Original Research Article

Iron deficiency anemia as a risk factor for simple febrile seizures in pediatric patients

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ABSTRACT

Background: Febrile seizure (FS) is the most common cause of seizure in children, occurring between 6-60 months. It coincides with peak age of incidence for Iron deficiency anemia (IDA). Iron is required for optimal growth and development and its deficiency is associated with numerous problems including persistent cognitive and motor delays. The objective was to study the role of IDA as a risk factor for simple febrile seizure and its recurrence
Methods: A case control study was conducted among 90 febrile children - 45 cases with simple febrile seizure and 45 cases with febrile illness, between the age group of six months to five years of age at Sri Manakula Vinayagar Medical College and Hospital, Pondicherry, between September 2013 and June 2015. The hematological parameters like Hemoglobin, Serum ferritin and RDW were compared between the two groups with respect to fever and different temperature intervals, recurrence of FS.
Results: Hb and Serum Ferritin levels were found to be significantly associated with simple febrile seizure, with p value of <0.002 and 0.001 respectively. Similar association was found at different temperature intervals. However, there was no association of hematological parameters with FS recurrence.
Conclusions: IDA is a significant risk factor for FS in children while same may not have any effect on the recurrence of FS.

Keywords: Iron deficiency anemia, Febrile seizures, S. Ferritin

INTRODUCTION

The International League Against Epilepsy has defined Febrile Seizure (FS) as a seizure occurring in childhood after one month of age, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures.[1]

Febrile seizures are the most common type of seizure and occur in 3-4% of all children below 5 years of age.[2] Majority of FS are Simple 70-75% whereas 9-35 % FS are complex.[3] Frequency of simple febrile seizure in

India is 10-17%, which is higher than the developed countries like Japan (9-10%), Western Europe and USA (2-7%) and in Guam (14%).[4-10]

Febrile seizures are considered benign, but there is recent evidence that a small subset of children may have recurrent febrile seizure or develop epilepsy.[11] The risk of later epilepsy after a simple febrile seizure is 2-7.5% and the risk of developing epilepsy after complex febrile seizure is about 10-20%.[12] Recurrence of FS varies between 25-100% based on the number of risk factors involved.[13] Both recurrent FS and Epilepsy are apparent life threatening events and carry a burden on the child's

growth and development and impose extra health expenditure on the family.

Iron deficiency anaemia is one of the most prevalent micronutrient deficiencies in young children in India and other parts of the world, and it is strongly associated with persistent cognitive and motor delays even after the anaemia and iron deficit have been corrected[14]. Iron deficiency has been postulated to affect the brain functioning by multiple mechanisms like lack of neuronal iron, hypoxia due to anaemia and by changes in neurotransmitter receptors and consequent signal transduction process.[15,16] Many studies have been done to find association between IDA and febrile seizure with conflicting results.[17-25] Frequent recurrence could expose the brain to hypoxic damage possibly increasing the chances of future epilepsy. But effect of IDA on seizure recurrence is understudied. Hence, we conducted the present study.

METHODS

This prospective case control study was conducted at Sri Manakula Vinayagar Medical College and Hospital, Pondicherry, between September 2013 and June 2015. The sample size was calculated as 90 (45 cases and 45 control samples) based on consecutive cases and concurrent controls selected using 95% confidence limit 80% power and 5% of alpha error and odds ratio for iron deficiency anaemia is 5.34.[17]

Cases were children of age group 6 months to 5 years presenting with simple febrile seizures. Controls were children of same age group presenting with short febrile illness but without any seizures. A total of 90 cases with 45 cases in each group were finally included in the study.

Children presenting with simple febrile seizure to Pediatrics out-patient department and Casualty/Emergency, were included in the study after obtaining consent from the parents and assent from the children. Iron deficiency anemia was diagnosed as per WHO criteria hemoglobin value <11 g/dl, red cell distribution width of >15% and serum ferritin value <12 ng/ml. Other explanatory variables such as urine routine, stool routine and chest x-ray which can be the potential confounders were also included in the study and considered for analysis. All blood counts were calculated by Horiba ABX Pentra DX 120 and Serum Ferritin was calculated by Siemens Immulite auto-analyser.

