A HOSPITAL BASED OBSERVATIONAL STUDY TO STUDY THE ASSOCIATION OF IRON DEFICIENCY ANEMIA WITH FEBRILE SEIZURES IN CHILDREN OF AGE GROUP 6 MONTHS TO 5 YEARS AT TERTIARY CARE CENTER, HYDERABAD

Paediatrics

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ABSTRACT

BACKGROUND: Febrile convulsion (FC) is the most common CNS disorder in childhood. 2-5% of children (or 4.8 out of every 1000) are affected every year. Studies conducted on the effect of iron deficiency on febrile convulsions found in children have yielded completely conflicting results. Iron deficiency has been a risk factor for febrile convulsions in some studies, while in others, it was proved to be protective against febrile seizure as iron deficiency increases the threshold of neuron excitation. **Aims:** To study the relationship between iron deficiency anemia and febrile convulsion in children to prevent the treatable cause of FC. **Objectives:** Is to determine the relationship between iron deficiency anemia and febrile seizures and to find out the incidence of anemia in the febrile seizure in males and females. **Methods:** A Hospital-based observational study carried out at Andhra Mahila Sabha Hospital, Hyderabad, during the period May 2014 to May 2016 involving children aged about 6 months to 5 years of age group with typical febrile convulsions meeting inclusion and exclusion criteria. The temperature at admission and nutritional status was recorded, and investigations like hemoglobin, blood indices (MCV, MCH, MCHC), RDW (Red Cell Distribution Width), serum iron, and peripheral smear did for detection of iron deficiency anemia and their relationship with febrile seizure was observed.

Results: Out of 350 children enrolled, 131 (37.4%) were female, and 219 (62.6%) were males. In our study males was slightly more prone to febrile seizure with the ratio of M: F is 1.6:1. There is a significant association of iron deficiency anemia with FC, and there is increased frequency with increased incidence of iron deficiency anemia, (i.e.) seizures tend to repeat itself in the presence of iron deficiency anemia (with P-value of <0.001, at CI of 95%).

Conclusion: low serum iron levels and the presence of anemia can serve as strengthening factors for febrile seizures in children. Accordingly, children with febrile seizures are suggested to be monitored for the diagnosis and treatment of IDA.

KEYWORDS

Febrile convulsions (FC), Iron Deficiency Anemia (IDA)

INTRODUCTION:

Febrile convulsion (FC) is the most common CNS disorder found in childhood. 2-5% of the children (or 4.8 out of every 1000) are affected every year.[1] Risk factors of this disorder include high-grade fever, head injury, history of convulsion, or FC in the family, mothers who smoke or consume alcoholic beverages.[2-6] Whereas various studies have been carried out to detect correctable risk factors of febrile convulsions to reduce the prevalence of FC and hence of epilepsy and convulsion. Studies conducted on the effect of iron deficiency on febrile convulsions in children have produced conflicting results. Iron deficiency was identified as a risk factor in some studies [7-9], while in others, it has been hypothesized that iron deficiency has a protective role against febrile convulsions as it increases the threshold of neuron excitation.[10,11] Iron is essential for the metabolism of the brain and neurotransmitters and in the production of myelin, which is required for nerve cells and can change the amplitude and the threshold of neuron excitation.[12]

METHODOLOGY:

- A Hospital-based Observational study conducted after obtaining permission from the institutional scientific, ethics committee, and informed consent from parents of enrolled children. The study conducted during the period May 2014 to May 2016 involving children aged about 6 months to 5 years of age with typical febrile convulsions meeting inclusion and exclusion criteria, At Andhra Mahila Sabha, Durgabai Deshmukh Hospital, Hyderabad.
- With informed consent from parents of the enrolled children, Demographic data, seizure details (including the seizure episode were noted based on the history given by informant), nature of the febrile illness, family history of epilepsy / febrile seizures, the temperature at admission and nutritional status was recorded, and IAP weight for age classification was used to grade protein-energy malnutrition.
- An investigation like hemoglobin, blood indices (MCV, MCH, MCHC), RDW (red cell distribution width), serum iron, and peripheral smear did for the detection of iron deficiency anemia and their relationship with febrile seizure was observed.
- Methods and diagnostic criteria for iron deficiency anemia used in our study are as follows:-[13]
- Hemoglobin in gm%- measured by Sahli's method (<11gm%

considered as anemia)

- Hemogram measured by cell counter and microscopy.
- MCV - (<72.7fl considered as microcytic)
- MCH - (<24.1 pg considered as hypochromic)
- MCHC - (<32.4%)
- RDW- cell counter and microscopy(>14.5 considered as increased)
- Peripheral smear- microscopy
- Serum iron- measured by spectrophotometry (< 70 ugs/dl indicates iron deficiency).
- Temperature(rectal) - mercury thermometer (>38°C)
- Seizure episodes were based on the history given by an informant.

