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Evaluating the association between iron deficiency and simple febrile seizure in children aged 6 months to 5 years: a case control study

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ABSTRACT

Background: Febrile seizures are one of the most common neurologic problems during infancy and childhood periods, occurring in 3-4% of the children, with an excellent prognosis. Iron deficiency is postulated as a risk factor for febrile seizures in children and it is an easily correctable condition. This study was done to evaluate the association between iron deficiency and simple febrile seizure in children aged 6 months to 5 years.

Methods: This study included 50 (25 boys and 25 girls) children of 6 months to 5 years of age with simple febrile seizure as cases and 50 (25 boys and 25 girls) age and sex matched children with minor febrile illness without simple febrile seizure attended (IPD and OPD) IGGGH and PGI, Pondicherry from December 2011 to November 2012. Both case and control group were analyzed for biochemical tests including complete blood count for measurement of Hb, Hct, MCV, MCH, MCHC and RDW. Peripheral smear used for confirmation of microcytic, hypochromic picture of RBCs and confirmatory test for iron deficiency anaemia by serum ferritin level also included.

Results: 22 out of 50 (44%) cases had iron deficiency anaemia whereas, 10 out of 50 (20%) controls were found to have iron deficiency anaemia. Odds ratio derived from these results was 3.14 (CI: 1.29-7.65, P - 0.01).

Conclusions: Screening for iron deficiency should be done in children presenting with simple febrile seizure.

Keywords: Iron deficiency, Odds ratio, Simple febrile seizure, Serum ferritin

INTRODUCTION

Febrile seizures are one of the most common neurologic problems during infancy and childhood periods, occurring in 3-4% of the children, with an excellent prognosis. They occur rarely before 9 months and after 5 years of age, with a peak incidence between 14-18 months of age. Iron deficiency anaemia, as the most common type of anaemia during infancy and childhood, occurs usually between 9-24 months of age and this period coincides with the peak incidence of febrile seizures. Anaemia secondary to iron deficiency is linked with depressed mental and motor development during

infancy and early childhood. It may be reversible if detected and treated adequately. Iron deficiency anaemia (IDA) during childhood also results in decreased physical activity and decreased interaction with the environment.

Learning capability and school achievements are adversely affected in presence of severe and persistent IDA.^{3,4} In India 1998-99 National Family Health Survey-2 (NFHS-2) documented a prevalence of IDA as 75% among children between 6-35 months of age. Iron is needed for brain energy metabolism, for metabolism of neurotransmitters and for myelination. Thus, iron deficiency may alter the seizure threshold of a child.^{5,6}

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Iron has an important role in multiple physiological functions of neurotransmitters. Many of the nervous system enzymes are iron-dependent for their proper activities. It has been determined that iron depletion has negative effects on neurocognitive functions of children and supplemental iron can reduce breath-holding spells. On the other hand, fever can exaggerate the negative effects of anaemia on brain.7 Iron deficiency is postulated as a risk factor for febrile seizures in children and it is an easily correctable condition.^{8,9} Several studies with controversial results have attempted to evaluate the relationship between iron deficiency anaemia and febrile convulsions in different areas of the world. To rule out the controversies regarding the positive or negative effect of iron on the occurrence of febrile seizures, the study was conducted.

METHODS

A case control study was done on 100 children attending to IGGGH and PGI, Pondicherry from December 2011 to November 2012. Fifty children for simple febrile convulsion between the age group of 6 months to 5 years were considered for the study and 50 children for concurrent controls were selected from the same setting of same age group (i.e. 6 months to 5 years) who present with short duration of fever (<3 days) but without seizures.

No differences were made in distribution of gender and sex among cases and controls. Children with normal birth history, developmental history, good nutritional status and those without family history of epilepsy were selected for the study as cases and controls. Cases and controls were being selected in 1:1 ratio. After taking detailed history a thorough clinical examination were done. Demographic data, seizure details, nature of febrile illness, family history of epilepsy/febrile seizures, temperature at admission and nutritional status were recorded. These patients were subjected to CBC includes Hb, Hct, MCV, MCH, MCHC, RDW; peripheral smear; serum ferritin; complete blood count which includes red blood cell indices (RBC indices) and red cell distribution width using an automated hematology analyzer (Sysmex Kx -21) and serum ferritin estimation using chemi luminescence immuno assay (Advia Centaur-Fully Automated).

Diagnostic criteria for simple febrile seizures used in the study was based on AAP clinical practical guidelines and for iron deficiency anaemia as per WHO. 10-12 Exclusion criteria are major febrile illness like enteric fever, severe pneumonia, patient already on iron supplement therapy, developmental delay, patient known for other causes of anaemia, complex febrile seizure, very sick children and family history of epilepsy/mental retardation.

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements were presented on Mean±SD and results on categorical

measurements were presented in number (%). Significance was assessed at 5% level of significance. Results were drawn with help of the statistical software SPSS 17 for the analysis of data. Microsoft word and excel had been used to generate graphs, tables etc.

