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# STUDY OF SERUM ZINC LEVELS IN CHILDREN WITH FEBRILE SEIZURES

Paediatrics

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## ABSTRACT

**Background:** Febrile seizures are the most common cause of convulsions in children and a frequent cause of emergency hospital admissions. Trace elements like Zinc are found in small quantities in the body but have important structural functional roles in a variety of biological processes. There are studies identifying the role of hypozincemia in febrile seizures but so far no studies have documented hyperzincemia in febrile seizures. An objective was to study the association between serum zinc levels and febrile seizures in children in our set up. **Methods:** The study was cross sectional study done in B.Y.L. Nair Hospital, Mumbai, India from January 2017- November 2018 . A total of 147 children aged 6 months to 6 years fulfilling our inclusion and exclusion criteria were enrolled for the study. Children were classified into 3 groups of 50 each. Out of 3 groups first group comprised of febrile seizure cases. The other 2 groups were control with first being the febrile patients without convulsions and the other being children without any history of fever or convulsion. The concentration of serum zinc was measured by colorimetric method using a Fully automated analyser. The three groups included in the study were compared with respect to serum zinc level. All data was analysed with SPSS (Statistical Package for the Social Sciences) and variables were analysed with t-test, chi-square test and ANOVA test. All p-values below 0.05 were considered statistically significant. **Results:** Out of 147 children enrolled, majority of the children in case group were between 6 to 12 months (46.8%). Mean serum zinc level in cases was 112.5 ugm/dl. Serum zinc level was found significantly high in cases of simple febrile seizures as compared to the controls ($P<0.05$). Amongst 47 cases 34.04% cases had hyperzincemia and 27.65% cases had hypozincemia. Thus cases with dysregulation in Zinc levels were 61.7%. **Conclusion:** This study reveals that there is a positive correlation between dysregulation (high as well as low) in serum zinc levels and febrile convulsions.

## KEYWORDS

Febrile seizures, Serum zinc

## INTRODUCTION:

Amongst the paroxysmal events, febrile seizures(FS) are commonest, affecting up to one in 10 children. (Khair & Elmagrabi, 2015)There are numerous definitions on FS mentioned in literature namely the International League against Epilepsy, National Institutes of Health, The American Academy of Pediatrics.(Commission on Epidemiology and Prognosis, 1993)(Mikati & Rahi, 2005)(Walsh, 2008)(Guideline, 2008) We adopted a practical approach and hence we proposed a working definition:- A seizure that occurs between the age of 6 and 60 months with perceived fever by parents with no pre-existing neurological or metabolic condition and that occur in the absence of a history of previous afebrile seizures with no clinical or lab evidence of underlying central nervous system infection. We included both simple and complex febrile seizure in our case group. Trace elements are elements found in small quantities in the body but have important structural functional roles in a variety of biological processes.(Ulvi et al., 2002) Antioxidative defense mechanisms are important pathways involving trace elements. The accumulation of free radicals may lead to seizures and increases the risk of their recurrence. Oxidative stresses produce peroxidated membrane lipids and damages the cells. Two major enzymes Glutathione peroxidase (GPx) and superoxide dismutase (SOD) are involved in antioxidative defense mechanisms. (Hayashi, Miyata, & Tanuma, 2012) Zinc (Zn) is one of such important trace elements that participate in the structure of these enzymes. Imbalance in trace element Zn may be involved in epileptogenesis. (Hedin & Fowler, 1999) Zn is an endogenous transition metal that can be synaptically released during neuronal activity.

