www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v7i2.48

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Low Zinc and Iron Status: A Possible Risk Factor For Febrile Seizure

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Abstract

Introduction: *The International League Against Epilepsy (ILAE) defines a febrile seizure as "a seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures."[1] Risk factors for febrile seizures include developmental delay, discharge from a neonatal unit after 28 days, day care attendance, viral infections, a family history of febrile seizures, certain vaccinations, and possibly iron and zinc deficiencies[2,3,4,5] by their co-enzyme activity or ability to influence ion channels and receptors.*

Objectives: *To focus specifically on iron and zinc levels and their correlation to febrile seizure in patients between 06-60 months of age.*

Materials and Method: *The study was conducted in the Department of Paediatrics, Hi-Tech Medical College & Hospital, Bhubaneswar, Odisha, from November 2016 - October 2018.*

Patients presenting with febrile seizures were considered as cases and patients presenting with fever without seizures were taken as controls. A proper history regarding the duration of fever, time of onset of seizure, type of seizure, duration of seizure, past & family history of convulsive disorder was obtained and a series of haematological workup was done. Serum ferritin & Serum Zinc levels were also estimated.

Results: *The mean haemoglobin levels in cases and controls included in this study was 10.51 ± 1.38 and 11.20 ± 1.53 g/dl respectively. The mean corpuscular haemoglobin in cases and controls included in this study was 25.29 ± 4.01 and 24.39 ± 2.66 pg respectively. The mean serum ferritin in cases and controls included in this study was 25.88 ± 7.57 and 79.85 ± 61.98 ng/ml respectively . The mean serum zinc in cases and controls included in this study was 73.10 ± 44.31and 79.85 ± 61.98 mcg/ml respectively.*

Moreover, there was statistical significance observed between haemoglobin, serum ferritin and serum zinc levels of cases and controls ($p < 0.01$).

Conclusion: *The present study has shown that iron and zinc deficiency are few of the predisposing factors for simple and complex febrile convulsions thereby establishing the relationship between zinc deficiency and febrile seizures.*

Keywords: *Febrile seizure, serum zinc, iron status.*

Introduction

The International League Against Epilepsy (ILAE) defines a febrile seizure as "a seizure occurring in childhood after one month of age associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting the criteria for other acute symptomatic seizures"[1].

Risk factors for febrile seizures include developmental delay, discharge from a neonatal unit after 28 days, day care attendance, viral infections, a family history of febrile seizures, certain vaccinations, and possibly iron and zinc deficiencies[2,3,4,5]by their co-enzyme activity or ability to influence ion channels and receptors.

Iron plays a critical role in the metabolism of several neurotransmitters, and in low iron status, aldehyde oxidases and monoamine are reduced. In addition, the expression of cytochrome C oxidase, a marker of neuronal metabolic activity, is decreased in iron deficiency[6,7] In developing countries, iron deficiency is one of the most prevalent nutritional problem[8] especially among infants aged between 6 and 24 months[9,10]. In developing countries 46–66% of all children under 4 years of age are anaemic; with half of the prevalence attributed to iron deficiency anaemia[11].

In the brain, zinc is present in large quantities in the hippocampus. Zinc regulates glutamic acid decarboxylase activity, which is an important enzyme in production of γ- amino butyric acid. It also regulates the neurotransmitter affinity. It mediates inhibition of calcium on N-methyl-D-aspartate receptors there by reducing excitatory discharge of neurons. In deficiency of zinc, these receptors get stimulated which may produce epileptiform discharges in children with fever[12].

Zinc also activates pyridoxal kinase, which in turn helps in the pyridoxal phosphate synthesis from pyridoxal Pyridoxal phosphate in turn activates glutamic acid decarboxylase, which involved in synthesis of GABA. Post synaptic receptors in interaction with zinc assists in GABA action. Hence, zinc deficiency leads to decrease in GABA level, which leads to development of seizures[12]. Neurons rich in zinc carry the element in their synaptic vesicles.[13]

Role of Iron and Zinc deficiency in febrile convulsions were studied in western countries with conflicting results. Moreover, in India, there are very few studies. This study was done to study the etiology and outcome of febrile seizures in children and correlate with iron and zinc status. The study was done in the Department of Pediatrics, Hi-Tech Medical College and Hospital, a tertiary care teaching hospital in Bhubaneshwar, Odisha.

