IRON DEFICIENCY ANAEMIA- A RISK FACTOR FOR FEBRILE SEIZURE- A CASE CONTROL STUDY

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ABSTRACT

BACKGROUND

The association between Iron Deficiency Anaemia (IDA) and Febrile Seizures (FS) is still obscure. The aim of this study is to assess any possible association between FS and IDA and to identify any contributory risk factors which if modified can prevent the occurrence of FS.

MATERIALS AND METHODS

A case control study was carried out at the Department of Paediatric Medicine, Vivekananda Institute of Medical Sciences (VIMS), Kolkata, India from 2013-2015 on children aged 6 months to 5 years with simple FS. Sample size was 100 cases and 100 age- and sex-matched controls. Patients were selected randomly with the help of computer generated random numbers. Children with atypical/ afebrile seizures, central nervous system infection, neurodevelopmental or haematological problems and children on iron supplementation were excluded. Consent of parents was taken, and ethical council of VIMS approved the study. Statistical analysis was done with the help of Epi Info (TM) 3.5.3. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age (Mean±S.D.) of the patients was 2.18±1.22 years with a range of 0.56-4.83 years. The mean level of haemoglobin (Mean±S.D.) was 10.79±1.38 g/dL with a range of 6.1-14 g/dL. The mean level of total iron binding capacity (Mean±S.D.) was 380.48±64.43 µg/dL with a range of 266-489 µg/dL. The mean level of red blood cell distribution width (Mean±S.D.) was 14.74±1.11% with a range of 13.0-18.4%. The mean level of mean corpuscular volume (Mean±S.D.) was 73±6.98 fL with a range of 41.0-104.7. The mean level of ferritin (Mean±S.D.) was 48.33±25.41 ng/mL with a range of 13.0-190 ng/mL.

CONCLUSION

In this study, the incidence of IDA in the FC group was higher than in the control group.

KEY WORDS

Iron Deficiency, Febrile Convulsion.

HOW TO CITE THIS ARTICLE: Guha S, Bandopadhya R. Iron deficiency anaemia- a risk factor for febrile seizure- a case control study. J. Evolution Med. Dent. Sci. 2018;7(44):4731-4735, DOI: 10.14260/jemds/2018/1056

BACKGROUND

Although, FS is a benign condition and rarely leads to brain damage it causes emotional, physical and mental changes which are stressful both for the child and the caregivers.(1) The precise cause is still not known. It could be an interplay of environmental and genetic factors.

The relationship between IDA and FS is still not determined. Iron deficiency reduces the metabolism of some neurotransmitters such as monoamine and aldehyde oxidase(2,3) and iron also plays a key role in the transport of oxygen to vital tissues such as brain.(4) Several lines of evidence led to the hypothesis that iron deficiency may have a role in the first onset of convulsion. The results so far have been conflicting.

Considering this, the present study was carried out to compare the IDA rates in FS children with those in febrile children without seizure.

'Financial or Other Competing Interest': None.
Submission 05-09-2018, Peer Review 10-10-2018,
Acceptance 16-10-2018, Published 29-10-2018.
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DOI: 10.14260/jemds/2018/1056

Aims and Objectives

1. To assess and evaluate any possible association between febrile convulsion and iron deficiency anaemia.
2. To identify any contributable risk factors, which if modified can prevent the occurrence of the seizure.

MATERIALS AND METHODS

Type of study- case control study.

Place of Study

Department of Paediatric Medicine, Vivekananda Institute of Medical Studies (VIMS).

Duration of Study

2 years, 2013-2015.

Sample Size

100 cases and 100 age and sex matched controls. Sample size is taken as per our convenience.

Study Population

Children aged 6 months to 5 years with first/ recurrent episode of simple febrile seizure.

Inclusion Criteria

1. Cases- children aged 6 months-5 years, presenting with simple febrile seizure.

2. Controls- age and sex matched who present with fever <3 days, but without seizures.

Exclusion Criteria

1. Atypical/ afebrile seizure episodes.
2. Central nervous system infection.
3. Chronic neurodevelopmental problems.
4. Other haematological problems- haemolytic anaemia, malignancy, bleeding/ coagulation disorders.
5. Those on iron supplementation.

