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Original Research Article

Iron deficiency and febrile seizures: a retrospective analysis

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ABSTRACT

Background: Febrile seizures (FS) are the commonest cause of seizures in children, with 2-5% of neurologically healthy children experiencing at least 1 episode. Iron deficiency is reported to be one of the most prevalent nutritional problems in the world today, especially in developing countries, with an estimated 46%-66% people affected. Our study is an attempt to clarify the relation between iron deficiency and first febrile seizure.
Methods: The present study was a case control study carried from December 2016 till June 2018 in a tertiary care hospital at Aurangabad, Maharashtra, India. The study was done after obtaining approval from Institutional ethical Committee.
Results: 77 cases and equal number of controls were included. Males were most commonly affected (>50%) as compared to females in both groups. Highest number of cases and controls were in the age group 0.5 to 1 year group, followed by 1-2 and 2-3 years group. Upper respiratory tract infection was most common etiological factor. Anemia (Hb<11 gm/dl) was seen in in 84% of the cases and 65% of the controls. Serum iron and total iron binding capacity (TIBC) was reduced in cases as compared to controls and this difference was highly statistically significant.
Conclusions: Iron deficiency is a modifiable risk factor for first episode of febrile seizures in Indian children of age group 6 months to 5 years its early detection and timely correction may be an important determinant for prevention of febrile seizure in children.

Keywords: Anemia, Febrile seizures, Ferritin haemoglobin, Iron deficiency, TIBC

INTRODUCTION

Febrile seizures (FS) are the commonest cause of seizures in children, with 2-5% of neurologically healthy children experiencing at least 1 episode.[1] Febrile seizure episodes are agonizing to the parents and child and can cause psychological trauma to both.[2] Seizure is one of the most common neurological symptom in children accounting for 1% of visits to the emergency department. Iron deficiency is reported to be one of the most prevalent nutritional problems in the world today, especially in developing countries, with an estimated 46%-66% people affected.[4] There is considerable evidence that iron is important for neurological functioning, with a role in neurotransmitter metabolism, myelin formation and brain energy metabolism. In the rodent model, iron deficiency affects regional monoamine metabolism, in part through iron-dependent enzymes such as tryptophan hydroxylase (for serotonin) and tyrosine hydroxylase (for dopamine and norepinephrine). Iron deficiency decreased the expression of cytochrome C oxidase, a marker of neuronal metabolic activity. Iron deficiency anemia patients have shown an altered rapid eye movement density in active sleep, poorer recognition memory with event-related potentials, and altered electroencephalographic frontal asymmetry.[5-7] Recent

studies of auditory evoked potential changes in iron deficient infants point to possible irreversibly slowed central processing.

A basic principle of fetal/neonatal iron biology is that iron is prioritized to red cells at the expense of other tissues, including brain. When iron supply does not meet iron demand, brain may be at risk even if the infant is not anemic. Evidence that iron might be important for neurological functioning has generated considerable optimism that this material might also play a role in initiation of febrile convulsions. Previous studies examining the relationship between iron deficiency anemia and febrile convulsions like Sherjil A et al, concluded that febrile patients with seizures are 1.93 times more likely to have iron deficiency anemia compared to those without seizures.[8] Similarly, Abdurrahman K et al, suggested that iron deficiency anemia may be a risk factor for febrile seizures.[9] In contrast, Kobrinsky N et al, reported that iron deficiency raises the threshold for seizures and Bidabadi E et al, have found iron deficiency anemia to be less frequent among the cases with febrile convulsion.[10,11]

In past, numerous studies have been done on iron deficiency anemia and febrile seizure, but, with conflicting results. Present study is an attempt to clarify the relation between iron deficiency and first febrile seizure.