Inclusion criteria were children in the age group between 6 months to 5 years with simple febrile seizure who were considered as cases and those in age group between 6 months to 5 years with fever who were considered as controls.

Children with atypical febrile seizures, or symptomatic seizures (meningitis, tuberculoma), epileptics syndromes, like Syndromic (LKS), Cryptogenic epilepsy, CNS anomalies/ infections, developmental delay, and child on iron therapy were excluded from the study and control groups.

Statistical analysis

Statistical Analysis was worked out by Chi square test and Student T test by using Epi info 3.4.3 software package. Odds ratio with 95% of confidence limit was calculated with p value <0.05 was considered statistically significant.

RESULTS

A total of 90 children were included in the study with 45 cases in each group. The mean age in the case group was 1.46 (0.74) years and in the control group was 1.62 (0.89) years. Table 1 shows the distribution of children in the different age groups amongst the cases and controls. Maximum children belonged to the age group of 6 months to 1 year in both the groups 20 (44.4%). Least number of children was in the age group above 3 years in both groups.

Table 1: Age distribution among case and control in the study population.

Sr. No.	Age in years	Number of Children (%)	
		Febrile Seizure (Case)	Febrile Illness (Control)
1	6 months to 1 year	20 (44.4)	20 (44.4)
2	1.1 to 2 years	19 (42.3)	17 (37.8)
3	2.1 to 3 years	5 (11.1)	6 (13.3)
4	3.1 to 4 years	1 (2.2)	1 (2.2)
5	4.1 to 5 years	0 (0)	1 (2.2)
Total		45 (100)	45 (100)

Comparing the gender distribution, males were 28 in both groups and females were 17 in both groups suggesting that incidence of febrile seizure is more common among males (62%).

Clinical profile of the cases and controls

Incidence of febrile seizure

First episode of febrile seizure is more common during 6 months-1 year (54.5%) and then between 1.1-2 years (42.5%) and recurrence is more common between 1.1-2 years (50% of 2nd episode and 33.3/5 of 3rd episode) and 2.1-3 years (25% of 2nd episode, 33.3% of 3rd episode and 100% of 4th episode). The youngest and oldest children to present with the 1st episode of FS were 7

months and 3 years respectively with mean age at first episode being 1.2 years. The mean age at 2nd, 3rd and 4th episodes was 1.8, 2.7 & 2.5 years respectively. Table 2: Depicts the incidence of FS and its recurrence in the study group.

Table 2: Incidence of febrile seizure and its recurrence in the study group.

Sr. no.	Age in years	Number of cases (%)			
		1st Episode	2nd Episode	3rd Episode	4th Episode
1.	6 months to 1 year	18 (54.5%)	2 (25.0%)	0	0
2.	1.1 to 2 years	14 (42.5%)	4 (50.0%)	1 (33.3%)	0
3.	2.1 to 3 years	1 (3.0%)	2 (25.0%)	1 (33.3%)	1(100.0%)
4.	3.1 to 4 years	0	0	1 (33.3)	0
5.	4.1 to 5 years	0	0	0	0
6.	Total	33 (100.0)	8 (100.0)	3 (100.0)	1 (100.0)

Seizure occurrence related to onset of fever

The mean duration of fever at the onset of seizures was 10.7 hours. The occurrence of seizure in 19 cases (42.2%) was noticed within first 8 hours of febrile period and 16 cases (35.6%) developed between 9-16 hours of febrile period and 7 cases (15.6%) developed seizure between 17-24 hours and 3 cases (6.7%) after 24 hours of the febrile phase, Hence this signifies that occurrence of seizure is common between 1-16 hours of the febrile phase.

Significant family history

A total of 13 (29%) cases had positive family history of either FS or epilepsy in study group. The significant family history of FS for the 1st episode was present in 6 (13.3%) cases while the same was noted in 7 (15.6%) cases with recurrent episodes of febrile seizure.

