RESEARCH PAPER

Iron Deficiency as a Risk Factor for Simple Febrile Seizures– *A Case Control Study*

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Objective: To study the role of iron deficiency as a risk factor for simple febrile seizures.

Design: Case control study.

Setting: Pediatric department of a tertiary care teaching hospital.

Participants: 154 cases and 154 controls were included in the study. Consecutive cases and concurrent controls were selected. Cases were children of age group 6 months to 3 years presenting with simple febrile seizures. Controls were children of same age group presenting with short febrile illness but without any seizures.

Methods: After informed consent, detailed history was taken and clinical examination done in both cases and controls and blood investigations were done to diagnose iron-deficiency in both cases and controls. Iron deficiency was diagnosed as per WHO criteria (hemoglobin value <11g%, red cell distribution width of >15% and serum ferritin value < 12ng/mL). Other explanatory variables, which can be the potential confounders were also included in the study and considered for analysis.

Results: Highly significant association was found between iron deficiency and simple febrile seizures in both univariate and multivariate analysis. Crude odds ratio was 5.34 (CI 3.27- 8.73, *P*<0.001) and adjusted odds ratio in the logistic regression analysis was 4.5 (CI 2.69- 7.53, *P* <0.001).

Conclusions: Iron deficiency is a significant risk factor for simple febrile seizures in children of age group 6 months to 3 years.

Key words: *Febrile seizures, Hemoglobin, India, Iron deficiency, Risk.*

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Febrile seizures are the commonest cause of seizures in children, occuring in 2-5% of children [1]. Complications like aspiration can occur during each episode of seizures [2-5]. Febrile seizure episodes are agonizing to the parent and child and can cause psychological trauma to both [6]. Iron deficiency is the commonest micronutrient deficiency worldwide, and is a preventable and treatable condition [7]. 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 [8,9]. Iron deficiency is postulated as a risk factor for febrile seizures in children and it is an easily correctable condition [10,11]. We, therefore, studied the association between iron deficiency and simple febrile seizures.

METHODS

This case control study was done in the Department of Pediatrics, SAT Hospital, Thiruvananthapuram during August 2009 to February 2010. Ethical clearance was obtained for the study from the Ethical committee, Medical College, Thiruvananthapuram. Cases were children of age group 6 months to 3 years presenting with simple febrile seizures to the Pediatrics Emergency Department and wards of the hospital during the study period. Diagnostic criteria for simple febrile seizures (based on AAP Clinical Practice Guidelines) included seizures associated with fever and the seizures were generalized, short duration (less than 15 minutes), no recurrence of seizures within 24 hours, child is otherwise neurologically healthy and without any neurological abnormality before and after the episode of seizures, with age group between 6 months to 5 years [2]. Consecutive cases were selected for the study and concurrent controls were selected from the same setting and included febrile

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children of age group 6 months to 3 years who presented with short duration fever (<3 days) but without seizures. Cases and controls were selected in 1:1 ratio. No matching was done. Children presenting with atypical febrile seizures, afebrile seizures, those having any signs of central nervous system infection, those with any chronic neurodevelopment problems, those who were previously diagnosed cases of other hematologic problems like hemolytic anemias, bleeding or coagulation disorders, haematologic malignancy, those who were on iron supplementation, and very sick children were excluded from the study.

After informed consent, detailed history was elicited and physical examination was done. Hospital records were also examined for relevant data. 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 <12 ng/mL and RDW > 15% (WHO) [7]. Other variables studied included age of the child, sex, socioeconomic status, family history of febrile seizure in first degree relatives, family history of epilepsy in first degree relatives, consanguinity, neonatal hospital admissions (NICU or special care nursery admissions), daycare attendance for more than one month, prematurity (<37 weeks gestational), protein energy malnutrition (IAP classification), immunization status of child, and Hib vaccine status.

Sample size was calculated using Epi Info program based on the assumptions that alpha error 5%, beta error 20% i.e. power of study 80%, Odds ratio 2, and prevalence of exposure (iron deficiency) in the non-ill group (controls) 30% (obtained from a pilot study) provided a value of 153 children in each group. Data were entered in MS Excel, cleaned and completeness checked. Analysis was done using SPSS Version 11. Analysis includes univariate analysis for crude odds ratio and confidence interval, bivariate analysis for confounding and interaction and multivariate analysis for adjusted odds ratio.