METHODS

A case control study carried from December 2016 till June 2018 in a tertiary care hospital at Aurangabad, Maharashtra, India. The study was done after obtaining approval from Institutional ethical Committee. Informed and written consents were taken from subjects' parents before enrolling into study. Seventy seven consecutive cases were selected for the study and concurrent controls were selected from the same setting after satisfying inclusion criteria. Cases and controls were selected in 1:1 ratio. No matching was done. General flow of the study is shown in Figure 1.

Iron deficiency anemia was diagnosed by hematologic investigations of hemoglobin value <11 g%, RDW > 15% (WHO).[12] Serum iron concentration <40 mcg/dl in younger than 1 year and<50mcg/dl in older than 1 year, serum ferritin value <12 ng/mL and TIBC >430 mcg/dl.[13]

The statistical analysis was done using SPSS (Statistical Package for Social Sciences) Version 15.0 statistical Analysis Software. The values were represented in Number (%) and Mean±SD.

To test the significance of two means the chi square test was used. Logistic regression makes no assumption about the distribution of the independent variables. They do not have to be normally distributed, linearly related or of equal variance within each group.

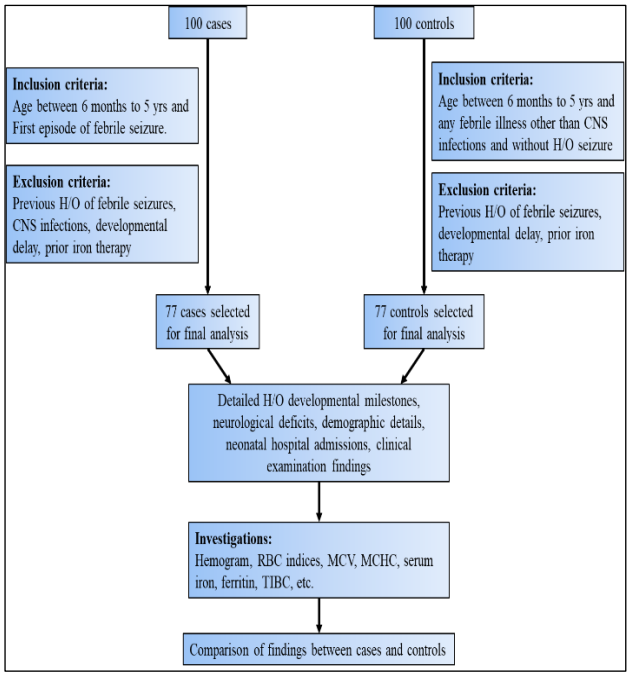

Figure 1: Flow of methodology adopted for the present study.

RESULTS

The patients were further subdivided in 5 groups (0.5-1yr) (>1yr-2yr) (>2yr-3yr) (>3yr-4yr) (>4yr-5yr). A total of 22(28.57%) patients in case group and 26(33.77%) in control group were aged below 1 year also 57.14% of patients in cases were less than 2 yrs which implies younger the age group higher the chances of febrile convulsion. There was no statistically significant difference between mean age of cases and controls. (Figure 2)

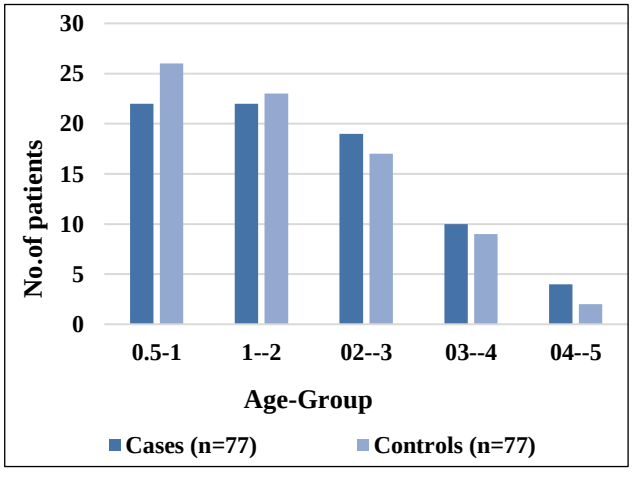

Figure 2: Age wise distribution of cases and controls.

