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Association between Iron & Other Trace Elements Deficiency and Febrile Seizure in Children

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Authors' contributions

This work was carried out in collaboration among all authors. Author GD designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors DS and DPS managed the analyses of the study. Author RT managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Febrile seizures are the most common type of seizure in children occurring in 2-5 % of them with a peak incidence in 16-18 months. Various factors have been described in the pathophysiology of febrile seizures like susceptibility of the immature brain to temperature, an association between interleukins, circulating toxins, and trace elements deficiency.
Aim: To study the association between serum levels of trace elements (Iron, zinc, copper, calcium and magnesium) in children with febrile seizures.
Study Design: An observational cross-sectional study.
Place and Duration of Study: Department of Pediatrics of PGIMER, Dr RML Hospital, New Delhi between November 2016 and March 2018.

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Methodology: This study was conducted at a tertiary care centre and enrolled 75 children of which 55 were febrile seizures and 20 patients were controls. The serum specimen was collected with all aseptic techniques, and all due precautions were taken for the blood sample to protect them from sunlight exposure, haemolysis and contamination. Then samples were centrifuged at 3,000 rpm for 5 minutes and were stored at -20 c until the final assay. Serum Iron, Zinc, Copper and Magnesium levels were measured using a fully automated chemistry analyser (AU400). Data was entered in MS Excel spreadsheets and analysed using the statistical package for social science (SPSS) version 21.0.

Results: Children with febrile seizures (cases) were found to have significant iron deficiency (higher TIBC, higher UIBC and lower Ferritin) than the controls (P<0.001). There was no significant difference in the serum levels of copper, zinc, magnesium, and ionized calcium in the two groups. There was no difference in serum levels of trace elements in cases with simple or complex febrile seizure.

Conclusion: Children with febrile seizures showed significant iron deficiency (higher TIBC, higher UIBC and lower Ferritin) in cases than those with controls. But, there was no significant association between other serum trace elements (zinc, copper, calcium, magnesium) and febrile seizure. However, further large multi-centric trials are required to suggest any association between them.

Keywords: Febrile seizures; trace elements; iron deficiency in seizures; neonatal seizures.

1. INTRODUCTION

"Febrile seizure is one of the most common neurological problems in children. The incidence of febrile seizures varies between 2% and 4 % in the western population, 7% in Japan and 5-10 % in developing countries" [1]. Febrile seizures are defined as any seizure activity in children of the preschool age group which are associated with fever but without any evidence of intracranial infection. Febrile seizures should be distinguished from epilepsy which is characterised by recurrent episodes of unprovoked seizures.

"The aetiology and pathogenesis of febrile seizure remain unknown, however, several factors including genetic and environmental are being implicated in previous studies. Various factors have been described in the pathophysiology of febrile seizures like bacterial and viral infections [2], susceptibility of the immature brain to temperature [3], association with circulating toxins and interleukins [4], trace elements and iron deficiency". Although several susceptibility genes associated with fever-induced seizures have been identified, the precise pathophysiologic mechanism that triggers seizures is unclear.

"Iron has been found to be a cofactor in a number of enzymatic reactions and it affects neurotransmitter production and DNA replication" [5]. The roles of trace elements like selenium, magnesium, copper and zinc have been described with conflicting results in previous studies. They appear to play a role in their ability to modulate neurotransmission by acting on ion channels and their co-enzymatic activity. In this study, we investigated whether there is any association between trace elements and febrile seizures.

2. MATERIALS AND METHODS

This study was conducted at a tertiary care centre, and children were enrolled at the paediatric emergency unit or attending the outpatient clinic. All the children who presented with recurrent episodes of febrile seizures (> 38 C) between ages group 6 months to 5 years were enrolled as cases. Patients who were having developmental delay, intracranial infection, past history of non-febrile seizures or underlying blood disorder have been excluded from the study. Controls were patients who presented with fever but without seizures.

2.1 Data and Sample Collection

All the details including history and examination findings were collected and documented in structured Performa. CNS examinations including signs of meningeal irritation were documented. Lumbar puncture was done in selective cases as per need and indications.

The serum specimen was collected with all aseptic techniques, and all due precautions were taken for the blood sample to protect them from sunlight exposure, haemolysis and contamination. Then samples were centrifuged at 3,000 rpm for 5 minutes and were stored at -20 c until the final assay.

