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Original Research Article

A study of febrile seizures in children in relation to iron deficiency anemia

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ABSTRACT

Background: Febrile seizures are the most common cause of convulsions in children between 6 months to 5 years, occurring in 2-5% of children. Iron deficiency is postulated as a risk factor for febrile seizures in children and it is an easily correctable condition. The objective of the study was to study the clinical profile and risk factors of febrile convulsions and to establish an association between febrile seizure and iron deficiency anemia.
Methods: The study was carried out in Department of Pediatrics, Dhiraj General Hospital, Piparia, a tertiary care teaching hospital. 34 cases and 34 controls were included in the study. Controls were children of same age group presenting with short febrile illness but without any seizures. Febrile seizures were defined according to the AAP (American Academy of Pediatrics) criteria. Iron deficiency was diagnosed by hematologic investigations of haemoglobin value < 11 g/dl, MCV <70 fL and RDW > 15.6%.
Results: Iron deficiency anemia was present in 23.52% (8/34) of cases as compared to 17.64% (6/34) in the control group. Odds ratio was 1.436 (95% CI 0.439-4.669, p value 0.549), which suggest there is no significant association of iron deficiency anemia with febrile convulsions. Subgroup analysis for association of iron deficiency anemia with simple febrile convulsion cases showed Odds ratio of 1.11 (95% CI 0.298-4.138), which suggests there is poor association of iron deficiency anemia with simple febrile convulsions. Subgroup analysis for association of iron deficiency anemia with complex febrile convulsion cases showed Odds ratio of 2.809 (95% CI 0.521-15.041), which suggests there is poor association of iron deficiency anemia with complex febrile convulsions. Wide confidence interval indicates less sample size. Study with large sample size is required for reliable interpretation.
Conclusions: The study reveals iron deficiency anemia is not a significant risk factor in children presenting with febrile seizures. Further study with large sample size is required.

Keywords: Febrile seizures, Haemoglobin, Iron deficiency

INTRODUCTION

Febrile convulsion is one of the most common neurological disorder seen in children between 6 months to 5 years, which is benign in nature and generally carry excellent prognosis. The prevalence of febrile seizures in children is approximately 2 to 5%.[1] Clinically, distinction has to be made between children with febrile seizures and children having epilepsy so as to allay the tension of parents as febrile seizures are benign in nature.[2] In children with febrile convulsions the risk of long term effects on behavior or intelligence is less and the risk of later development of epilepsy is minimal.[3]

According to AAP (American Academy of Pediatrics) the definition of febrile seizures includes a child who has febrile illness or certainly fever, is neurologically healthy between 6 months and 5 years of age; whose seizure is

brief (<15 min), generalized and occurs only once (simple febrile seizures) or more times (complex febrile seizures) within 24 hours during fever. Children whose seizures are attributable to the central nervous system infection and those who have had a previous afebrile seizures or central nervous system abnormality are not febrile seizures.[4] Earlier studies have shown the occurrence of certain risk factors for development of febrile seizures and its recurrence which are as follows:[5]

- Young age at onset (<15 month)
- Epilepsy in first degree relative.
- Febrile seizures in first degree relatives.
- Many previous episodes of febrile seizures.
- First complex febrile seizure.

An increased frequency of febrile seizures has been found among parents and siblings of children with febrile seizures.[6] Although it is generally agreed that a genetic predisposition exists, the estimates of how frequently the first-degree family members experience febrile seizures is varied. Possibilities include inheritance patterns consistent with single gene dominant trait, a recessive trait or polygenic inheritance.[6]

A family history of convulsions, maternal smoking and alcohol consumption during pregnancy have been associated with febrile seizures but the risk factors remain largely unknown. Iron is involved in the metabolism of several neurotransmitters, and monoamine and aldehyde oxidase are reduced in iron deficiency anemia. Iron deficiency is common during second and third year of life and has been associated with behavioral and developmental disturbances.[7]

Thus, we investigated the association between iron deficiency anemia and febrile seizures with the help of case-control study. The objective of the study was to study the clinical profile and risk factors of febrile convulsions. To evaluate an association between febrile seizure and iron deficiency anemia.