Synaptically released Zn can likely function to modulate neuronal excitability under normal conditions. The Glutaricacid decarboxylase enzyme activity is regulated by Zn. This enzyme plays a vital role in the synthesis of gamma amino butyric acid, which is the major inhibitory neurotansmitter in the brain, and it has been shown that levels of GABA are reduced in CSF of children with seizure disorders.(Petroff, Rothman, Behar, & Mattson, 1996) Many ionic channels such as sodium and T type channels are activated by Zn.(Mathie, Sutton, Clarke, & Veale, 2006) Superoxide dismutase is another antioxidant enzyme that acts by removing free oxygen radicals from the intracellular environment which requires Zn for its action.(Liochev & Fridovich, 2000) However, Zn could be neurotoxic, and is speculated to be associated with a variety of conditions, such as Alzheimer disease, stroke, and seizures. (Hedin & Fowler, 1999) There are studies identifying the role of hypozincemia in febrile seizures but so far no studies have documented hyperzincemia in febrile seizures. It is also believed that inflammatory markers like Tumor Necrosis Factor (TNF) and interleukin (IL) during fever or tissue injury may result in reduction of serum zinc level.(Tütüncüoğlu et al., 2001) Lee et al. have reported an association between serum zinc level and febrile seizure.(Lee & Kim, 2012) In another study by Saqib et al., the serum zinc levels were significantly lower in children with simple febrile seizure compared to febrile children without seizure.(Saqib & Qazi, 2018) Garty et al. reported that there was no relation between CSF zinc level and febrile seizure.(B.Z., R., T., & M., 1995) Salehiomran MR et al. reported that serum zinc level was significantly lower in children with simple febrile seizure in comparison with febrile children without seizure.(Salehiomran & Mahzari, 2013) A study in India done by Kapil et al have estimated the overall prevalence of zinc deficiency in five states was 43.8% . The prevalence of zinc deficiency was highest in Orissa (51.3%), followed by Uttar Pradesh (48.1%), Gujarat (44.2%), Madhya Pradesh (38.9%) and Karnataka (36.2%).(Kapil & Jain, 2011) Hence our study would identify likelihood of febrile seizures in Indian children especially in their febrile phase with an already established background of zinc deficiency prevailing in an Indian pediatric population. A study in Metropolitan Mumbai where immigration from all states of nation is present, the study would represent the most diversified population from all parts of India. Brain contains significant amount of Zinc, especially in hippocampus region. Five to fifteen percent of zinc is concentrated as vesicle zinc in glutamatergic synapses.(Cole, Robbins, Wenzel, Schwartzkroin, & Palmiter, 2000) Zinc also acts as a neurotransmitter thus its dysregulation is attributable to seizures and zinc deficiency thus diminishes hippocampal zinc and leads to seizures.(Tian, Yang, & Zhang, 2010) The purpose of this study was to evaluate the possible associations between Zn and children with Febrile Seizures by comparing the levels of Zn, between patients with Febrile seizures, Children with fever but no seizures, and age matched afebrile children without seizures or without systemic illness.

## MATERIAL & METHODS:-

The study was cross sectional study done in B.Y.L. Nair Hospital ,Mumbai, India from January 2017- November 2018 . A total of 147 children aged 6 months to 6 years from Pediatric Ward , Outpatient Department and Casualty presenting with febrile seizures after fulfilling our inclusion and exclusion criteria were enrolled for the study. Informed consent was taken from their attendants and classified into 3 groups of 50 each. Out of 3 groups first group comprised of febrile seizure cases. The other 2 groups were control with first being the febrile patients without convulsions and the other being children without any history of fever or convulsion. A detailed history was taken, and complete physical examination was done on the patients

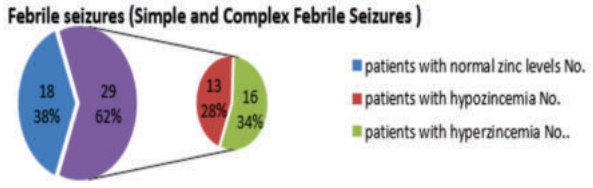
and recorded on a pre-approved proforma. Blood was either collected within 24 hours of convulsion in a febrile seizure patient or within 24 hours of fever in a febrile patient or after interviewing in an asymptomatic child. The concentration of serum zinc was measured by colorimetric method using an Fully automated analyser. In the present study serum zinc level less than 65 µgm/dl was taken as cut off for zinc deficiency and hyperzincemia was considered above 120 µgm/dl as provided in kit literature for testing zinc levels.(B., I., L., O., & C., 2007) The three groups included in the study will be compared with respect to serum zinc level. All data was analysed with SPSS (Statistical Package for the Social Sciences) and variables were analysed with t-test, chi-square test and ANOVA test. All p-values below 0.05 were considered statistically significant.