Materials and Methods

Study site: The study was conducted in the Department of Pediatrics, HI-TEC Medical College & Hospital, Bhubaneshwar, Odisha.

Study Population: Hundred cases and fifty controls were included in this study.

Cases: The patients who experienced febrile seizures were defined as cases. Eighty-three cases were included in this study.

Controls: The patients who had fever but did not have febrile seizures were defined as controls. Fifty age and gender matched controls were included in this study.

Study Design: The study is a case-control study.

Sample Size: A total sample of 150 was taken for this study, which included 100 cases and 50 controls.

Duration of Study: The study was conducted from November 2016 to October 2018.

Inclusion Criteria

1. Children aged from 6-60 months.
2. Children presenting to emergency department or admitted in the hospital with fever more than 38^0C and with history of convulsion.
3. Children visiting the outpatient department with history of febrile seizures though presently asymptomatic.
4. Children of parents willing to give written informed consent.

Exclusion Criteria

1. Patients with any history of birth asphyxia or hypoxic-ischemic encephalopathy (HIE).
2. Patients with features of CNS infection.
3. Cerebral palsy.
4. Seizure disorder.
5. Chronic illness.
6. Dysmorphic features.
7. Children on zinc supplementation.
8. Children on antiepileptic drugs.
9. Electrolyte imbalance.
10. Children with hereditary metabolic disorders.

Methodology

A proper history was obtained regarding the duration of fever, time of onset of seizure, type of seizure, duration of seizure, past & family history of convulsive disorder. A series of haematological workup was done which included Haemoglobin, Mean corpuscular volume (MCV), Mean corpuscular haemoglobin (MCH) and serum ferritin to document Iron insufficiency/deficiency. Serum Zinc levels were also estimated.

Statistical Analysis

The study involved 100 cases and 50 controls. The data was collected, compiled and compared statistically by frequency distribution and percentage proportion. Shapiro-Wilk test was done to check for normality of data. Qualitative data variables were expressed by using frequency and Percentage (%). Quantitative data variables were expressed by using Descriptive statistics (Mean ± SD.). Student's 't' test was used to compare normally distributed data. Wilcoxon's test was used to compare non-normal data. Chi-square ($\chi 2$) test was used to know the statistically significant difference (p value) between different groups. P-values of < 0.05 were considered statistically significant. Data analysis was performed by using SPSS Version 25.0 (Chicago, SPSS Inc.).

Results

The study population had 100 cases and 50 age and gender matched controls. Data of cases and controls were compared within the results obtained.

The mean age of the cases and controls included in this study was 23.33 ± 13.89 and 25.94 ± 14.71 months respectively. The least age was 06 months whereas the highest was 60 months in both cases and controls. Table 1

Table 1: The Mean Age of Cases and Controls

Age (in Months)						
Groups	N	Mean ± SD	Min	Max	95 % CI	P value
Cases	100	23.33 ± 13.89	6	60	20.30 – 26.37	NS
Controls	50	25.94 ± 14.71	6	60	21.75 – 30.12	

Male patients were higher than female patients in both cases and controls. However, there was no statistical significance between males and females (p = Not Significant) depicting a homogenous population in both cases and controls. Table 2

Table 2: The gender distribution in cases and controls

Groups	Gender		P value
	Males	Females	
Cases	60	40	NS
Controls	31	19	

The mean temperature of the cases and controls included in this study was 101.36 ± 1.17 and 101.14 ± 0.95 ^{0}F respectively. The least and the highest temperatures were almost similar in both cases and controls. However, there was no statistical significance between the temperatures of cases and controls (p = Not Significant) depicting a homogenous population in both cases and controls. Table 3

Table 3 : The Mean Temperature of Cases and Controls

Temperature in Fahrenheit						
Groups	N	Mean ± SD	Min	Max	95 % CI	P value
Cases	100	101.36 ± 1.17	100	104.40	101.10 – 101.62	NS
Controls	50	101.14 ± 0.95	100	104.00	100.87 – 101.41	

In cases respiratory tract infection accounted for 46%, gastroenteritis 17%, urinary tract infection 16%,other nonspecific causes 21% as cause of fever . In controls respiratory tract infections accounted for 36%, gastroenteritis for 20%, urinary tract infections for 18%,other nonspecific causes for 24%. However there was no statistical difference observed between cases and controls. Table 4.