RESULTS

Over a period of one year, total 100 subjects including, 50 children with simple febrile convulsion and 50 febrile children with no seizure were studied. Comparison of case and control group regarding number, age and sex was done (Table 1 and 2).

Table 1: Frequency distribution of patients based on age (months).

Character	Number	Mean age±SD	P Value	
Cases	50	23.12±10.75	0.259	
Controls	50	25.54±10.57		

Table 2: Frequency distribution of patients based on sex.

		Gender			
Character	No.	Male		Female	
		No.	%	No.	Female
Cases	50	25	50%	25	50%
Controls	50	25	50%	25	50%

Both case and control group were analysed for biochemical tests including complete blood count for measurement of Hb, Hct, MCV, MCH, MCHC and RDW. Peripheral smear for confirmation of microcytic, hypochromic picture of RBCs and confirmatory test for iron deficiency anaemia include serum ferritin level.

Table 3: Comparison of hematological analysis in cases and controls.

Cases (n = 50) (Mean±SD)	Controls (n=50) (Mean±SD)	P value
9.84±1.63	10.75±1.35	0.003
30.40 ± 4.06	33.23 ± 3.73	< 0.001
45.46±2.81	43.14±3.28	< 0.001
70.60±6.94	74.61±6.81	0.004
23.42±3.57	24.14±3.09	0.286
31.35±2.15	31.48±1.49	0.726
	(n = 50) (Mean±SD) 9.84±1.63 30.40±4.06 45.46±2.81 70.60±6.94 23.42±3.57	(n = 50) (n=50) (Mean±SD) (Mean±SD) 9.84±1.63 10.75±1.35 30.40±4.06 33.23±3.73 45.46±2.81 43.14±3.28 70.60±6.94 74.61±6.81 23.42±3.57 24.14±3.09

Mean value of Hb (gm/dl) in case group was 9.84 ± 1.63 and control group was 10.75 ± 1.35 (P - 0.003). Mean value of Hct (%) in case group was 30.40 ± 4.06 , control group was 33.23 ± 3.73 (P <0.001) while mean value of RDW (fl) in case group was 45.46 ± 2.81 and control group was 43.14 ± 3.28 (P <0.001). Mean value of MCV (fl) in case group was 70.60 ± 6.94 and control group was 74.61 ± 6.81 (P-0.004). Mean value of MCH (pg) in case group was 23.42 ± 3.57 and control group was 24.14 ± 3.09

(P-0.286). Mean value of MCHC (gm/dl) in case group was 31.35±2.15 and control group was 31.48±1.49 (P-0.726) (Table 3).

Table 4: Comparison of Serum ferritin analysis in cases and controls.

Variables	Cases (n = 50) (Mean±SD)	Controls (n = 50) (Mean±SD)	P value
Serum ferritin (ng/ml)	41.92±20.37	66.26±26.40	< 0.001

When comparison for serum Ferritin value was done, significant difference was observed between case and control group. Mean value of serum ferritin (ng/ml), in case group was 41.92 ± 20.37 while, in control group was 66.26 ± 26.40 (P <0.001) (Table 4).

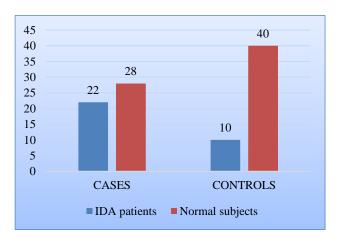


Figure 1: Iron deficiency anaemia patients among cases and controls.

In this study, diagnosis of iron deficiency anaemia was based on W.H.O. criteria. 22 out of 50 (44%) cases had iron deficiency anaemia whereas, 10 out of 50 (20%) controls were found to have iron deficiency anaemia. Odds ratio derived from these results was 3.14 (CI 1.29-7.65, P-0.01) (Figure 1).

DISCUSSION

It has been hypothesized that many factors are involved in febrile convulsions including familial (genetic) and prenatal factors, present acute illness, highest degree of fever and finally iron deficiency anaemia.¹³

Iron is an essential element in the metabolism and functioning of enzymes required in neurochemical reactions. These include monoamineoxidase, cytochrome, peroxidase and catalase. ¹⁴ Clinically neurological symptoms like poor attention span, learning deficits, poor memory, delayed motor development and behavioural changes caused by iron deficiency are well known. ¹⁵ Its association with febrile seizures was first observed and published in mid-90's in an Italian study. ¹⁴ This was

followed by few more international studies. 16-18 Some international studies denied any role of iron insufficiency in febrile seizures. Momen et al compared 100 children suffering from febrile seizures with 100 febrile children affected by acute febrile illnesses without seizure including upper and lower respiratory, gastrointestinal and urinary tracts infections. There was no significant difference between the two groups regarding anaemia.¹⁹ In fact, in an Iranian study, Bidabadi and Moushaf from University of Guilan, concluded that iron deficiency is less frequent in children with first febrile seizure.²⁰ Vaswani et al conducted a case control study from King Edward Memorial Hospital, Parel, Mumbai, India to determine the role of iron deficiency as a risk factor for first febrile seizure in children.²¹ Kumari L did a case control study in the Department of Pediatrics, SAT Hospital, Thiruvananthapuram, Kerala, India, reported iron deficiency as a modifiable risk factor for simple febrile seizures in Indian children of age group 6 months to 3 years.²² These handfuls of studies are too few and bear conflicting results.