RESULTS

154 cases and 154 controls were included in the study. The average age of cases and controls was 17.5±8.81 and 17.6±8.54 months, respectively. Variables found to be significantly associated with simple febrile seizures on univariate analysis included iron deficiency, family history of febrile seizures in first degree relatives, family history of epilepsy in first degree relatives, daycare attendance, and prematurity (***Table* I**). Significant variables were considered for multivariate analysis. Variables found to be significant in multivariate analysis included iron deficiency (adjusted odds ratio 4.5, 95% CI 2.69- 7.53, *P*=0.001), family history of febrile seizures in first degree relatives (adjusted odds ratio 2.44, 95%CI 1.26- 4.73, *P*=0.008), family history of epilepsy in first degree relatives (adjusted odds ratio 2.21, 95% CI 1.11-4.38, *P* value 0.02), daycare attendance (adjusted odds ratio 2.80, 95% CI 1.29- 6.06, *P*= 0.009), and prematurity (adjusted odds ratio 2.58, 95% CI 1.19-5.62, *P*=0.01).

TABLE I RELATION OF VARIOUS STUDY VARIABLE WITH SIMPLE FEBRILE SEIZURES IN CHILDREN BETWEEN 6 mo AND 3 y

	Cases (n=154)	*Controls (n=154)*	*Crude Odds Ratio (CI)*	*P value*
Age ≤17 mo	86(55.8%)	87(56.5%)	1.027 (0.6551.610)	0.909
Female	71(46.15%)	81(52.6%)	1.297 (0.829-2.03)	0.254
Social Class 4	115(74.7%)	109(70.8%)	1.217 (0.737-2.01)	0.443
Full Term	124(80.5%)	142(92.2%)	2.86 (1.41-5.83)	0.003
NICU admission	46 (29.9%)	37 (24%)	1.35 (0.81-2.23)	0.248
Family H/O febrile seizure	40 (26%)	20 (13%)	2.35 (1.30-4.25)	0.004
Family H/O epilepsy	36 (23.4%)	17 (11%)	2.46 (1.31-4.60)	0.004
Daycare attendance	32 (20.8%)	12 (7.8%)	3.1 (1.53-6.29)	0.001
Not Immunized for age	29(18.8%)	27(17.5%)	1.09 (0.61-1.99)	0.768
No Hib vaccine	110(71.4%)	105(68.2%)	1.17 (0.72-1.89)	0.535
Iron deficiency	98 (63.6%)	38 (24.7%)	5.34 (3.27-8.73)	0.001
Malnutrition	62 (40.3%)	52(33.8%)	1.32 102(66.2%)	0.238

H/o: history of; NICU: Neonatal Intensive Care Unit.

WHAT THIS STUDY ADDS?

- Iron deficiency is a significant risk factor for simple febrile seizures in children 6 mo - 3 y age.

DISCUSSION

Iron deficiency was found as a significant risk factor for simple febrile seizures in children of age group 6 months to 3 years in our study. In the study done by Pisacane, *et al*. [12], among children of the same age group, similar results were noted and the odds ratio was 3.3 (95% CI of 1.7-6.5). Iron status was measured by hemoglobin, MCV and serum iron in that study. Dawn, *et al*. [13] also found similar results with children with febrile seizures almost twice likely to have iron deficiency compared to controls.

In the study by Daoud, *et al*. [14], the significance of iron status as a possible risk factor was evaluated. The mean serum ferritin level in the cases was 29.5 mcg/L, much lower than the values in the controls (53.5 mcg/L). Similar observations were made in a study done by Vaswani, *et al*. [15] from Mumbai. The mean serum ferritin level was significantly low in children with first febrile seizures (31.9±31.0 mcg/L) as compared to controls (53.9±56.5 mcg/L) (P=0.003). However, no significant difference was noted in the mean hemoglobin value of cases (9.4±1.2 g/dL) and controls (9.5±1.0 g/dL) (P=0.7), or in the mean value of blood indices. In our study, iron deficiency was diagnosed by three criteria *i.e*. hemoglobin, red cell distribution width, serum ferritin, and all three parameters were significantly different among cases and controls.

The strength of our study included standardized criteria for diagnosing febrile seizures, and iron deficiency, elimination of incidence prevalence bias, concurrent enrollment 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 enrollment. Iron deficiency and lead poisoning may be associated. Blood lead levels could not be determined in our subjects.

We report iron deficiency as a modifiable risk factor for simple febrile seizures in Indian children of age group 6 months to 3 years. Early detection and timely correction of iron deficiency may be helpful for prevention of simple febrile seizures in children of this age group.

Contributors: PLK collected, analyzed and interpreted the data, performed literature review and drafted the manuscript. MKCN designed the study, supervised data collection and analysis, reviewed and approved the final manuscript. SMN assisted in data analysis. LK was the pediatrician in charge of study participants and supervised data collection, SG assisted in data collection and analysis.
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