Table: 4 Focus of Infection

Focus of infection	Cases		Controls		P value
Causes	NO	%	NO	%	
Respiratory tract illness	46	46%	18	36%	NS
Gastroenteritis	17	17%	10	20%	NS
UTI	16	16%	9	18%	NS
Nonspecific causes	21	21%	12	24%	NS

There was statistical significance observed between haemoglobin levels of cases and controls ($p < 0.01$). The mean haemoglobin levels in cases and controls included in this study was 10.51 ± 1.38 and 11.20 ± 1.53 g/dl respectively. Table 5

Table 5: The mean Haemoglobin levels in cases and controls

Haemoglobin (in g/dl)							
Groups	N	Mean ± SD	Normal	Decreased	Odds Ratio	95 % CI	p value
Cases	100	10.51 ± 1.38	65(65%)	35 (35%)			
Controls	50	11.20 ± 1.53	37 (74%)	13 (26%)	0.654	0.301 – 1.422	< 0.01

The mean corpuscular haemoglobin in cases and controls included in this study was 25.29 ± 4.01 and 24.39 ± 2.66 pg respectively. There was statistical significance observed betweenmean corpuscular haemoglobin of cases and controls ($p < 0.01$). Table 6

Table 6: The Mean Corpuscular Haemoglobin levels in cases and controls

Mean Corpuscular Hemoglobin (in pg.)							
Groups	N	Mean ± SD	Normal	Decreased	Odds Ratio	95 % CI	p value
Cases	100	25.29 ± 4.01	53 (53%)	47 (47%)	3.211	1.494 – 6.900	< 0.01
Controls	50	24.39 ± 2.66	13 (26%)	37 (74%)			

The mean serum ferritin in cases and controls included in this study was 25.88 ± 7.57 and 79.85 ± 61.98 ng/ml respectively. Statistical significance observed between cases and controls ($p < 0.01$). Table 7

Table7: The Mean Serum Ferritin levels in cases and controls

Serum Ferritin (in ng/ml)							
Groups	N	Mean ± SD	Normal	Decreased	Odds Ratio	95 % CI	p value
Cases	100	25.88 ± 7.57	62 (62%)	38 (38%)	15.619	1.890 – 129.069	< 0.001
Controls	50	79.85 ± 61.98	42 (84%)	8 (16%)			

There was significant statistical difference observed between cases and controls in serum zinc levels. The mean serum zinc in cases and controls included in this study was73.10 ± 44.31 and87.30 ± 24.70mcg/ml respectively. Table 8.

Table 8 : The Mean Serum Zinc Levels in Cases and Controls

Serum Zinc (in mcg/ml)							
Groups	N	Mean ± SD	Normal	Decreased	Odds Ratio	95 % CI	p value
Cases	100	73.10 ± 44.31	51 (51%)	49 (49%)	0.225	0.097 – 0.521	< 0.001
Controls	50	87.30 ± 24.70	41 (82%)	9 (18%)			

Discussion

Febrile seizure are the most common type of seizures observed in the paediatric age group. Although described by the ancient Greeks, it was not until this century that febrile seizures were recognized as a distinct syndrome separate from epilepsy. They occur in young children at a time in their development when the seizure threshold is low. Moreover, young children are susceptible to frequent childhood infections such as upper respiratory infection, otitis media and viral infections. Animal studies suggest a possible role of endogenous pyrogens, such as interleukin1 beta, that, by increasing neuronal excitability, may link fever and seizure activity[14]. Preliminary studies in children appear to support the hypothesis that the cytokine network is activated and may have a role in the pathogenesis of febrile seizures, but the precise clinical and pathological significance of these observations is not yet clear[15,16].

