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Iron defeiciency anemia in children with simple febrile seizures-A cohort study.

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Abstract

The present study was conducted to evaluate the role of iron deficiency as a risk factor for simple febrile seizures in children aged 6 months to 5 years. This is a prospective cohort study recruiting 108 cases with simple febrile seizures and 100 controls with febrile illness without any seizures. All patients were assessed for iron deficiency anaemia by measuring haemoglobin level, serum ferritin level, Mean Corpuscular Haemoglobin Concentration (MCHC) and Mean Corpuscular Volume (MCV). Patients with iron deficiency anaemia amongst controls and cases were documented. Percentages and Odds ratio were derived from the collected data. 39.96% of cases (37 out of 108) had iron deficiency anemia and 22% of controls(22 out of 100) were found to have iron deficiency anaemia as revealed by low levels of haemoglobin level, serum ferritin level, Mean Corpuscular Haemoglobin Concentration and Mean Corpuscular Volume. Odds ratio was 1.847. Patients with febrile seizures were 1.847 times more likely to have iron deficiency anaemia compared to febrile patients without seizures.

Keywords: Simple febrile seizures, Iron deficiency anemia, Serum Ferritin.

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Introduction

Febrile seizures are the commonest cause of seizures in children, occuring in 2-5% of children [1]. The peak incidence is around the age of approximately 18 months. Febrile seizures is defined as an event in infancy or childhood usually occurring between 6 months to 5 years of age associated with fever but without evidence of intracranial infection or defined cause [2].

Febrile seizures occurring before 6 months should raise the suspicion of serious infections like bacterial meningitis. Animal studies suggest a possible role of endogenous pyrogens such as interleukin 1β that by increasing neuronal excitability, may link fever and seizures activity [3]. A simple febrile seizure is generalized, tonic clonic in nature, lasts for a few seconds and rarely up to 15 min, is followed by a brief period of postictal drowsiness and occurs only once in 24hrs [4]. There are many independent risk factors (genetic factors, age, gender, fever, type and duration of seizure, family and developmental history, multiple seizures, perinatal exposure to antiretroviral drugs, history of maternal smoking and alcohol consumption during pregnancy) which are potential predictors of recurrent febrile seizures [5-8].

Iron deficiency is the commonest micronutrient deficiency worldwide, and is a preventable and treatable condition [10]. In developing countries 46–66% of children under 4 years are anemic, with half attributed to iron deficiency anemia, which overlaps with the peak in incidence of simple febrile seizures i.e., 14 to 18 months age. Iron is needed for brain energy metabolism, for metabolism of neurotransmitters and for myelination and in low iron status, aldehyde oxidases and monoamine are also reduced. In addition, the expression of cytochrome C oxidase, a marker of neuronal metabolic activity, is decreased in iron deficiency [11]. Because iron is important for the function of various enzymes and neurotransmitters in the central nervous system, low serum levels of ferritin may lower the seizure threshold [12,13].

While most studies have suggested iron insufficiency as a predisposing factor for febrile seizures, some have even described iron deficiency anaemia to be less frequent in children with febrile seizures [9]. Keeping in view the prevalence of these two clinical entities as well as difference of opinion in available studies, we conducted a cohort study to evaluate iron deficiency anemia in simple febrile convulsions. We compared iron status in children with febrile seizures and a control group in order to

determine the relationship between iron status and febrile seizures in pediatric patients.

Material and Methods

This cohort study was done by the Department of Paediatrics, KIMS Bangalore from July 2013 to June 2014. Children aged 6 months to 5 years presenting to the Emergency department with fever (≥ 38ºC) and history of seizures, having normal cerebrospinal fluid examination and normal; serum glucose, sodium, potassium, calcium and magnesium levels were considered for the study. Cases and controls were selected in almost 1:1 ratio. No matching was done.

The patients with evidence of central nervous system infection, epilepsy, metabolic seizures, atypical febrile seizures; patients previously diagnosed with hematologic problems like haemolytic anemias, bleeding or coagulation disorders, haematologic malignancy; those who were on iron supplementation, and very sick children were excluded from the study. Controls were selected from the same setting as cases comprising of febrile children aged 6 months to 5 years (fever duration < 3 days) without seizures.

Informed consent of parents of children (cases and controls) was taken in printed form. All the questions were answered, doubts were cleared and signature of the parents was taken. The study protocol was approved by the ethics committee of our hospital.

A detailed history of presenting complaints were recorded, history included duration of fever, time of onset of seizures, type of seizures, duration of seizures, past and family history of seizures in first degree relatives, consanguinity . In addition history suggestive of any triggering factors for febrile episode like cough, cold, nasal discharge, ear discharge, burning micturition or crying during micturition were also recorded. Vitals signs namely heart rate, respiratory rate, and blood pressure were measured and recorded. The axillary temperature was recorded for all the children with mercury thermometer placed in axilla for three minutes.