2.2 Trace Elements Assay

Trace elements were measured under strict monitoring so as to minimise the margin of error. Serum Iron, Zinc, Copper and Magnesium levels were measured using a fully automated chemistry analyser (AU400). Beckman Coulter reagent kit was used for the iron assay whereas the Zinc assay was done using a reagent kit (Randox). Serum ferritin was done using the Chemiluminescent immunoassay method with the help of Vitros ECiQ Immuno-analyser and ionised calcium was measured using the ion electrode method (ISE method).

2.3 Statistical Analysis

Data was entered in MS Excel spreadsheets and analysed using statistical package for social science (SPSS) version 21.0.

3. RESULTS

This study was conducted at a tertiary care centre and enrolled 75 children of which 55 were febrile seizures and 20 patients were controls. The median age of children with febrile seizures in this study was 26 months which was comparable to controls (36 months). There was no gender dissociation with a mean age of onset of seizures at 21.53 ± 15.35 months. The majority of the cases were simple febrile seizures while complex febrile seizures are only 29% of the total cases. Patient characteristics and Iron profile of cases and controls are outlined in Table 1. Serum total iron and saturation index was low in FS whereas Total iron binding capacity (P<0.001) and unsaturated iron binding capacity (P<0.003) were significantly higher in cases (FS) in comparison to controls. Mean serum ferritin was significantly low in cases (27.58 ± 21.06 ng/ml) as depicted in the scatter plot (Fig. 1) in comparison to controls which was 232.54 ± 105.25 ng/ml (P<0.0001). There was no significant difference in iron profile was seen in simple and complex febrile seizures.

Table 1. Patients characteristics and iron deficiency profile in children with febrile seizures and controls

Patients characteristic and Iron profile index	Cases(n=55)	Control(n=20)	P value
Age (months)	28.62± 16.09	33.3± 19.68	
Sex(male)	65.4%	50%	
Temperature(˚F)	101.66 ±0.85	101.24 ±0.71	0.074
Serum total iron(µg/dl)	30.94± 22.33	43.05 ±38.06	0.267
TIBC(µg/dl)	412.89± 70.1	347.9± 78.77	0.001
UIBC(µg/dl)	382.66 ±79.14	304.85± 79.87	0.0003
Iron saturation (%)	7.54± 5.77	12.45± 10.1	0.014
Serum ferritin(ng/ml)	27.58±21.06	232.54±105.25	0.0001

Note. TIBC, total iron binding capacity; UIBC, unsaturated iron binding capacity

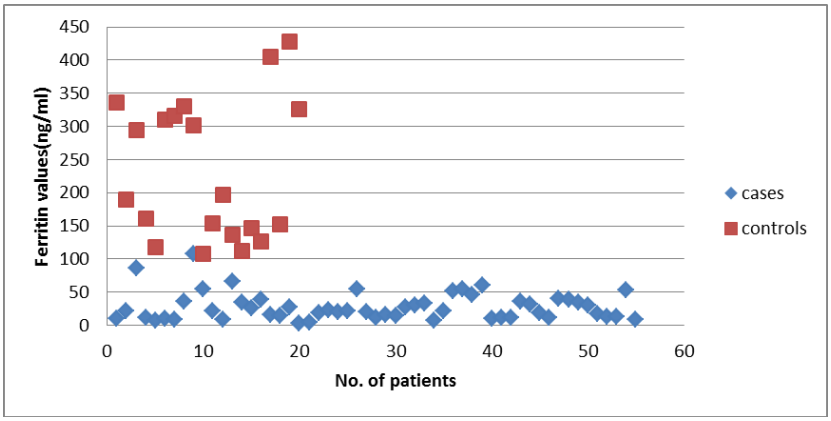

Fig. 1. Scatter plot showing significantly low levels of serum ferritin (ng/ml) in febrile seizures than in controls

Table 2. Serum levels of trace elements and ionised calcium in children with febrile seizures and the control

Serum trace elements	Cases(n=55)	Controls(n=20)	P value
Serum zinc levels (µg/dl)	83.18± 34.76	81.76 ±33.42	0.82
Serum copper levels(µg/dl)	145.67 ±31.25	150.18± 36.48	0.50
Serum magnesium levels(mg/dl)	2.02 ±0.20	2.12± 0.23	0.083
Serum ionised calcium(mmol/l)	1.16 ±0.2	1.20± 0.09	0.267

Mean serum levels of other trace elements (Zinc, Copper and magnesium) and ionised calcium were outlined in Table 2. Mean serum zinc levels (83.18± 34.76 µg/dl) were higher in febrile seizure while copper (145.67 ±31.25 µg/dl), magnesium (2.02 ±0.20 mg/dl) and ionised calcium (1.16 ±0.2 mmol/l) were low in cases but none of them reached statistical significance. There were no significant differences in these trace elements in simple and complex febrile seizures.

