Original Research Article

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Is iron deficiency anaemia a risk factor for febrile seizure? A case control study

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ABSTRACT

Background: The relationship between iron deficiency anaemia and febrile convulsions has been examined in several studies with conflicting results. The authors aimed to evaluate the relation, if any, of iron status with febrile seizures. Methods: In this case-control study, 36 cases and 36 controls were taken. The study group consisted of all children with a diagnosis of febrile convulsion, aged between 6 months and 6 years, without developmental delay, neurological deficit, or CNS infection, who were treated at SMIMER Hospital, a tertiary care centre of Surat, India, from November 2014 to November 2015. The control group consisted of febrile children without convulsion; controls were matched to the cases by gender and age. Sample size was calculated by using SPS based on the alpha error 5%, beta error 10%, power of the study = 90% and using the case (29.5±21.3) and control (53.3±37.6) from previous study. Provided sample size n = 72, where n_1 (cases) = 36 and n_2 (controls) = 36. Discrete variables expressed as counts (%) and compared using the chi-square tests. Continuous variables are expressed as mean±S.D. and compared by means of the unpaired, two-sided t-test. Adjusted odds ratios and 95% Wald confidence intervals were calculated. Results: Mean age of patients and controls were 27.33±14 and 27.2±18.7 months respectively. Risk factors like prematurity, prior history of febrile convulsions and family history of convulsions showed statistical significance (p value being 0.001, 0.003 and 0.011) among cases. Serum ferritin levels in study group was found to be 57.10±42.8 microgm/L compared to 135.42±15 microgm/L of control group and it was the only haematological variable which was statistical significance (p-value 0.04). IDA was found in 30.6% of cases and 8.3% of controls (p value 0.0172). A patient with febrile seizures was 2.4 times more likely to have IDA. (Crude odd ratio 2.4; 95% CI 39.5-40.52). **Conclusions:** The study found positive association between iron deficiency anaemia and febrile seizures.

Keywords: Febrile convulsions, Iron deficiency anaemia

INTRODUCTION

Febrile seizures (FS) are the single most common seizure type and occur in 2 to 5% of children younger than age 5 years with a peak incidence in the second year of life. Provoking factors which have been studied are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors which have been studied are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors which have been studied are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors which have been studied are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors which have been studied are genetics, low birth weight, vaccinations and metabolic disturbances. Provoking factors are genetics are genetics and provoking factors are genetics.

generated considerable optimism that this element might also play a role in initiation of febrile convulsions. Previous studies examining the relationship between iron deficiency anemia and febrile convulsions have been conflicting. ¹³⁻¹⁶ Pisacane et al reported that anemia was more common in children younger than 2 years with febrile convulsions, whereas, in contrast, Kobrinsky et al reported that iron deficiency raises the threshold for seizures. ^{13,14} Vaswani et al, reported that 68% of cases with febrile convulsions were iron-deficient compared to 30% of controls. ¹⁷ In a study by Bidabadi, iron deficiency

in the febrile convulsion group (44%) was less than in the control group (48%), but since there was no significant difference, the protective effect of ID against febrile convulsions was not confirmed. The major causes that have led to different results between the two studies may include, not considering the effect of age on interpretation of the tests for ID diagnosis, difference in age and number of samples, and difference in the diagnostic criteria of IDA.

The purpose of the present study was to assess the relation, if any of iron deficiency anaemia with febrile convulsion.

METHODS

The study group consisted of all children with a diagnosis of febrile convulsion, aged between 6 months and 6 years, without developmental delay, neurological deficit, or CNS infection, who were treated at SMIMER hospital, a tertiary care centre of Surat, India, during November 2014 to November 2015.

Inclusion criteria

For cases were patients with typical febrile convulsions between 6 months to 6 years. (AAP clinical practice guidelines).²⁹

Exclusion criteria

The control group consisted of febrile children (fever <3 days) without convulsion or previous history of convulsion who required hospital admission. Controls were without any blood dyscrasias and not on iron supplementation. Demographic information collected for cases and controls included age, and gender. Age (in months) was calculated from the date of birth. Information on birth weight and current weight, developmental milestones, body temperature upon admission, cause of fever, history of iron supplement therapy, family history of febrile convulsion, and family history of epilepsy were recorded for all cases and controls, as well as details of the seizure history, duration, frequency, type of seizure (simple or complex).