Consent of parents was taken and ethical council VIMS approved the study. 5 mL blood was drawn from each child and complete blood count with iron profile (Serum Iron, Ferritin, TIBC or Total Iron Binding Capacity) was studied.

Sampling Techniques

Patients were selected randomly with the help of computer generated random numbers.

Statistical Analysis

Statistical Analysis was performed with the help of Epi Info (TM) 3.5.3 of the Centres for Disease Control and Prevention (CDC).

Using this software, basic cross-tabulation and frequency distributions were prepared. Odds Ratio (OR) with 95% Confidence Interval (CI) was calculated to measure the different risk factor.

Descriptive, distribution and Chi-square tests were performed for the qualitative variables. Multiple Logistic Regression was also performed to calculate odds ratio after adjusting confounding factors. Significance level was set at 0.05 and confidence intervals were at 95 percent level. p </=0.05 was considered statistically significant.

RESULTS

Age in Years	Number	%
< 1	41	20.5
1-2	62	31
2.1-3.0	47	23.5
3.1-4.0	32	16
4.1-5.0	18	9
Total	**200**	**100**
Age Distribution		

The mean age (Mean±S.D.) of the patients was 2.18 +/-1.22 years with range 0.56-4.83 years and the median age was 2.0 years.

Level of Hb	Number	%
< 11	94	47
> 11	106	53
Total	**200**	**100**
Distribution of the Level of Haemoglobin		

47% of subjects were having level of Hb < 11 gm/dL and the rest 53% were having Hb > 11 gm/dL.

The mean level of Hb (Mean±S.D.) of the subjects was 10.79±1.38 gm/dL with range 6.1-14 gm/dL and the median was 11 gm/dL.

Level of TIBC-µg/dL	Number	%
>400	87	43.5
≤400	113	56.5
Total	**200**	**100**
Distribution of the Level of TIBC		

43.5% of the subjects were having level of TIBC > 400 µg/dL and the rest 56.5% were having level of TIBC ≤ 400 µg/dL.

The mean level of TIBC (Mean±S.D.) of the subjects was 380.48±64.43 µg/dL with range 266-489 µg/dL and the median was 378 µg/dL.

Level of RDW (%)	Number	%
>14	94	47
≤14	106	53
Total	**200**	**100**
Distribution of the Level of RDW		

Normal reference range of RDW= 12.8±1.2

47% of the subjects were having level of RDW > 14% and the rest 53% were having level of RDW ≤ 14%.

The mean level of RDW (Mean±S.D.) of the subjects was 14.74±1.11% with range 13.0-18.4% and the median 14.

Level of MCV	Number	%
<72 or 76	98	49
≥72 or 76	102	51
Total	**200**	**100**
Distribution of Level of MCV		

Normal range of MCV for patients with age between 1-23 months is ≥ 72 fL, for 24-48 months it is ≥ 76 fL.

49% of the subjects were having MCV < 72/76 fL and the rest 53% had MCV ≥ 72/76 fL.

The mean level of MCV (Mean±S.D.) of the subjects was 73±6.98 fL with range 41.0-104.7 and the median was 74.55 fL.

Level of Ferritin (ng/dL)	Number	%
<30	73	36.5
≥30	127	63.5
Total	**200**	**100**
Distribution of Level of Ferritin		

Normal reference range of ferritin is < 30 mg/dL in presence of infection and < 12 without infection.

The mean level of ferritin (Mean±S.D.) of the subjects was 48.33±25.41 ng/mL with range 13.0-190 ng/mL and the median was 45.0 ng/mL.

36.5% of the subjects were having level of ferritin < 30 ng/mL and the rest 63.5% were having ferritin > 30 ng/mL.

The mean level of ferritin (Mean±S.D.) of the subjects was 48.33±25.41 ng/mL with range 13.0-190.0 ng/mL and the median was 45.0 ng/mL.