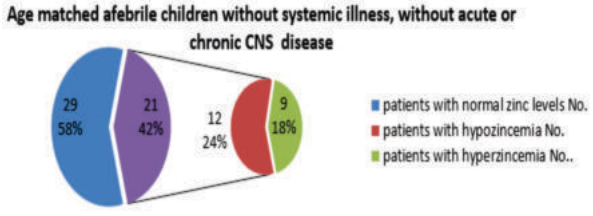
## RESULTS:-

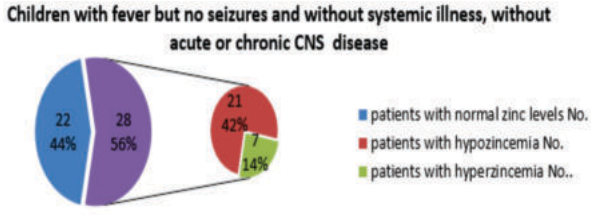
Cross sectional study was conducted and 147 patients fulfilling inclusion and exclusion criteria were enrolled in the study

### Study of Zinc levels (hypozincemia/hyperzincemia/dysregulated zinc metabolism) in different study groups:-

In our case group of Children with febrile seizures we got 27.65%(n=13) patients with hypozincemia and 34.04% (n=29) patients with hyperzincemia, hence accounting to 61.7%(n=29) patients with dysregulated zinc metabolism. In our first control group of Children with fever but no seizures and without systemic illness, without acute or chronic CNS disease, we got 42%(n=21) patients with hypozincemia and 14%(n=7) patients with hyperzincemia, hence accounting to 56%(n=28) patients with dysregulated zinc metabolism. In our second control group of Age matched afebrile children without systemic illness, without acute or chronic CNS disease, we got 24%(n=12) patients with hypozincemia and 18%(n=9) patients with hyperzincemia, hence accounting to 42%(n=21) patients with dysregulated zinc metabolism.



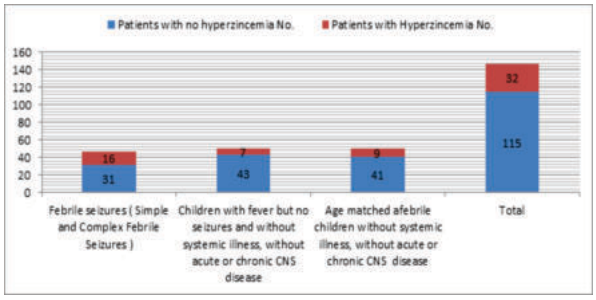




### Study of hypozincemia in different study groups

In our case group of Children with febrile seizures, there were 27.66%(n=13) patients with hypozincemia.In our first control group of Children with fever but no seizures and without systemic illness, without acute or chronic CNS disease, there were 42%(n=21) patients with hypozincemia. In our second control group of Age matched afebrile children without systemic illness, without acute or chronic CNS disease, we got 24%(n=12) patients with hypozincemia. In a total study of 147 children, 31.2%(n=46) of children were having hypozincemia.Chi-square test has been applied to check if there is association between hypozincemia and seizures.The test turns out to be insignificant (p-value0.12) resulting in no association between hypozincemia and febrile seizures.

### Study of hyperzincemia in different study groups

In our case group of Children with febrile seizures we got 34.04% (n=29) patients with hyperzincemia. In our first control group of Children with fever but no seizures and without systemic illness, without acute or chronic CNS disease, we got 14%(n=7) patients with hyperzincemia. In our second control group of Age matched afebrile children without systemic illness, without acute or chronic CNS disease, we got 18%(n=9) patients with hyperzincemia. In a total study of 147 children, 21.77%(n=32) of children were having hyperzincemia




Chi-square test has been applied to check if there is association between hyperzincemia and seizures.The test turns out to be significant (p-value0.04) resulting in association between hyperzincemia and seizure.

### Study of mean serum zinc levels in different study groups

ANOVA has been applied to see if there is any significant difference between the zinc levels among cases, control1 and control2. The p-value(0.005) turns out to be significant, which suggests that there is significant difference between group means with study group of children with febrile seizures having higher mean serum zinc levels.

We have also used unpaired t-test to check which group means differ significantly.There is no significant difference found between cases and control 2. Suggesting no significant difference amongst mean values in our case versus control group 1 with p-value 0.12.

The t-test turns out to be significant, which means there is significant difference between means of Control 1 and Control 2.Thus hypozincemia is a significant finding with p-value 0.024 in our control group 1 i.e. Children with fever but no seizures and without systemic illness, without acute or chronic CNS disease(mentioned in exclusion criteria).