The following routine hematological investigations were performed at the time of hospital admission for all cases and controls: Red blood cell count, hemoglobin (Hb), Hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and serum ferritin were evaluated. Ferritin assay in a microparticle enzyme immunoassay (MEIA) for quantitative determination of human serum ferritin. Acetaminophen was used, 10-15 mg/kg/dose every 4-6 h, for its antipyretic effects, for all cases and controls with body temperature higher than 38.5°C and clobazam for seizure prevention in cases. Iron deficiency anemia as per WHO Criteria for febrile illness (hemoglobin value <11.5 g%, MCV <72, MCHC

<23, red cell distribution width of >15% and serum ferritin value <30 ng/ml).³⁰ Written informed consent from all parents for inclusion were obtained in the study. The study was cleared by hospital ethical committee.

Statistical methods

Sample size was calculated by using SPS based on the alpha error 5%, beta error 10%, power of the study = 90% and using the case (29.5±21.3) and control (53.3±37.6) from previous study. Provided sample size n = 72, where n_1 (cases) = 36 and n_2 (controls) = 36. Discrete variables expressed as counts (%) and compared using the Chi-square tests. Continuous variables are expressed as mean±SD. and compared by means of the unpaired, two-sided t-test. Adjusted odds ratios and 95% Wald confidence intervals were calculated. Statistical significance was set at P < 0.05. Univariate and multivariate analysis were done of the several variables which are taken as a part of study (eg. age, sex, socioeconomic class, past or family history of epilepsy etc.) and logistic regression for discrete variables was applied.

RESULTS

A total of 72 patients were analyzed. 36 were patients with febrile seizures and 36 were age and gender matched controls as per inclusion criteria. In study group, majority belonged to age group of <2 years (i.e. 54.2%) while others mainly belonged to age group of 2-5 years (i.e. 44.4%). Mean age group for study group was 27.33±14 months with age ranging between 8 to 66 months while for control group mean age was 27.2±18.7 months. Males and females are equally distributed in the study group and control group. There was no statistical difference in distribution as per age, gender, socioeconomic strata and malnutrition in both groups.

Table 1: Various parameters that were compared between cases and controls.

Variables	Cases (n = 36)	Control (n = 36)	p- value
Prematurity	10 (27.78%)	0	0.001
History of NICU admission	4 (11.11%)	2 (5.56%)	0.394
Previous history of febrile seizures	10 (27.78%)	0	0.003
Previous history of convulsion	3 (8.3%)	0	0.077
Family history of epilepsy	6 (16.67%)	0	0.011
H. Influenza vaccination	25 (70%)	18 (50%)	0.093

Prematurity, prior history of febrile convulsions and family history of convulsions showed statistical significance in cases (p value being 0.001, 0.003 and

0.011), as compared to the control group. Symptomatology wise there was no difference in the history of fever at presentation, degree of fever among cases and controls. The most common case of fever in both groups was respiratory illness. Among hematological investigations, mean hemoglobin was lower in cases, 10.03 g% versus 10.11g% in controls, though it was not statistically significant. Similarly MCV and MCH and MCHC also were lower in cases though not statistically significant. Serum ferritin levels in study

group was found to lower 57.10±42.8 microgm/L than in the control group where they were 135.42±15 microgm/L and it was the only variable which was statistical significance with p value of 0.04.

IDA was found in 30.6% of cases and 8.3% of controls. This was statistically significant for cases (p-value of 0.0172). Its crude's odd ratio is 2.4 (95% confidence interval 39.5-40.52). Patients with febrile seizures was 2.4 times more likely to have IDA.

Table 2: Various hematologic parameters compared between cases and controls	Table 2: Various	hematologic	parameters compa	red between cases	and controls.
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Hematological parameters	Cases (n = 36)	Control (n = 36)	p value
Hemoglobin (g/dL)	10.03±1.2	10.11±1.8	0.84
TLC (per cumm)	17027.77±21275	11938.88±4749	0.16
Platelet count (10 ⁵ per cumm)	3.51±1.3	3.64 ± 2	0.75
MCV (femtoliter)	66.47±8.7	69.36±7.8	0.14
MCH (picogram)	20.83±4	22.05±4.3	0.22
MCHC (g%)	30.63±2.4	31.27±2	0.22
RDW (%)	17.07±3.4	16.38±3.3	0.37
S Ferritin (microgram/L)	57.10±42.8	135.42±153	0.04
Anaemia rate (Hb<11 g%)	28 (77.8%)	26 (72.2%)	0.586
Iron deficiency anaemia	11 (30.6%)	3 (8.3%)	0.017

Table 3: Multivariate analysis (Among historical data and haematological data).

	n volue	Odd's ratio	95% C.I.	
	p-value	Oud's ratio	Lower	Upper
Prematurity	0.99	0.00	-	-
Previous H/o of febrile seizures	0.013	0.057	-	-
Family H/o of epilepsy	0.99	0.00	-	-
Hemoglobin	0.410	0.841	0.557	1.270
MCV	0.227	1.060	0.965	1.164
MCH	0.463	0.921	0.738	1.148
MCHC	0.425	1.160	0.805	1.672
RDW	0.727	0.969	0.810	1.158
S. Ferritin	0.013	1.014	1.003	1.026

Multivariate analysis

Logistic regression was applied to various significant variables (like prematurity, previous history of febrile seizures, family history of epilepsy, serum ferritin and probable etiology of infection) among study and control group. Previous history of febrile seizures was significantly associated with study group as compared to other variables (p-value of 0.013).