A total of 54 patients in case group and 51 patients in control group were males whereas 23 patients in case group and 26 patients in control group were females with no statistically significant difference (p=0.458) though

the absolute number of males in comparison to females are more in cases (Figure 3). The most common cause of fever leading to convulsion was URTI. Other causes included acute gastroenteritis, otitis media, urinary tract infection and lower respiratory tract infection (Figure 4).

Where, URTI-upper respiratory tract infection, AGE-acute gastroenteritis, OM-otitis media, UTI-urinary tract infection, LRTI-lower respiratory tract infection.

Table 1 shows that 84.42% (n=65) children had Hb <11 gm/dl from the case group as compared to 64.94% (n=50) in control group with significant p value (p=0.005). Proportion of patients with anemia was significantly higher in cases (84.42%) as compared to that of controls (64.94%) (p=0.005). It was further observed that degree of anemia was significantly lower in cases as compared to controls(p=0.000). From this observation we conclude that the risk of first episode of febrile seizure increases with the degree of anemia.

Mean hemoglobin (p=0.0028), and serum iron (p=0.000) levels in cases were significantly lower as compared to that in controls. Also, MCV (fl) (p=0.991), MCH (pg)(p=0.468) and serum ferritin(ng/ml) (p=0.141) were found to be on the lower side in cases as compared to controls but without any statistically significant difference. Mean RDW% (p=0.011) and TIBC (µg/dl) (p=0.000) levels in cases were significantly higher as compared to that in controls.

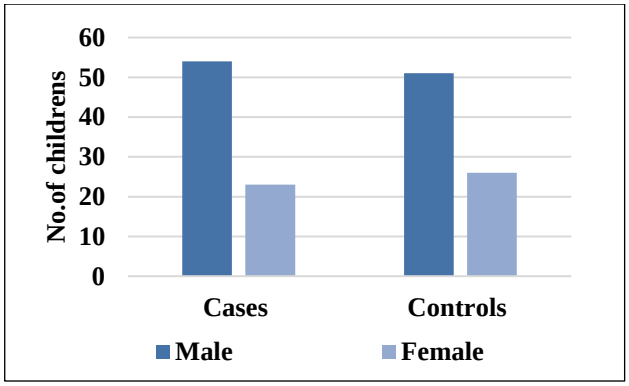

Figure 3: Sex wise distribution in cases and controls.

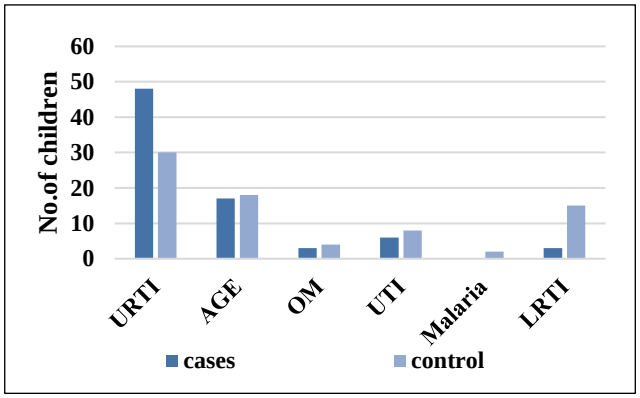

Figure 4: Etiology of fever in cases and controls.

Table 1: Distribution of cases and controls according to hemoglobin level (Hb).

	Cases (n= 77)		Controls (n=77)	
	No.	%	No.	%
No Anemia (≥11 g/dl)	12	15.58%	27	35.06%
Anemia (< 11 g/dl)	65	84.42%	50	64.94%
	Chi-square value = 7.73		p-value = 0.005 S	
Mild Anemia (10-10.9 g/dl)	21	32.31%	29	58%
Moderate Anemia (7.0-9.9 g/dl)	42	64.61%	14	28%
Severe Anemia (< 7 g/dl)	02	3.08%	07	14%
	Chi-square value = 16.4		p-value = 0.0000 S	

Table 2: Comparison of hematological indices of cases and controls.