The t-test turns out to be significant, which means there is significant difference between means of Case and Control 2.Thus hyperzincemia is a significant finding with p-value 0.005 in our Case group 1 i.e. Children with febrile seizures.

## DISCUSSION:-

There are studies in the past to establish the relationship between zinc levels and febrile seizure, few have established hypozincemia as a significant finding in cases with febrile seizure, however some have concluded normal zinc levels in febrile seizures. We present a study whereby hyperzincemia was significant in cases with febrile seizures. In our study we meticulously analysed the influence of zinc metabolism. In our case group of febrile seizures we had 27.65% of patients with hypozincemia, 34.04% of patients with hyperzincemia, summing up to 61.7% patients with dysregulation in zinc metabolism. A study done by Salehiomran MR and Mahzari M.concluded that mean serum zinc level were significantly lower in the febrile seizure group compared to the control group.(Salehiomran & Mahzari, 2013) However this study have concluded hypozincemia based on mean levels only. The study did not mention the percentage of children having hypozincemia because an extremely low zinc level in a minor 52 group of children can affect the mean value. If percentage of children having hypozincemia would have been revealed, it would be prudent in understanding the magnitude of problem and thus planning an intervention.The limitation was also that there was no control group of healthy children of that population to statistically outcast the hypozincemia patients effectively as there was a possibility of asymptomatic hypozincemia in healthy children. A study by Heydarian et al. reported that the mean serum level of zinc was significantly lower in children with simple febrile seizure compared to febrile children without seizure however this study also concluded hypozincemia on the basis of mean value in case group and no control group of healthy children planned.(Farhad MD, Farah MD, & Ahmad MD, 2010) A study conducted in Jammu and Kasmir by Gattoo et al

stated the presence of hypozincemia in presence of other risk factors of febrile seizures may enhance the occurrence of febrile seizures explaining a possible correlation between low serum zinc levels and simple febrile seizures.(Gattoo, Harish, & Quyoom Hussain, 2015) However Gattoo et al have reported 60% of patients in their febrile group as zinc deficient below a cut off serum zinc level of 65ug/dl apart from concluding hypozincemia solely on the basis of mean serum zinc levels. Gatto et al have presented a tabular presentation of various other studies establishing correlation of zinc levels with febrile seizures. The limitation was again not taking the zinc levels of healthy children in account. We impress upon taking the healthy children in our study to understand that with no stressors like fever or a febrile seizure, how would the serum zinc levels be in a designated study population.The article published in Japan Medical Association Journal by Yanagisawa have stated that factors like fasting(increase in Zinc levels), food ingestion(decrease in Zinc levels), stress(increase in Zinc levels) and age group of neonates and infancy(decrease in Zinc levels) are driven with some fluctuations in serum zinc levels.(Yanagisawa, 2004) In our study we had hypozincemia, hyperzincemia and normal zinc levels in every study group. The percentage of individuals with normal zinc levels in our study groups namely:- Control group of afebrile 53 healthy children , Control group of febrile patients without seizures and Case group of febrile seizures were 58%,44% and 38% respectively.Hence a steady decline of individuals with normal zinc levels was observed from healthy children to febrile children and furthermore decline was observed from febrile children to case group of febrile seizures.Thus establishing the concept of dysregulation in zinc metabolism with febrile seizures and febrile children. If only two groups namely case group of febrile seizures and control group of febrile children were taken into consideration we could have only established hyperzincemia in febrile seizures in comparison to afebrile patients being unaware of the fact that significant hypozincemia was prevailing in our febrile children group as compared to age matched healthy children.There was an identical group selection in a study by Sreenivasa et al whereby a control group of healthy children was also included apart from majority studies which were taking case group of febrile seizures and control group of febrile children with no seizures.(Sreenivasa, P, & Manjunatha, 2015) However the study by Sreenivas et al have also reported hypozincemia on the virtue of mean serum zinc levels and not on the virtue of percentage of children affected with hypozincemia. This study established hyperzincemia in children with febrile seizures by virtue of statistical study of mean serum zinc levels and by virtue of percentage of children having hyperzincemia. Also it is noteworthy that our standard deviation in case group of febrile seizure, control group of febrile children and control group of healthy children was 68.73, 35.6 and 30.0 respectively thus impressing upon the greater standard deviation portraying a probability of gross fluctuations reported in children with febrile seizures. Hence owing to greater fluctuations of zinc levels seen in our case group of febrile seizures it would be prudent to ascertain a distinct zinc dysregulated group which included hypozincemia and hyperzincemia of children. The zinc dysregulation was hence observed more in Case group of febrile seizures. We also reviewed a study with contradictory results to this Korean study by Khosroshahi N at Tehran stating no association between serum and CSF levels of magnesium and the presence of febrile seizures.(Khosroshahi, Ghadirian, & Kamrani, 2015) The concept of analysing CSF Zinc levels in cases with febrile seizure was hence also prudent as the closest internal mileu of the Brain is maintained by CSF. A study done by Mollah et al in 1999 at Bangladesh reported that CSF Zinc levels were significantly lower in case group of febrile seizures as compared to control group of febrile patients however the case group was of 50 patients as compared to control group of 30 patients and an ideal equal sample size of control group would be statistically satisfactory. (Mollah et al., 2008)