4. DISCUSSION

"The developing brain is more susceptible to febrile and other seizures. Experimental evidence has suggested the maturational change of both inhibitory and excitatory neurotransmitters and other mechanisms that influence the brain's susceptibility to seizure activity" [6]. In the present study, the median age of children with febrile seizures were 28 months, which corresponds to the usual age of presentations. Fever is attributed to upper respiratory tract infection, pneumonia, urinary tract infection and gastroenteritis in majority of cases. Simple febrile seizures accounts for 70% of cases and the rest were complex febrile seizures.

"Iron deficiency (ID) is one of the most prevalent nutritional problems worldwide, especially in developing countries, affecting up to 2 billion people. ID has been associated with different neurological problems including restless leg syndrome, breath holding spell, stroke and ADHD. Iron participates in cerebral energy production and is important in myelin formation by oligodendrocytes. It is involved in the metabolism of inhibitory neurotransmitter GABA and monoamines- neurotransmitters, acting as cofactor of tyrosine hydroxylase and aldehidoxidase" [7]. A reduction of GABA levels postulated to predispose neuronal hyper-excitability leading to occurrence of seizures. The diagnosis of ID in the presence of fever is challenging. Haematological parameter like haematocrit, plasma iron, and Total iron binding capacity, transferrin saturation and plasma ferritin may assist in diagnosis.

Iron deficiency was significantly seen in patients with febrile seizures in this study in comparison to controls. Total iron binding capacity (412.89 ± 70.1µg/dl), Serum unsaturated iron binding capacity (382.66 ±79.14µg/dl), Iron saturation (7.54 ± 5.77%) and Serum ferritin (27.58 ± 21.06 ng/ml) were significantly deranged in febrile seizures and might have precipitated in induction of seizures. Our findings are consistent with the previous study by Zarifer et al. [8], which suggested FS was two times more common in iron deficiency anaemia. However, there are some studies suggesting no association like kobrinsky et al, Bidabadi et al which showed serum ferritin and TIBC were normal in children with FS. Byung Ok Kwak [9] in his meta-analysis involving 17 studies and enrolling 2416 children concluded that Iron deficiency was associated with febrile seizure and conflicting results in some studies may be attributed to small sample size, different diagnostic criteria and selective inclusion and exclusion criteria.

"Zinc has been identified as having both pro convulsant and anti-convulsant activity. The functions of certain proteins, particularly histidine, cysteine, aspartate, and glutamic acid residue, as well as specific members of voltage and ligand gated channel superfamily are influenced by zinc" [10]. In our study the mean level of zinc in cases with febrile seizures is slightly higher (83.18 µg/dl) compared to the control group (81.76 µg/dl); however, the difference was not significant. Result of our study is similar to the case control study by Amouian S et al. [11]; however other studies by Namakin et el. [12], and meta-analysis by Amene Saghazadeh et al. [13] found significant reduced serum level of zinc(P=0.018) in cases with febrile seizures. The

difference of our study finding may be due to geographical and genetic variation, small sample size; different timing of blood sampling or in true sense there may not be any association.

Copper act on various types of ion channels, including N-methyl-D-aspartate receptor and voltage gated calcium channels [14]. In our study mean value of serum copper in cases (145.67 µg/dl) was found to be lower than control group (150.18 µg/dl); however, the difference was not statistically significant (p=0.599). We also study serum levels of ionized calcium levels in febrile seizures as it is also involved in many enzymatic processes of neuronal excitation and can contribute to the epileptiform activity. The mean value of serum calcium was slightly lower but insignificant in cases (1.16 mmol/l) in comparison to controls (1.20 mmol/l).The mean level of magnesium was lower but not significant in cases (2.02 mmol/l) in comparison to controls (2.12 mmol/l).

5. CONCLUSION

This study shows some insights of the aetiology of febrile seizures, but its limitation narrows down the validity of this study. Of the previously reported association, we found only iron deficiency as a risk factor for febrile seizure in this cross section study while rest of the trace metals like zinc, copper, magnesium and ionised calcium were within normal limits. Further exploration is also warranted of the effect on the brain of erythropoiesis in the context of iron deficiency as it is possible that gene expression is altered in this situation and alters the seizure threshold.

CONSENT

As per international standard or university standard, parental(s) written consent has been collected and preserved by the author (s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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