A multivariate analysis was done among case and controls for hematological investigations for iron deficiency anaemia.

It was statistically significant only for S. Ferritin which was 0.013. Children with febrile seizures were 1.003 to 1.026 times more likely to have lower serum ferritin levels. (CI = 1.003-1.026)

DISCUSSION

The results of our study found that mean age of the cases was 27.33±14 while for the control was 27.2±18.7 in months, while male:female ratio for the cases was 1.11:1. This was comparable to Piscane where mean age was 27.13±15.74 and male to female ratio was 2:1. Similar results have been reported by Daod et al, Vaswani et al Kumari et al. 13,17,20

The risk factors found to be significant in present study were, prematurity (p-value of 0.001), previous history of febrile seizures (p-value of 0.003) and family history of epilepsy (p-value of 0.01). It was also observed in Kumari et al.²⁰ (p-value of 0.003) for prematurity, Korbinsky et al (p- value of 0.01) for previous history of febrile seizures, and Bidabadi et al Yousefchaijan et al for family history of epilepsy.^{14,21,22}

There was no positive correlation for history of NICU admission, *H. influenza* B vaccination, or malnutrition in our as well as in other studies. Respiratory tract infection was the most commonly observed probable illness, as a cause for fever. This was also seen in studies by Piscane et al, Daod et al and Srinivasa et al. ^{13,19,23} Malaria was the common infection found in Idro et al in about 67%. Temperature at time of admission in cases was not found statistically significant in present study though it was significant in Piscane et al (p-value of 0.000) and in Bidabadi et al (p-value of <0.001). ^{13,24}

Anaemia was defined as hemoglobin level below 11gm% and it was found in 77.8 versus 72.2% of cases v/s controls but it was not statistically significant with pvalue of 0.586, in present study. In Sadeghzadeh et al, anaemia was defined as Hb<10.5 g% and it was observed in 21.5% of cases with p-value of 0.47 while in Silva VD et al anaemia was defined as Hb<11 g% and it was observed in 40% of cases. 25,26 Only Yousefchaijan et al found anaemia to correlate with febrile convulsions.²² To find an association of iron deficiency anaemia and seizures, in the current study, various hematological parameters were compared between study and control group (i.e. Hb, MCV, MCH, MCHC, RDW and S. Ferritin), among these only serum ferritin was found to be significant with p-value of 0.04. Daod et al Piscane et al and Fallah et al also found serum ferritin to be statistically correlating with febrile seizures. 13,19,27 Vaswani et al, Kumari et al among Indian studies have reported the same correlation between febrile seizures and serum ferritin levels. 17,20 In studies by Bidabadi et al, Yousefchaijan et al and Idro et al, patients did not show any statistical correlation between ferritin levels and febrile convulsions. ^{20,22,28} Piscane et al also showed that IDA was 1.9 times more common with patients of febrile convulsion this has also been reported by Idro et al and Fallah et al. 13,27,28 Numerous studies have addressed the association between iron deficiency anaemia and febrile seizure in children both in India and abroad. The results, however, have been controversial and even primary researches with high number of cases have failed to provide unequivocal results. A systematic review and meta-analysis done by Idro et al of 8 case control studies that examined the association between iron deficiency anaemia and febrile seizures described 310/1018 (30.5%) cases and 230/1049 (1.9%) controls, showed that iron deficiency anaemia was associated with a significantly increased risk of seizures, weighted or 1.79 (95% CI 1.03-3.09). In present study, patients with febrile seizures were more likely to have IDA as compared to control

group (30.6% versus 8.3%) (p-value of 0.017). Patients with febrile convulsion had 2.4 more chances of having iron deficiency anaemia. (Crude's odd ratio is 2.4 with 95% CI 39.5-40.52).

An analysis of the individual studies and the combined result of case control studies to date suggest that iron deficiency can be associated with an increased risk of febrile seizures in children. However, interventional studies may be designed to verify this hypothesis.

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Institutional Ethics Committee

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