SN	Parameter	Cases		Controls		p-value	
		Mean	SD	Mean	SD	z-value	
1.	Hb (g/dl)	9.42	1.41	10.19	1.77	2.98	P=0.0028 Highly Significant
2.	MCV (fl)	71.52	10.65	71.57	10.52	0.0117	P=0.991 Not Significant
3.	MCH (pg)	22.46	4.10	22.90	3.39	0.725	P=0.468 Not Significant
4.	RDW (%)	18.31	6.21	16.27	3.73	2.55	P=0.011 Significant
5.	IRON (µg/dl)	62.78	29.37	83.14	24.88	4.64	P=0.000 Very highly Significant
6.	Serum Ferritin(ng/ml)	41.80	34.77	48.40	24.13	1.47	P=0.141 Not Significant
7.	TIBC(µg/dl)	290.66	62.57	243.10	51.42	5.15	P=0.0000 Very highly Significant

Table 3: Hematological indices of cases with respect to Gender.

Hematological indices	Cases		t-value	p-value
	Male (Mean±SD)	Female (Mean±SD)		
Hemoglobin(g/dl)	9.48±1.45	9.30±1.35	0.507	P=0.614
MCV(fl)	71.70±10.55	71.10±11.15	0.224	P=0.823
MCH(pg)	22.68±4.24	21.96±3.79	0.704	P=0.484
RDW(%)	17.56±6.34	20.09±5.67	1.65	P=0.103
Serum Iron(µg/dl)	61.21±28.85	66.48±30.90	0.717	P=0.476
Serum Ferittin(ng/ml)	41.00±33.89	43.71 ±37.47	0.311	P=0.757
TIBC(µg/dl)	295.18±64.25	280.04±58.43	0.971	P=0.334

The difference in levels of Hemoglobin, MCV, MCH, RDW, Serum iron, Serum ferritin and TIBC amongst cases in relation to gender were statistically insignificant.

On a multivariate predictive model with febrile seizures as a dependent variable on Hb<11, MCV<75, MCH<24, RDW>15%, SFe<50, SF<12 and TIBC >430, only Serum Iron was found to be significantly associated with the outcome. After serum iron, low serum ferritin levels were seen in cases but were statistically insignificant. This could be explained as serum ferritin is an acute phase reactant and therefore its value rises in any febrile illness. (Table 4)

Table 4: Multivariate analysis.

Model	B	Std. Error	Sig.
Constant	0.330	0.081	0.000
HB < 11	0.160	0.105	0.131
MCV<75	0.056	0.087	0.520
MCH < 24	-0.099	0.083	0.234
RDW>15	-0.027	0.085	0.752
Serum Iron < 50	0.265	0.102	0.011
Serum Ferritin <12	0.323	0.179	0.073
TIBC > 430	0.461	0.110	0.215

DISCUSSION

In the present study, the majority of cases (57.14%) of febrile seizure occurred in the age group of <24months age group only. This is in accordance with the study by various other researchers.[14-16] Febrile Seizures are age dependent and age group of 12-24 months is regarded critical for developing febrile seizure.[2] Although the mechanism of this increased susceptibility is unclear, animal models suggest that there is enhanced neuronal excitability during the normal brain maturation.

Reviewing the literature, febrile seizures are more commonly seen in males. In the present study majority of subjects in both the groups i.e. case and control group were males. Gender analysis reveals that 70.13% were males with 29.87% females in case group. Present study did not find male gender as a risk factor for febrile seizure. Some studies reported 58% and 53% male children respectively in their studies, but both these studies had cases and controls matched for gender.[14,15] Though we did not match, our cases and controls were comparable with respect to gender.