A detailed history was elicited, and Physical examination was done to rule out other causes of seizures.

Inclusion Criteria:

- Children are with typical febrile seizure between 6 months and 5 years.

Exclusion Criteria:

- Children aged < 6 months and > 5 years.
- Children are presenting with an atypical febrile seizure.
- Children are presenting with afebrile seizures or those having any signs of CNS infection.
- Those children with a history of birth asphyxia/developmental delay/epilepsy.
- Those children are on Iron supplementation therapy.
- Very sick children.
- Children those fall into Grade III PEM category on IAP charts
- Family h/o Epilepsy/mental retardation

RESULTS:

They were analyzed by descriptive statistics, frequencies, percentages, ChiSquare, and SPSS window Version 19.0. In this study, Out of 350 children enrolled, 131 (37.4%) were female, and 219 (62.6%) were males. In our study males was slightly more prone to febrile seizure with the ratio of M: F is 1.6:1. Out of the 350 children, 185 (52.9%) were found to have associated iron deficiency anemia, which included 108(49.3%) of males and 77 (58.8%) of females. Females with

associated iron deficiency were more when compared to males given by the percentages above. There was a significant association of iron deficiency anemia with 1st, 2nd and 3rd episode of febrile seizure, associations were 27.4%, 53.4%, and 80.9% respectively, showing an increasing frequency of seizure with increasing incidence of iron deficiency anemia, (i.e.) seizures tend to repeat itself in the presence of iron deficiency anemia (with P-value of <0.001, at CI of 95%). By taking 1st episode as a reference, in the presence of iron deficiency anemia chance of 2nd episode is increased by 3 times (Odds ratio 3.039 at a CI 95%) and 3rd episode by 11 times (Odds ratio 11.218 at a CI 95%) showing a significant association of iron deficiency anemia with the frequency of episodes. There is a declining trend of occurrence of seizure as the age progresses was found in our study, indicating febrile seizure to be an age-dependent disorder.

Table 1: Iron Deficiency Anemia With Febrile Seizures To Sex

IDA	F	M	Total
No	54(41.8%)	111(50.7%)	165
Yes	77(58.8%)	108(49.3%)	185
Total	131	219	350

Table 2: Iron Deficiency Anemia With Febrile Seizures To Age Distribution

IDA	Age in months					
	6-12	13-18	19-24	25-36	37-48	49-60
No	26 (63.4%)	80 (58%)	22 (38.6%)	33 (38.4%)	4 (25%)	2 (16.6%)
Yes	15 (36.6%)	58 (42%)	35 (61.6%)	53 (61.4%)	12 (75%)	10 (83.4%)
Total	41	138	57	86	16	12
Percentage	11.7%	39.4%	16.3%	24.6%	4.6%	3.4%

Table 3: Iron Deficiency Anemia With Febrile Seizures With Order Of Episodes In Different Age Groups

	Age in months					
	06-12	13-18	19-24	25-36	37-48	49-60
Episode - 1	14	15	2	3	0	34
Episode - 2	1	34	19	6	1	62
Episode - 3	0	9	14	43	13	89
Total	15	58	35	52	14	11

Figure1: Bar Diagram Showing The Number Of Children With Febrile Seizures To Their Association With IDA And Age Distribution.

DISCUSSION:

Iron deficiency anemia and febrile seizure are two common conditions in children worldwide as well as in our country. Iron deficiency is known to cause neurological symptoms like behavioral changes, poor cognition, and attention span; thereby, it may be associated with another common neurological condition in childhood like a febrile seizure.

In this study, Out of 350 children, 62.6% were males and was slightly more prone for febrile seizure with the ratio of M: F is 1.6:1. The association of iron deficiency anemia with 1st, 2nd and 3rd episode of febrile seizure were 27.4%, 53.4%, and 80.9% respectively, showing increased frequency of seizure with increased incidence of iron deficiency anemia, (i.e.) seizures tend to repeat itself in the presence of iron deficiency anemia (with P-value of <0.001, at CI of 95%). By taking 1st episode as a reference, in the presence of iron deficiency anemia chance of 2nd episode is increased by 3 times (Odds ratio 3.039 at CI 95%) and 3rd episode by 11 times (Odds ratio 11.218 at a CI 95%) showing a significant association of iron deficiency anemia with the increasing frequency of episodes. There is also a declining trend of occurrence of seizure as the age progresses, indicating that febrile seizure to be an age-dependent disorder.