Another study reported a contradictory conclusion by Garty et al in Israel however concluded that febrile convulsions are not related to reduced zinc in the CSF.(Mollah et al., 2008) Our study was only limited to estimation of zinc levels in febrile seizures compared to control groups and did not estimate other element Our study could not study CSF Zinc levels in febrile seizure patients which would help in understanding the dysregulated zinc level in the closest mileu to the brain. The result of statistically significant hyperzincemia has so far been only reported by our study.The reason of this contradictory result was not clear. This could be because of any acute disease can result into hypozincemia and fever could be a reason behind hypozincemia in febrile group (Sones, Israel, Dratman, & Frank, 1951), however as speculated with this explanation we should have got further hypozincemia in our febrile seizure group also as majority of the studies. Stress causes hyperzincemia (Yanagisawa, 2004) and hence fever could also give rise to this stress and cause hyperzincemia. Hyperzincemia itself could be a cause of seizure (Kambe, Tsuji, Hashimoto, & Itsumura, 2015). Thus supporting our finding of hyperzincemia in febrile seizures This could be also be because seizure per se also results in a stress response itself and can manifest with leucocytosis, elavated CRP, elavated prolactin levels.(R. et al., 2011) Hence hyperzincemia to be ascertained as a cause or effect of febrile seizure is unclear and a temporary serological hyper/hypozincemia with no clinical manifestations should denote a transient dysregulation of levels and warrants a serial study of zinc levels at different point of time.

**Strength of study:**

We used Colorimetric method as compared to absorption spectroscopy which was cheaper for screening purpose not at the cost of losing significant sensitivity. We also included complex febrile seizures which are excluded in other studies. In our study we established normal serum zinc levels in pediatric population treated by our instituition Benefits to the participant – After establishing hypozincemia as a causative factor in febrile seizure ,we referred children to OPD for supplementing the children with deficient levels. Benefit to the community –A gap in knowledge exists in role of Zinc as Seizure protective trace element. Specifically the objective of this study was to test for deficiency of Zinc levels in children with febrile seizures however we concluded hyperzincemia hence not warranting any need for supplementation.The study was helpful to assess prevalence of zinc deficiency in case and control groups.

**Limitation of the study:**

We couldn't review our patients to assess the subsequent response of zinc supplementation in children with febrile seizures. hence the role of zinc supplementation in reducing seizure recurrence couldn't be established.The ideal time of sampling was controversial as immediately after seizure dysregulation would be a stress response hence serial monitoring of zinc levels would be helpful which couldn't be done in our study.We couldn't test CSF zinc levels to assess zinc deficiency in the closest mileu to the Brain.

## CONCLUSION:-

1. Children with febrile seizures had dysregulation in zinc metabolism with hyperzincemia more than hypozincemia.
2. Comparitively less children in control group had shown dysregulation in zinc metabolism. In contrast to our hypothesis we found hyperzincemia as a statistically significant finding in children with febrile seizures.
3. An ideal study should include serial monitoring of serum zinc levels , corresponding CSF zinc levels of 3 groups namely:- Case group of children with febrile seizures, control group of febrile patients with no seizures and control group of age matched healthy children.
4. Zinc dysregulation being a cause for febrile seizure is still controversial because it could be merely a result of stress response in febrile seizure.

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