The causes of febrile illnesses leading to seizures in our study were upper respiratory tract infection (62.34%) was the most common febrile illness precipitating seizure. This observation was similar to that in other studies.[15- 18]

Anemia was found more in our cases as compared to controls (64.94%), the difference being statistically significant (p=0.005). Derakhshanfar H et al, found a mean Hb of 10.97+0.73 in the cases less than that in the controls with a 'p' value < 0.014.[19] Modaresi M et al, also reported significantly low Hb in cases as compared to controls.[20] Others reported a lower hemoglobin in cases but in both studies results were not statistically significant.[14,15]

In present study attempt was also made to co-relate the degree of anemia with febrile seizure and it was found that children suffering from moderate to severe anemia have higher chances of febrile seizure and this result is statistically significant (p=0.0000) as compared to control group. Severe anemia was more common in controls but comparing the increase in severity of anemia amongst cases and controls revealed a significant association in the cases. None of the other authors have correlated the degree of anemia with the incidence of febrile seizure.

The mean MCV in our study was 71.52+10.65 fl with a p value of 0.991. Derakhshanfar H et al, found a mean MCV of 76.5+6.45 fl which was significantly lower as compared to controls p value of<0.003. The mean MCH in our study was 22.46+4.10 with a p value of 0.468. Same study found a mean MCH of 2.17+1.48 which was significantly lower as compared to controls, p value of<0.013.[19]

The role of iron deficiency anemia in febrile seizure is well substantiated by different workers. Pisacane A et al, were one of the first researchers to look into the association of iron deficiency anemia and febrile

seizures.[21] They compared the levels of serum iron among controls and patients with febrile seizures and they reported that iron deficiency anemia is significantly more frequent among the cases than among the controls. In present study the mean serum iron levels in cases was62.78+29.37 µg/dl and 83.14+24.88µg/dl in controls with a p value of 0.000. Thus, serum iron levels in our study significantly correlated positively with first febrile seizure.

Daoud A et al, reported that the mean level of ferritin in cases with first febrile seizure is significantly lower than that in a control group.[21] The cut off that Daoud A et al, used to define low serum ferritin levels was less than 30 µg /L. This level is higher than the cut off of 12 µg/L used by most standard bodies to define low serum ferritin indicative of iron deficiency. This level was chosen by them as serum ferittin is an acute phase reactant which tends to rise in febrile illness.

The mean TIBC in our cases was 296.66+62.57 µg/dl which was higher than that in controls with a p value of 0.000. The TIBC though, was not higher than cut off used to describe iron deficiency >430 µg/dl. The mean TIBC in the study done by Derakhshanfar A et al, was also less than this cut off (333.72+37.31) with a p value of <0.016 similar to our study.[19]

As we saw in the multivariate predictive model with febrile seizures as a dependent variable on Hb<11, MCV<75, MCH<24, RDW>15%, SFe<50, SF<12 and TIBC >430, only Serum Iron was found to be significantly associated with the outcome. This indicates amongst the cases serum iron is the most sensitive indicator of iron deficiency. After Serum Iron, Serum ferritin proved to be associated with the outcome but is statistically insignificant.

Present study has some limitations. It was a tertiary care hospital-based study, thus the prevalence of exposure and outcome variables may be different from a community setting. Also, in our study and all studies on this subject in literature, iron deficiency anemia has not been defined. A study using a precise definition of iron deficiency anemia and then comparing the incidence of first febrile seizure would further help to know the association of IDA and first febrile seizure.

The strength of our study includes standardized criteria for diagnosing febrile seizures, and establishing iron deficiency status, elimination of incidence and prevalence bias by concurrent enrollment of cases and controls with no recall bias to iron supplementation.

CONCLUSION

Iron deficiency is a modifiable risk factor for first episode of febrile seizures in Indian children of age group 6 months to 5 years its early detection and timely correction may be an important determinant for prevention of febrile seizure in children.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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