Fever aetiology in both study groups

The commonest aetiology of fever was respiratory tract infection in both groups with 37 (82%) and 35 (77.8%) in the case and control groups respectively, followed by Acute gastroenteritis 4 (8.9%) in case and 5 (11.1%) in control and then UTI 1 (2.2%) in case and 3 (6.66%) in control and other non-specific illnesses 3 (6.66%) in case and 1 (2.2%) in control.

Distribution of temperature °F in the study population

The distribution of temperature pattern suggests that maximum of 14 cases (58%) developed seizures during interval of 100-101.9°F. The mean temperature was 101.5°F with minimum of 99.2°F and maximum of 105°F in the case group and the mean temperature in the control group was 101.1°F with minimum of 100°F and maximum of 104°F.

Incidence of IDA in case and control group based on comparison of hematological parameters

Table 3 depicts the incidence of IDA in cases and controls. Low Hb (<11 g/dl) was noticed in 37 cases (82.2%) and 20 controls (44.4%) with p value of 0.0002 which is highly significant and RDW >15 % was noticed in 9 cases (20%) and 8 controls (17.8%) with p value of 0.79 which is insignificant and SF <12 ng/ml was noticed in 40 cases (88.9%) and 19 controls (42.2%) with p value of 0.00 which is highly significant Peripheral smear showing Microcytic Hypochromic anemia was noticed in 30 cases (66.7%) and 18 controls (40%) with p value of 0.011 which is significant

Table 3: Incidence of IDA in cases and controls.

Sr. no.	Parameter	Cases (no of children) (%)	Controls (no of children) (%)	P value
1.	Hb (<11 g/dl)	37 (82.2)	20(44.4)	0.0002
2.	RDW (>15%)	9 (20)	8(17.80)	0.79
3.	SF (< 12 ng/ml)	40 (88.9)	19(42.2)	0.00
4.	MCV (< 70 fl)	23 (51.1)	16(35.6)	0.14
5.	MCHC(<30 %)	7 (15.6)	4(8.9)	0.33
6.	PS MCHC	30 (66.7)	18(40)	0.011

Comparison of Hb, RDW, SF in the study population with temperature >98.6°F to 101°F

Table 4 depicts the comparison of Haemoglobin (Hb), Red Cell Distribution Width (RDW), Serum Ferritin (SF) in case Versus control groups with temperature >98.6°F to101°F. The mean Hb was 9.8±1.58 g/dl in the case group whereas mean Hb in the control group was 10.8± 1.52g/dl with p value of 0.002 which is highly significant. The mean RDW was 13.8 (1.26%) in the case group whereas mean RDW in the control group was 13.2 (1.47%) but the difference is not statistically significant(p value 0.59).The mean SF was 10.7 (1.45) ng/ml and mean SF in the control was 13.5 (5.47) ng/ml with p value of 0.001 which is highly significant.

Table 4: Comparison of Haemoglobin (Hb), Red Cell Distribution Width (RDW), Serum Ferritin (SF) in case versus control groups with temperature >98.6°F to 101°F.

Sr. no.	Variables	Case n =26 Mean (SD)	Control n₁ =22 Mean (SD)	P value
1.	Hb (g/dl)	9.8 (1.58)	10.8 (1.52)	0.002
2.	RDW (%)	13.8 (1.26)	13.2 (1.47)	0.059
3.	SF (ng/ml)	10.7 (1.45)	13.5 (5.47)	0.001

n=no of cases included in the study group, n_1=no of cases included in the control group

Comparison of hematological parameters in both study groups with temperature >101°F

Table 5 depicts the comparison of Haemoglobin (Hb), Red Cell Distribution Width (RDW), Serum Ferritin (SF) in case versus control groups with temperature >101°F. Mean Hb was 9.8 g/dl in case groups whereas mean Hb was 10.8g/dl in the control group with a statistically significant difference (p value 0.002). The mean RDW was 13.8 in the case and 13.2 in controls with no statistical significance. The mean SF was 10.7 (1.45) ng/ml in the case and 13.5 in controls with a statistically significant difference (p value 0.001).

Table 5: The comparison of Haemoglobin (Hb), Red Cell Distribution Width (RDW), Serum Ferritin (SF) in case versus control groups with temperature >101°F.