Of the children who had simple febrile convulsion 25.5% had a positive family history of febrile seizures, while the rest 74.5% did not give any family history of such seizures.

Of the 100 cases 48 came from a rural background, while 52 resided in urban areas.

Analysis of the Results

Age Group	Case	Control	Total
>2	41	50	91
Row%	45.1	54.9	100
Col%	41	50	45.5
<2	59	50	109
Row%	54.1	45.9	100
Col%	59	50	54.5
Total	100	100	200
Row%	50	50	100
Col%	100	100	100
Mean±S.D.	2.11±1.17	2.2 5±1.64	
A) Age and Simple Febrile Seizure			

x^2= 1.63; p= 0.20; NS- Not significant.

Gender	Case (n= 100)	Control (n= 100)	Total
Male	58	59	117
Row%	49.6	50.4	100
Col%	58	59	58.5
Female	42	41	83
Row%	50.6	49.4	100
Col%	42	41	41.5
Total	100	100	200
Row%	50	50	100
Col%	100	100	100
B) Sex and Simple Febrile Seizure			

Hb (gm/dL)	Case (n= 100)	Control (n= 100)	Total
< 11	54	40	94
Row%	57.4	42.6	100
Col%	54	40	47
> 11	46	60	106
Row%	43.4	56.6	100
Col%	46	60	53
Total	100	100	200
Row%	50	50	100
Col%	100	100	100
Mean±S.D.	10.65±1.28	10.93±1.46	
Median	10.80	11.20	
Range	7.8-13.2	6.10-14.0	
C) Level of Haemoglobin and Simple Febrile Seizure			

TIBC (Microgram/dL)	Case (n=100)	Control (n=100)	Total
> 400	52	35	87
Row%	59.8	40.2	100
Col%	52	35	43.5
≤ 400	48	65	113
Row%	42.5	57.5	100
Col%	48	65	56.5
Total	100	100	200
Row%	50	50	100
Col%	100	100	100
Mean±S.D.	391.24±67.78	369.72±59.31	
Median	406.0	345	
Range	267-489	266-481	
D) Level of TIBC and Simple Febrile Seizure			

x^2= 5.87; p= 0.01; S= significant.

RDW (%)	Case (n=100)	Control (n=100)	Total
> 14	72	40	112
Row%	64.3	35.7	100
Col%	72	40	56
≤ 14	28	60	88
Row%	31.8	68.2	100
Col%	28	60	44
Total	100	100	200
Row%	50	50	100
Col%	100	100	100
Mean±S.D.	14.88±1.13	14.16±1.01	
Median	14.80	14.3	
Range	13.0-17.5	12.2-17.9	
E) Level of RDW and Simple Febrile Seizure			

x^2= 20.77; p= .000006; NS= Not significant.

MCV (fL)	Case (n=100)	Control (n=100)	Total
< 72 or 76	53	45	98
Row%	54.1	45.9	100
Col%	53	45	49
≥ 72 or 76	47	55	102
Row%	46.1	53.9	100
Col%	47	55	51
Total	100	100	200
Row%	50	50	100
Col%	100	100	100
Mean±S.D.	73.89±5.01	73.87±8.53	
Median	73.15	75.45	
Range	65.7-84.0	41.0-104.7	
F) Level of MCV and Simple Febrile Seizure			

x^2= 1.28; p= 0.25; NS- Not significant.

Ferritin (ng/mL)	Case (n=100)	Control (n=100)	Total
< 30	44	29	73
Row%	60.3	39.7	100
Col%	44	29	36.5
≥ 30	56	71	127
Row%	44.1	55.9	100
Col%	56	71	63.5
Total	100	100	200
Row%	50	50	100
Col%	100	100	100
Mean±S.D.	46.82±30.05	49.85±19.76	
Median	32.5	51.0	
Range	13-190	17-91	
G) Level of Ferritin and Simple Febrile Seizure			

x^2= 4.85; p= 0.02; S= Significant.