METHODS

The study was performed in the Department of Pediatrics, Dhiraj General Hospital, Sumandeep Vidyapeeth between January 2013 and June 2014. Both (case and control) study groups comprised of children aged 6 months to 5 years admitted in the Department of Pediatrics, Dhiraj General Hospital. Children with febrile seizures as per AAP criteria were enrolled in the case group and those with febrile illness without convulsions were included in the control group. Each group contained 34 children.

Definition of febrile seizure according to American Academy of Pediatrics.

According to AAP (American Academy of Pediatrics) the definition of febrile seizures includes a child who should have febrile illness or certainly fever, is neurologically healthy between 6 months and 5 years of age; whose seizure is brief (< 15 min), generalized and occurs only once (simple febrile seizures) or more times (complex febrile seizures) within 24 hours during fever.

Inclusion criteria

- Children whose parents were willing to allow their children to participate in the study.
- Children of age between 6 months to 5 years.
- Children with febrile convulsions as per AAP criteria as well as with acute febrile illness without convulsion.

Exclusion criteria

- Children who presented afebrile seizures
- Children who had features of CNS infections and CNS malformation.
- Children with history of birth asphyxia/developmental delay/ epilepsy.
- Children on iron supplementation therapy.
- Chronic multisystem disease.

Sample size: Cases-34 children with febrile seizures. Controls-34 children without febrile seizures but presenting with acute febrile illness. The study was conducted after approval from Institutional Ethics Committee, Sumandeep Vidyapeeth was obtained. The study was conducted as per the applicable national guidelines (ICMR, 2006) respecting the elements of research involving human participation.

The selected children's parents of both the study groups were informed about the nature, purpose of the study, risks and benefits associated with the participation in the study with the help of Patient information sheet. After obtaining written informed consent, a detailed clinical history and physical examination for each child was recorded in a standardized format. Relevant data was collected in the prescribed proforma.

Routine laboratory workup was done in all the children. CSF examination was done in those children with suspected meningitis. Other investigations were done to find out the cause of fever if required. To find out the presence of iron deficiency investigations such as complete blood count which includes red blood indices (RBC indices) and red cell distribution width using automated hematology analyzer were done.

Traditional measures of iron status (ferritin, serum iron, TIBC, transferrin saturation) are influenced by infection and are therefore not reliable indicators of iron status in the setting of acute infection. MCV and RDW are not affected by acute infections typical of early childhood. Iron deficiency was diagnosed as hemoglobin value <11g%, red cell distribution width of >15.6% and MCV<70 FL.

Statistical analysis

Data were entered in MS Excel and completeness checked. Pearson's Chi-square test was applied to check association between two qualitative variables. Fisher's exact test was applied along with chi-square test when it required. Student's independent t-test was applied to check difference in mean values of various quantitative variables between case and control groups. For each statistical test, p-value was obtained to get conclusion. Throughout the discussion, statistical significance was put at 5% level.

RESULTS

Clinico-laboratory profile of children with febrile convulsions.

Table 1: Age of onset of febrile convulsions.

Age in months	% (n= 34)
6-12	29.4% (10/34)
13-24	38.23% (13/34)
25-36	20.58% (7/34)
37-48	8.8% (3/34)
49-60	2.94% (1/34)

Table 2: Sex distribution of children.

Age months	Male % (n= 34)	Female % (n= 34)	Total
6-12	70% (7/10)	30% (3/10)	10
13-24	69.2% (9/13)	30.8% (4/13)	13
25-36	42.9% (3/7)	57.1% (4/7)	7
37-48	100% (3/3)	0% (0/3)	3
49-60	0% (0/1)	100% (1/1)	1
6-60	64.7% (22/34)	35.29% (12/34)	34

64.7% (22/34) of children with febrile convulsions were boys, 35.29% (12/34) children were girls. 91.17 % (31/34) children had generalized tonic clonic type of convulsions (GTCS). 8.82% (3/34) of children had generalized tonic type of convulsions. None of the patients had focal neurological findings on arrival and even after the episode of convulsion. Recovery was complete after the episode of febrile convulsion in all.