In this study iron deficiency was found as a significant risk factor for simple febrile seizures in children of age group 6 months to 5 years. In present study, diagnosis of iron deficiency anaemia was based on WHO criteria. 22 out of 50 (44%) cases had iron deficiency anaemia whereas, 10 out of 50 (20%) controls were found to have iron deficiency anaemia. Odds ratio derived from these results was 3.14 (95% CI of 1.29-7.65, P = 0.01). Similar results were observed in study done by Kumari L, (crude odds ratio 5.34, 95% CI 2.69-7.53, P = 0.001). Iron deficiency was diagnosed by hematologic investigations of haemoglobin, RDW and serum ferritin value in that study. All three parameters were significantly different among cases and controls.²² In the study done by Pisacane et al similar results were noted, and the odds ratio was 3.3 (95% CI of 1.7-6.5).14 Iron status was measured by haemoglobin, MCV and serum iron in that

Rehman, et al in Pakistan, who performed a study similar to Batieha et al, declared that plasma ferritin level was significantly depleted in cases compared to controls and suggested that iron deficient children were more vulnerable to febrile convulsions.¹⁷

In 2006, Vaswani, et al conducted a study to determine the role of iron deficiency as a risk factor for first febrile seizure in children. Fifty children between 6 months to 6 years with first febrile seizure (cases) and 50 children with febrile illness but without convulsions (controls) were enrolled from the Pediatric ward of KEM hospital, Parel, Mumbai, India. Iron deficiency was determined by estimation of haemoglobin, red blood cell indices and serum ferritin. The mean serum ferritin level (μ g/L) was significantly low in Cases (31.9±31.0) as compared to Controls (53.9±56.5) with P - 0.003. Iron deficiency could be a potential risk factor for febrile seizure in children.²¹

Hartfield et al conducted a retrospective case control study to determine the association between iron deficiency and febrile seizures in a large cohort of children aged 6 to 36 months. Iron status was measured by using the MCV, RDW, and hemoglobin. A total of 9% of cases had iron deficiency (ID) and 6% had iron deficiency anemia (IDA), compared to 5% and 4% of controls respectively. The conditional logistic regression odds ratio for ID in patients with febrile seizures was 1.84 (95% CI, 1.02-3.31). ¹⁸

Present study revealed mean serum ferritin level (ng/ml) was significantly low in cases (41.92±20.37) as compared to controls (66.26±26.40) with P <0.001. Values of Hb (gm/dl), Hct (%), and MCV (fl) in children suffering from febrile seizures were significantly less than children in the control group (P - 0.003, <0.001, 0.004). RDW (fl) was significantly high in case group compare to control group (P <0.001). While MCH (pg) and MCHC (gm/dl) values were relatively low in case group compare to control group but not statistically significant (P - 0.286, 0.726). Mean corpuscular haemoglobin begins to decrease when iron reserves are depleted, and iron deficiency has developed. However, mean corpuscular haemoglobin may not reach abnormally low levels until sometime after iron deficiency sets in. 11

Kobrinsky, et al suggested that iron deficiency anaemia raised the seizure threshold.²³ Bidabadi, et al suggested that iron deficiency anaemia was less frequent in cases with febrile convulsions compared to the controls and stated that iron deficiency was not protective against febrile convulsions.²⁰

This contrasting finding, along with the present findings, may explain what Kobrinsky et al reported in their study: the low number of children enrolled in their study (25 children with febrile seizures against 25 febrile children without seizures) and their criteria for assessing anaemia were only based on blood haemoglobin level, MCV and MCH, without measuring serum ferritin level. These parameters do not reveal the real bone marrow iron storage status. Ferritin is a protein carrier for iron and is the iron storage source in the body. Measuring serum ferritin level is a specific, sensitive and a reliable test for detecting iron depletion in the early stages of the disease and the best standard for determining the total body iron storage.

The strength of this study included standardized criteria for diagnosing febrile seizures, and iron deficiency, elimination of incidence prevalence bias, concurrent enrolment of controls and cases, and no recall bias regarding exposure. 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, although both cases and controls were having fever at the time of enrolment. It is

deficient in not being able to account for some confounding factors leading to iron deficiency anaemia like lead poisoning.²⁴

The present study suggests that oral supplemental iron therapy be given to children with febrile seizures who have a low serum ferritin level after recovery from their acute stage and subsiding of their fever to prevent the recurrence of febrile seizure attacks.

CONCLUSION

Finding suggests that children with febrile seizures are more likely to have iron deficiency anaemia as compared to children with a febrile illness without seizures. Of the two groups this study suggested that Iron deficiency anaemia can be regarded as a risk factor that predisposes to febrile seizures in children. So, screening for iron deficiency should be regarded in children presenting with febrile convulsions.

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Institutional Ethics Committee

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