Factors	Odds Ratio	95%	C.I.	Coefficient	S.E.	Z-Statistic	P-value
Ferritin > 30 ng/mL	1.7005	0.6565	4.4052	0.5309	0.4856	1.0933	0.2743
Hb > 11 gm/dL	0.5580	0.1461	2.1309	-0.5833	0.6836	-0.8533	0.3935
MCV < 72/ 76 fL	0.6375	0.2948	1.3785	-0.4502	0.3935	-1.144	0.2525
RDW > 14%	4.0880	2.0541	8.1361	1.4081	0.3511	4.0099	0.0001
TIBC > 400 microg/dL	1.6906	0.5287	5.4062	0.5251	0.5931	0.8853	0.3760
Constant				-0.7211	0.2468	-2.9217	0.0035
Multiple Logistic Regression Analysis							

After adjusting all the factors, multiple logistic regression analysis showed that the risk of simple febrile seizure was 4.08 times more for RDW > 14% {OR- 4.08 (2.05, 8.13); p= 0.0001} and the risk was significant.

DISCUSSION

This study set out to examine the hypothesis that iron deficiency is associated with febrile convulsions and also increases risk of acute febrile seizures in children. However, previous case-controlled studies that have examined the relationship between febrile seizures or acute seizures and iron deficiency anaemia till date suggested that iron deficiency may or may not be associated with febrile seizures and certain studies also demonstrated that there was a decreased risk of febrile seizures in children.

The Relationship between Iron Deficiency and Febrile Seizures has been Controversial. Most of the Early and Conflicting Studies-

1. Examined the relationship between iron deficiency and febrile seizures.
2. Had small sample size.
3. Used different markers and definitions for iron deficiency.[5]

In this study to prove iron deficiency apart from Hb other parameters like TIBC, Ferritin, MCV and RDW have been taken into consideration.

The mean age of the patients was 2.18±1.22 years with range 0.56-4.83 years and the median age was 2.0 years.

The proportion of the patients with age between 1-2 years (31%) was higher, but it was not significant.

Test of proportion showed that proportion of males (58.5%) was significantly higher than that of females (41.5%). The ratio of gender was found as male: female= 1.4: 1.

Chi-square test showed that there was no significant association between age and gender of the subjects. The mean age of the males was 2.26 years with range 0.57-4.83 years and the median age was 2.08 years. The mean age of the females was 2.06 years with range 0.58-4.83 years and the median age was 1.75 years. There was no significant differences between the age of males and females. Thus, subjects of both sexes were distributed equally over age.

Proportion of rural based patients (53%) was higher than that of urban based patients, but it was not significant.

47% of the subjects were having level of haemoglobin < 11 gm/dL and the rest 53% were having haemoglobin > 11 gm/dL. The mean level of haemoglobin of the subjects was 10 gm/dL and the range was 6.1-14 gm/dL and the median was 11 gm/dL.

43% of the subjects were having level of TIBC > 400 micrograms/dL and the rest 56.5% were having TIBC < 400 micrograms/dL. The mean level of TIBC of the subjects was 380 micrograms/dL with range 266-489 micrograms/dL and the median was 378 micrograms/dL.

47% of the subjects were having level of RDW > 14.5% and the rest 53% were having RDW < 14.5%. The mean level of RDW of the subjects was 14.74 with range 13.0-18.4% and the median was 14.4%.

49% of the subjects were having level of MCV < 72 or 76 fL and rest 53% were having level of MCV > 72 or 76 fL. The mean level of MCV of the subjects was 73.88 fL with range 41.0-104.7 fL and the median was 74.55 fL.

36.5% of the subjects were having level of ferritin < 30ng/mL and the rest 63.5% were having ferritin > 30 ng/mL. The mean level of ferritin of the subjects was 48.33 ng/mL with range 13.0-190.0 ng/mL.

44% of the subjects were having respiratory illness and the rest 56% did not have any respiratory tract infections.

29.5% were having gastrointestinal infections and the rest 70.5% did not have evidence of any such infection.

25.5% of the subjects were having family history of simple febrile seizures and in the rest 74.5% of subjects no such family history could be elicited.

Chi-square test showed that there was no significant association between age and simple febrile seizure. No risk of simple febrile seizure was found for patients with > 2.18 years as compared with patients with age < 2.18 years. This is supported by a study conducted by Heydarian et al.