Table 3: Duration of convulsions in children.

Duration	% (n= 34)
0-1 min	5.88% (2/34)
1-2 min	14.70% (5/34)
2-3 min	61.76% (21/34)
3-4 min	2.94% (1/34)
4-5 min	14.70% (5/34)
>5 min	0% (0/0)

Table 4: Duration of post-ictal drowsiness.

Duration	% (n= 34)
Absent	11.76% (4)
0-5 min	8.82% (3)
6-10 min	44.11%(15)
11-15 min	29.41% (10)
16-20 min	2.94% (1)
21-25 min	0% (0)
26-30 min	2.94% (1)

76.45% children (26/34) had single episode of febrile convulsion while 23.52% (8/34) children had more 1 episode of convulsion during same febrile illness.

Table 5: Duration of fever.

Duration of fever	% (n= 34)
<24 hr	58.82% (20/34)
24-48 hr	29.41% (10/34)
>48 hr	11.76% (4/34)

Table 6: Cause of fever.

Cause of fever	%(n= 34)
Undifferentiated viral fever	52.94% (18/34)
Upper respiratory tract infection	32.4% (11/34)
Acute diarrheal disease	11.8%(4/34)
P. Vivax malaria	2.9% (1/34)

Table 7: Comparison of various study variables between cases and controls.

	Cases (n=34)	Controls (n=34)	Crude OR (95% CI)	p-value
AGE≤ 18 months	11 (32.35%)	10 (29.41%)	1.148 (0.410-3.214)	0.793
Male	22(64.70%)	19(55.88%)	1.447 (0.545-3.842)	0.456
Full Term birth	34(100%)	32(94.11%)	NA	0.145
NICU admission	0(0%)	1(2.94%)	NA	NA
Family History of epilepsy	0(0%)	0(0%)	NA	NA
Family History of Febrile seizures	0(0%)	0(0%)	NA	NA
Malnutrition	10(29.41%)	12(35.3%)	0.764 (0.276-2.117)	0.796
Iron Deficiency	8(23.52%)	6(17.64%)	1.435 (0.546-3.792)	0.548

76.45% (26/34) of children had simple febrile convulsions. 23.52% (8/34) of children had complex febrile convulsions. Past history of febrile seizures was present in 26.5% (9/34) children and absent in 73.52% (25/34) children.

Table 8: Association of iron deficiency anemia with all cases of febrile convulsions.

Study group	Iron deficiency anemia %	No iron deficiency anemia %
Cases (n=34)	23.52% (8/34)	76.47% (26/34)
Controls (n=34)	17.64% (6/34)	82.35%(28/34)
OD (95% CI)	1.435 (0.546-3.792)	
p value	0.548	

Iron deficiency anemia was present in 23.52% (8/34) of cases as compared to 17.64% (6/34) in the control group. Odds ratio was 1.436 (95% CI 0.439-4.669, p value 0.549), which suggest there is no significant association of iron deficiency anemia with febrile convulsions.

Table 9: Association of iron deficiency anemia with simple febrile convulsion.

Study group	Iron deficiency anemia %	No iron deficiency anemia %
Simple febrile seizures (n=26)	19.23(5/26)	80.76(21/26)
Controls (n=34)	17.64(6/34)	82.35(28/34)
OR (95% CI)	1.11 (95% CI; 0.298-4.138)	
P value	0.875	

Subgroup analysis for association of iron deficiency anemia with simple febrile convulsion cases showed OR of 1.11 (95% CI 0.298-4.138), which suggests there is poor association of iron deficiency anemia with simple febrile convulsions.

Table 10: Association of iron deficiency anemia with complex febrile seizures.

Study group	Iron deficiency anemia %	No iron deficiency anemia %
Complex febrile seizures (n=8)	37.5(3/8)	62.5(5/8)
Controls (n=34)	17.64(6/34)	82.35(28/34)
OR (95% CI)	2.809 (95% CI 0.521-15.041)	
P value	0.23	

Subgroup analysis for association of iron deficiency anemia with complex febrile convulsion cases showed OR of 2.809 (95% CI 0.521-15.041), which suggests there is poor association of iron deficiency anemia with complex febrile convulsions. Wide confidence interval indicates less sample size. Study with large sample size is required for reliable interpretation.