Sr. no.	Variables	Case n =19 Mean(SD)	Control n₁ =23 Mean(SD)	P Value
1.	Hb (g/dl)	9.8 (1.58)	10.8 (1.52)	0.002
2.	RDW (%)	13.8(1.26)	13.2(1.47)	0.059
3.	SF (ng/ml)	10.7(1.45)	13.5(5.47)	0.001

n=no of cases included in the study group, n_1=no of cases included in the control group.

Comparison of hematological parameters in 1st episode of febrile seizure with recurrent febrile seizure

The comparison of mean Hb, RDW and SF with 1st episode of FS and recurrent episodes had no statistical significance. Mean Hb was 10 g/dl in cases and 9.1 g/dl in controls. Mean RDW was 13.7% in cases and 14.1% in controls. Mean SF was 13.7 ng/ml in cases and 14.1ng/ml in controls Table 6 depicts the comparison of hematological parameters with 1st FS and recurrent FS.

Table 6: The comparison of Hb, RDW and SF in 1st FS with recurrent FS in the case group.

Variables	1ˢᵗ FS n=33 Mean(SD)	Recurrent FS n₁=12 Mean(SD)	P value
Hb (g/dl)	10(1.20)	9.1 (2.28)	0.09
RDW (%)	13.7(1.21)	14.1(1.40)	0.33
SF (ng/ml)	13.7(1.21)	14.1(1.40)	0.33

n= no of cases included in the 1st FS group, n1= no of cases included in the Recurrent FS group

Comparison of MCV in the case with control group

The mean MCV in the study group showed as 68 (8.3) fl and in control group was 72 (10.4) fl with p value of 0.048 which is significant (95% CI -7.93 to -0.03). Table 7 depicts the comparison of MCV in the case with control group.

Table 7: Comparison of MCV in the case with control group.

Sr. no.	MCV	Case (n=45)	Control (n1=45)
1	Mean (fl)	68	72
2	SD	8.31	10.41
3	Significance	0.048	

n=no of cases included in the study group, n_1=no of cases included in the control group

DISCUSSION

We conducted the present study to find the role of Iron deficiency anaemia in febrile seizures. There is evidence to suggest the possibility that iron deficiency anaemia and simple febrile seizure may have an association and many studies have been done to understand this association in detail. [17-24]

Our study compares the hematological parameters like mean Hb, MCV, RDW, SF, PS MCHC in the two groups. Biochemical parameters like serum iron, TIBC have not been compared due to financial limitation. In addition, we have compared the effect of different temperature intervals between the mean Hb, RDW and SF of the either groups which has not been reported previously. It was done to see the effect of low iron status on the lowering of seizure threshold. Our study also explored the possibility of low iron reserves playing any role on predisposing the children to recurrent febrile seizures if any.

The mean age for febrile seizures was 1.5 (0.74) years (18 months) in our study which is similar to that by Pisacane A et al [15 (5.6) months], Daoud AS et al [18.8 months], Ali A et al, had an mean age of 18.8 months, Kumari PL et al [17.5 (8.81) months] and Saeed T et al, [17.4 (8.04) months].[17,19,20,24,28] Few studies have obtained contrast results, Taee N et al, [27.13 (15.8) months], Waheed N et al, had an mean age of [23.41 (12.39) months], Amouian S et al, [25.9 (15.43) months], Srinivasa S et al, [24 months], Thomas S et al, [36 months].[23,26,27,30,31] So the comparison of mean age with previous studies suggests that occurrence of seizure ranges between 15 months to 36 months.

Our cases had family history of seizure in both 1st episode of febrile seizure 6 cases (13.3%) and recurrent episodes in 7 cases (15.6%). Family history of febrile seizures and epilepsy are well known risk factors and many studies have found similar results.[17,20,25,28,29] All studies suggests that family history of seizures could be one strong predisposing factor.