There were 150 patients in this study of which 100 were cases and 50 were controls. The mean age of cases and controls were 23.33 ± 13.89 and 25.94 ± 14.71 months respectively as seen in Table 1 and there was no statistical difference observed between the two groups representing a homogenous population across cases and controls. Kumari PL et al found the mean age of febrile seizures to be 17±8.81 month[17]. Hartfield DS et al found the mean age to be 17.9 months[5]. Daoud AS et al found the mean age to be 18.8 months[18]. Majority (67.63%) of the children with febrile seizures had age of onset of convulsions around two years of age. An age of less than 18 months is associated with increased risk of recurrence[18].

The gender of the study sample was also distributed similarly across the two groups with male preponderance in this study as shown in Table 2. However, there was no statistical difference observed between the two groups representing a homogenous population across cases and controls. Similar results were found in studies done by Daoudet al[18] and Hartfield DS et al[5]

In this study, Iron status was measured using haematological indices; Haemoglobin, Mean Corpuscular Volume, Mean Corpuscular Haemoglobin and Serum Ferritin. It was observed that the mean Haemoglobin was 10.51 ± 1.38 and 11.20 ± 1.53 g/dl in cases and controls respectively as shown in Table 5. The odds ratio was 0.654 (95 % CI: 0.301-1.422). Moreover, it was observed that the mean difference of haemoglobin between the two groups was statistically significant ($p<0.01$). Similar results were observed in the study done by Pisacane, et al [19]among children of the same age group. Dawn, et al[20] also found similar results with children with febrile seizures almost twice likely to have iron deficiency compared to controls.

It was seen that the Mean Corpuscular Hemoglobin was 25.29 ± 4.01 and 24.39 ± 2.66 pg. in cases and controls respectively as shown in Table 6. The odds ratio was 3.211 (95 % CI: 1.494-6.900). However, it was observed that the mean difference of Mean Corpuscular Hemoglobin between the two groups was statistically significant ($p < 0.01$).

The results of this study showed that the mean serum ferritin was 25.88 ± 7.57 and 79.85 ± 61.98 ng/ml in cases and controls respectively as shown in Table 7. The odds ratio was 15.619 (95 % CI: 1.890-120.069). The mean difference of serum ferritin between the two groups was statistically significant (p<0.001). The results of this study are similar to that of a study done by Daoud A et al**Error! Bookmark not defined.**[18]. WHO conducted a controlled study to investigate the relation of iron store and first febrile seizures. It was found that plasma ferritin level was significantly lower in children with first febrile seizure than in reference group, suggesting a possible role of iron insufficiency in first febrile seizures. In another multicentric study by Sherjil A et al[21], which included 310 children, concluded that patients with febrile seizures are 1.93 times more likely to have iron deficiency anemia compared to febrile patients without seizures.

The mean serum zinc in cases and controls included in this study was 73.10 ± 44.31 and 87.30 ± 24.70 mcg/ml respectively as shown in Table 8. The odds ratio was 0.225 (95 % CI: 0.097-0.521). It was observed that there was a statistical significance between the mean Zinc levels of cases and controls (p < 0.001). Our findings were similar to the study results of Sampath Kumar et al**Error! Bookmark not defined.**[22]**.** where it was found that children with febrile convulsions had statistically significant low serum zinc levels when compared to children with fever alone without convulsions.

There was significant correlations observed between the groups and iron and Serum Zinc levels, which shows that the febrile convulsions are correlated to these parameters. Hence, it is advisable to evaluate the Zinc levels of every febrile child aged 06 to 60 months to prevent febrile convulsions.

Conclusion

The present study has shown that iron and zinc deficiency are few of the predisposing factors for simple and complex febrile convulsions thereby establishing the relationship between zinc deficiency and febrile seizures. A follow –up study of patients found to be iron and zinc deficient to determine the incidence of subsequent febrile seizures after therapeutic trial of zinc and iron supplementation and formulate the zinc treatment regimen including its dose and duration.

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