Chi-square test showed that there was no significant association between gender and simple febrile seizure. No risk of simple febrile seizure was found among males as compared with females. This observation is in contrast to a study conducted by Verity CM, Butler NR et al.

Chi-square test showed that there was no significant association between area of residence and simple febrile seizures. No risk of simple febrile seizures was found among patients from rural areas as compared with patients from urban areas.

Chi-square test showed that there was significant association between level of haemoglobin and simple febrile seizures.

The level of haemoglobin of the cases was significantly lower than controls. The risk of simple febrile was 1.76 times more among the patients with level of haemoglobin < 11 gm/dL as compared with the patients with level of haemoglobin > 11 gm/dL and the risk was significant; although, a study conducted by Kulkarni et al did not find any significant p-value. On the other hand, a study conducted by Razieh F et al noticed low haemoglobin levels in cases of first attack of febrile convulsion.

Chi-square test showed that there was significant association between level of TIBC and simple febrile seizure. The risk of simple febrile seizure was 2.01 times more among patients with TIBC > 400 micrograms/dL as compared with patients with TIBC < 400 micrograms/dL and this risk was significant.

Chi-square test showed that there was significant association between level of RDW and simple febrile seizure. The risk of simple febrile convulsion was 3.85 times more among patients with RDW > 14% as compared to patients with RDW < 14% and this risk was significant. This is contrary to a study conducted by Hartfield et al.

Chi-square test showed that there was no significant association between level of MCV and simple febrile seizure. Such a similar observation was also made by Kulkarni et al.

Chi-square test showed that there was significant association between level of ferritin and simple febrile convulsion. The risk of simple febrile seizure was 1.92 times more among patients with ferritin < 30 ng/mL as compared to patients with levels of ferritin > 30 ng/mL and the risk was significant. Similar findings were also noted by Vaswani RK et al.

After adjusting all the factors, multiple logistic regression analysis showed that simple febrile seizure was 4.08 times more for RDW > 14% and the risk was significant.

In this study, incidence of iron deficiency anaemia in the febrile seizure cohort was more than in the control group. Similar association has been reported by Vaswani et al,[6]

Pisacane[7] et al and Momen[8] et al. A Kenya case control study as well as meta-analysis of 8 case-control studies have examined the relationship between simple febrile seizures and iron deficiency states and concluded that iron deficiency may be a risk factor for simple febrile seizures.

On the contrary conflicting observations were made by Hartfield[9] et al and Kobrinsky[10] et al. The major causes which lead to such conflicting observations were differences in age and number of samples and difference in diagnostic criteria of iron deficiency between their and our study.

According to our study, the incidence of iron deficiency in children suffering from fever and convulsion was observed to be more than the group with fever, but without convulsions.

So to conclude it may be stated that iron deficiency may be a contributory risk factor for simple febrile seizures. Furthermore, it is advisable to administer iron supplements to children who have well established risk factors for simple febrile seizures including positive family history.

In the present study, all samples of the case group suffered from febrile convulsion for the first time. In other studies, subjects usually had a prior history of febrile seizure. According to the findings of the present study, the incidence of iron deficiency in children suffering from fever and convulsion was observed to be more than that of the fever without convulsion group.

In conclusion, these findings suggest that low serum iron levels and the presence of anaemia can serve as cofounding risk factors for febrile seizures.

Accordingly, children with febrile seizures are suggested to be monitored for diagnosis and treatment of iron deficiency.

CONCLUSION

The association between iron deficiency and febrile seizures has been studied several times in the past, but with conflicting results.

The above study suggests that IDA should be considered as a risk factor for the first febrile seizure. Fever can worsen the negative effect of anaemia or iron deficiency on the brain resulting in seizure in consequence. Accordingly, children with febrile seizures are suggested to be monitored for diagnosis and treatment of iron deficiency anaemia. Furthermore, it is advisable to prescribe the iron supplements sooner and more carefully to children who have important and well known risk factors for febrile convulsion.

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