

In the present study significant difference of 47.54µg/dl ($p<0.0001$)(95% CI 60.68 to 34.39) was obtained in mean serum zinc level in cases as compared to controls. Similar findings have been reported by Amiri M et al [27], Margarethaet al [1] Siddarth S. Joshi et al [34] and other researchers [30, 35, 36, 33, 29, 31, 12, 37].

As per World Health Organization (WHO) recommendation the cut off value for hypozincemia has been taken as 65µgm/dl [38].Hence 65µgm/dl was taken as cutoff for hypozincemia as suggested by WHO. Hypozincemia was present in (42%) of cases and (10%) of controls and is statistically significant ($p<0.0003$). Although no statistically significant difference was found in the mean age, gender distribution, and nutritional status between the patients of hypozincemia and normal zinc level. Mahyar et al [31] have reported the similar findings.

The present study also did not reveal any significant difference in mean serum zinc level in relation to age groups or gender. Thus the present study reveals that no specific age group or gender is particularly predisposed to develop hypozincemia. Hypozincemia was observed to be more frequent in children with typical febrile seizures in the present study. Hypozincemia was observed to be more frequent in children with typical febrile seizures in the present study. Hence most of these patients had purely biochemical hypozincemia

CONCLUSION

This study was aimed to determine the correlation between serum zinc levels and typical febrile seizures in children in the age group of 6 months to 5 years fulfilling the inclusion criteria. A total of 100 children, 50 each in case group and control group were studied over a period of 2 years at a tertiary care

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institute. 64% of the children in FS group were Males and 36% were females. Male to female ratio was 1.77:1. Mean age of the cases who presented with typical febrile seizures in the present study was 21.74 months. Non-localized fevers, majority of which had clinical evidence to suggest viral etiology (50%), was the commonest trigger of febrile seizure in the present study.

In our study, serum zinc levels were low in children with typical febrile seizures in comparison with febrile children without seizures. The results were statistically significant ($p<0.05$). In conclusion, low serum zinc level can be considered one of the predicting and contributing factors of febrile seizure. Hence children with low serum zinc levels are more prone to get febrile seizures than children with normal serum zinc levels. It is important to answer these questions that how zinc level plays role in the pathophysiology of febrile seizure and whether zinc supplementation could be effective in preventing febrile seizures.

Results of this study can be viewed as being promising however further research is needed to establish the correlation between serum zinc and febrile convulsion and to identify indicators of exposure to zinc deficiency as well as effective strategies to reduce zinc deficiency and its consequences.

Abbreviations: FS =Febrile seizure

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