Blood investigations done to diagnose iron deficiency included hemoglobin estimation and red cell distribution width (RDW) using an automated hematology analyzer (Sysmex Kx-21) and serum ferritin estimation using ELISA method (Acubind ELISA). Iron deficiency was diagnosed by hematologic investigations of hemoglobin value <11g%, serum ferritin value <12ng/mL and RDW > 15% (WHO) [10]. SPSS-17 was used for statistical analysis for this data.

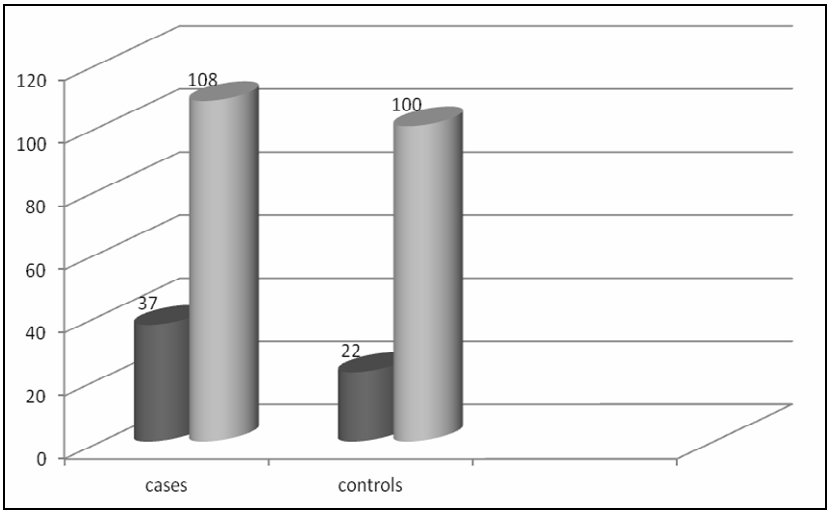
Results

Majority of children with febrile seizures (56%) were below the age of two years. Mean age of children was 24 months. 60% of them were males with male to female ratio being 1.4:1. Male children were 64 and females were 44 among cases.

Over a period of 1 year, 208 children aged 6 months to 5 years fulfilling the inclusion criteria, were considered for the study. 100 were controls and 108 were cases.

37 out of 108 cases had iron deficiency anemia (39.96%), where as 22 out of 100 controls were found to have iron deficiency anemia (22%). The difference in relation to iron deficiency anaemia among the two groups was significant ($p<0.05$).

Upper respiratory tract infection was the most common cause of fever in 57% cases followed by dengue, LRTI, viral fever, urinary tract infection and gastroenteritis in that order.



Iron deficiency Anaemia patients amongst cases and controls (odds ratio: 1.847)

Table 2. *Frequency of iron deficiency anemia with respect to cause of fever*

Cause of fever	No. of cases	%	Iron deficiency	%
URTI	62	57.4	21	33.8
Dengue fever	12	11.1	2	16.7
Viral fever	10	9.2	3	30
UTI	7	6.5	2	28.5
LRTI	11	10.1	6	54.5
Gastroenteritis	6	5.5	3	50
Total	108		37	

Discussion

Febrile seizure is a common neurologic problem occurring in children aged between 6 months to 5 years. Iron deficiency was found to be a significant risk factor for simple febrile seizures in our study, the risk becomes nearly twice (odds - 1.847) for simple febrile seizures in cases as compared to control group.

This study was conducted at the tertiary care hospital, Bangalore. Age of presentation in majority of children (56%) was 6 months to 2years. Frequency of iron deficiency anemia was found in almost 40% children with febrile seizures in our study, which was comparatively more than other international studies.

In the present study, febrile convulsion was more common in the 18-24 months age group, which makes them a population at risk, and a prime target for prevention. Iron is an essential element in the metabolism and functioning of enzymes required in neurochemical reactions. Its association with febrile seizures was first observed and published in mid 90's in an Italian study done by Pisacane, *et al*. [5], amongst the children of similar age group, (Odds ratio was 3.3 with 95% CI of 1.7-6.5). Iron status was measured by hemoglobin, MCV and serum iron in that study. In another study in Iran, Bidabadi and Mashouf *et al.* reported that iron-deficiency anemia was less frequent among patients with febrile seizure than in controls [9].

Previous studies have reported a relationship between iron-deficiency anemia and convulsions in patients with malaria [13]. In addition, iron-deficiency anemia can cause developmental delay and behavioral disturbances early in life, and correcting anemia early may reverse these processes [14-16]. Another study found that the incidence of febrile seizures in patients with thalassemia was much lower than among children in the general population [17]. Thus, iron overload may be a major factor in the brain metabolism that prevents febrile seizures.

The study does have some limitations. As it was a hospital-based study the prevalence of exposure and outcome variables may be different from a community setting. Serum ferritin, a nonspecific acute phase reactant can rise in any inflammatory conditions, but both cases and controls were having fever at the time of enrollment.

Conclusion

Children with febrile seizures are almost twice as likely to have iron deficiency anaemia as compared to children with febrile illness without seizures. Iron deficiency anaemia can be regarded as a modifiable risk factor that predisposes to febrile seizures in children between 6 months to 5 years. Early detection and timely correction of iron deficiency may help in preventing simple febrile seizures in children of this age group.

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