We found RTI as the commonest aetiology for fever in both groups 37 case (82%) in FS group and 35 case (77%) in control group followed by AGE in both groups 4 (8.9%) & 5 (11%) r then, UTI and other non-specifying illnesses. Similar results have been reported by Daoud AS et al, Bidabadi et al, Ali et al, and Srinivasa et al.[20,26,28,29] All studies suggests that the possible cause for fever in both study groups was RTI, and the second and third commonest was AGE & UTI respectively.

We compared hematological parameters in the study population to know the incidence of IDA in both groups as per WHO criteria Hb <11 g/dl, RDW >15% and S.Ferritin <12 ng/mland found 36 (80%) cases and 19 (42.2%) controls to have IDA in the study population. There was a statistically significant difference in Hb (p value 0.002) and S.ferritin (p value 0.00) between cases and controls suggesting higher incidence of anemia in those with febrile seizures.

Our study had an mean Hb of 9.8 (1.58) g/dl and 10.8 (1.52) g/dl in case and control respectively with a p value of 0.002 which is similar to study conducted by Pisacane A et al, with a mean Hb of 10 g/dl and 12.5 g/dl in case and control respectively (p value of 0.0001) , Taee N et al, had an mean Hb of 11.55 (1.34) g/dl and 12.2 (1.5) in case an control respectively with a p value of 0.01 , Aly I et al, had mean Hb of 8.1(1) g/dl and 11.1(1.8) in case and control respectively with a p value of 0.00.[19,25,27] Few have obtained contrast results of no statistically significant difference in Hb in cases and controls.[20,28,29]

Our study group had a mean Serum Ferritin (SF) of 10.7 (1.45) ng/ ml and 13.5 (5.5) in case and control respectively with a p value of 0.001. Similar results have been obtained in various similar case control studies.[20,24,25,27,28] S. ferritin being an acute phase reactant, low levels in the setting of fever makes it a more reliable indicator. Although RDW is an indicator of iron status our study did not have significant difference in RDW in cases and controls.

Low MCV is an indicator of iron deficiency and in our study mean MCV of 68 (8.31) fl and 72 (10.41) fl was seen case and control respectively with a p value of 0.048 which is statistically significant, but the results are in contrast with other similar studies.[20,27-29]

We have compared hematological parameters at different temperature intervals and found that mean Hb of 9.6 (1.3) g/dl at temperature between 98.6°-100.9°F in children with FS was significantly lower than that in children without seizures 11 (1.5) g/dl with a p value of 0.003 while the mean Hb of 9.9 (1.73) g/dl and 10.7 (1.57) g/dl in case and control respectively with a p value of 0.11 at temperature > 101°F had no statistical significance . This shows that low Hb is associated with increased risk of seizures at lower temperatures suggesting possibility of IDA lowering seizure threshold.

Although IDA is increasingly being recognized as a risk factor in FS, its role in recurrence risk is exactly not known. We have compared hematological parameters like Hb, S. Ferritin and RDW in those with first episode seizures versus recurrent episode and found no statistically significant difference. This is a potentially new finding and needs more large scale studies to confirm the finding. Thus, it becomes imperative to prevent IDA rather than correct it once febrile seizures occurs.

CONCLUSION

The results of our study show that Iron deficiency anaemia is a significant risk factor in lowering the seizure threshold for FS children between the age group of 6 months to 5 years. However, IDA did not have significant effect in FS recurrence. Comparing laboratory parameters Haemoglobin, S. ferritin and MCV were significantly low in those with febrile seizures and similar results were found in different temperature intervals. Haemoglobin and MCV have conflicting results with various studies as reliable indicators hence doing S. Ferritin is recommended in all those with febrile seizures .The implication of this study lies in the fact that the findings could actually reduce the incidence of simple febrile seizure by controlling, treatment and prevention of iron deficiency anemia which is a modifiable risk factor. Further case control studies with lager population size and on different ethnic backgrounds in the form of multicentric studies will be further helpful in elucidating the same. Although several national programmes focus on iron supplementation and prevention of IDA our study the need to effectively implement such programmes. Also, case control studies involving various neurotransmitters to which iron is a cofactor, would help in clarifying the exact mechanisms by which low iron

status becomes a risk factor for lowering the seizure threshold for FS children.

ACKNOWLEDGEMENTS

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