By our research, an Indian case-control study by Kumari et al. in 2012

suggested that there was a significant association between iron deficiency and febrile seizure with crude odd's ratio of 5.34 and adjusted odd's ratio in the logistic regression analysis was 4.5 with $p < 0.001$. [8]

Also, in another Indian study, by Vaswani et al., in 2010, 68% of cases were iron-deficient compared to 30 % of controls indicating iron deficiency could be a potential risk factor for febrile seizures in children. [14]

A study was done by Pisacane et al. Reported that anemia in their case group (30%) was higher than in the hospital control group (14%) and healthy group (12%). [18]

A study by Ur-Rahman and Billoo on children with febrile convulsion and children with other febrile illnesses indicated that iron deficiency anemia in their case group was significantly more prevalent than in controls. [15]

A Kenyan case-control study, as well as the meta-analysis of 8 case-control studies, have determined that the relationship between febrile seizure and iron deficiency, and suggested that the iron deficiency was a risk factor of febrile seizure in children. [16]

Iron deficiency and iron-deficiency anemia may play an important role in inducing seizures from the following mechanisms: [17]

- Decrease in GABA inhibitory neurotransmitter due to change in its metabolism.
- Reduction of enzymes such as monoamine and aldehyde oxidases
- leads to impairment in oxygenation and energy metabolism of the brain.

In Thailand, a study was conducted, which showed the rate of febrile convulsions in thalassemic children was reported as being 4.4% less than the general children population. The researchers suggested that the finding might be due to high levels of iron in their brain and their role in brain metabolism, which leads to a reduced occurrence of febrile convulsion in those children. This study could simply assess the role of increasing iron to febrile seizures and cannot be an appropriate scale to assess the role of iron deficiency anemia in febrile convulsion. On the other hand, a lower risk of febrile convulsion in the patients could be due to several other clinical conditions that they may have. [18]

Some studies have reported findings that are contradictory to the present study. for instance, in Kobrinsky et al.'s study, the febrile convulsion group suffered less from iron deficiency, and it was concluded that iron deficiency could have a protective effect against febrile seizure. [10]

In a study by Bidabadi, iron deficiency in the febrile convulsion group (44%) was found to be less than the control group (48%), but since there was no significant difference, the protective effect of iron deficiency against febrile convulsion was not confirmed. [19]

The possible explanation for these discrepancies are differences in age, nutritional habits, geographical area, sample size, general economic status, and diagnostic criterion.

Serum ferritin is a known acute phase reactant and is non-specific in any febrile disease. [20] the higher plasma ferritin levels confirm this in the patient groups than in the healthy group. Fever can lead to a lack of difference in ferritin levels between two patient groups. In any case, the use of plasma ferritin cannot merely be an efficient criterion for the diagnosis of iron deficiency in febrile children.

The strength of our study includes standardized criteria for diagnosing febrile seizures and iron deficiency and larger sample size. The study does have some limitations:

- As it was a hospital-based study, it may differ from community setting in the prevalence of exposure and outcome variables.
- As it is a prospective observational study finding only the prevalence of IDA in FC, it could not be compared with age-matched controls.
- Blood lead levels could not be determined in our subjects.
- Recall bias on the previous history of seizure.
- No, follow up after iron supplementation was available.

We report that iron deficiency as a modifiable risk factor for simple febrile seizures in Indian children of age group 6 months to 5 years. Early detection and correction of iron deficiency may be helpful for the prevention of simple febrile seizures in children of this age group.

CONCLUSION:

Our findings from the study suggest that low serum iron levels in the blood and the presence of iron deficiency anemia can serve as strengthening factors for febrile seizures in children. Therefore, ID (Iron deficiency) can be added to the list of risk factors for febrile convulsions. Accordingly, children with FC are suggested to be monitored for the diagnosis and treatment of IDA. Furthermore, iron supplements should be advised at the earliest to children who have important and well-known risk factors for febrile convulsions, such as positive family history. It would be beneficial to conduct a follow-up study of children with iron deficiency anemia, who have presented with febrile convulsions after the treatment of ID, in terms of the recurrence rate of febrile convulsion.

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