DISCUSSION

Age of onset of febrile seizures

The mean age of onset in present study is 24.62±13.77 months which is comparable with other studies. Pisacane A et al found that mean age of febrile seizure was 15 months.[8]

Kumari PL et al found the mean age of febrile seizures to be 17±8.81 months.[9] Hartfield DS et al found the mean age to be 17.9 months.[10] Daoud AS et al found the mean age to be 18.8 months.[11]

Shah SS et al found mean age to be 15.9 months.[12] Fallah R et al found mean age to be 22.78±11.08 months.[13] Rehmaan N et al found the mean age to be 22.97±9.52 months.[14] Majority (67.63%) of the children with febrile seizures had age of onset of convulsions below 2 years of age. An age of less than 18 months is associated with increased risk of recurrence.[15,16]

Gender distribution

There was preponderance of male (64.7%) in the present study group. Forefar text book of pediatrics also mentions preponderance of male gender.[17] Other studies have also found a preponderance of males-Daoud AS et al (53.33), Hartfield DS et al (57.35%).[11,10]

Family history of febrile seizures

In present study, none of the cases had family history of febrile seizures. Daoud AS et al found positive family history of seizures in 18% of his patients while Kumari PL et al found positive history in 26% of his patients.[11,9] Family history of febrile seizures is associated with an increased risk of recurrence.[15,16]

Type of convulsions

Majority (91.17%) of patients had Generalised tonic clonic type of convulsions.

Focal neurological findings

None of the patients had presence of focal neurological findings.

Duration of convulsions

All patients had duration of convulsions less than 5 minutes and none of them had convulsions lasting more than 5 minutes.

Postictal drowsiness

All patients had postictal drowsiness lasting for less than 30 minutes.

Number of convulsions during same febrile illness

23.52% children had more than 1 episode of convulsion during the same febrile illness.

Duration of fever before onset of convulsions

58.82% of children with febrile convulsion had convulsion within 24 hours of fever. Berg AT et al.[15] in 1989 studied the association between duration of fever before initial seizure and the risk of recurrence at one year; for fever lasting less than 1 hour, the risk of recurrence was 44%; for fever lasting 1 to 24 hours, 23%, and for fever lasting more than 24 hours, 13% ($p < 0.001$).

Type of febrile seizures

76.45% had simple febrile seizures and only 23.52% had complex febrile seizures. Verity CM Golding J.[18] in his study found 79% (305/382) to have simple febrile seizures while remaining 21% had complex febrile seizures.

Past history of febrile seizures

Past history of febrile seizures was present in 26.5% of children

Cause of fever

Undifferentiated viral fever and acute upper respiratory infections were common causes of fever. Viral fever was present in 52.94% of children, and acute upper respiratory tract infection was present in 32.4% of children. The possibility that fever of specific infectious etiologies might contribute to the generation of human febrile seizures is intriguing in this context: a disproportionate number of febrile seizures have been associated with infection with HHV6 (human herpes virus 6) in some but not all studies. This suggests that mechanisms specific to this virus, including perhaps a unique profile of cytokine induction, might augment neuronal excitability selectively and thus provoke seizures preferentially.[19] Vaccinations especially diphtheria, tetanus and pertusis (DTP) and against measles may also be associated.[20]

Association of iron deficiency anemia with febrile convulsion cases

Iron deficiency anemia was present in 23.52% of cases as compared to 17.64% in the control group. Odds ratio was 1.436 (95% CI 0.439-4.669, p value 0.549), which suggest there is no significant association of iron deficiency anemia with febrile seizures.

Auvichayapat P et al conducted a descriptive study in 430 thalassemic patients aged between 6 months and 10 years and found that the rate of febrile seizures in thalassemia patients was 4.4 times lower than that of general population.[21] Thus, iron overload may have a major factor affects brain metabolism and thereby prevents febrile seizures.

Daoud A et al conducted a controlled study to investigate the relation of iron store and first febrile seizures and found that plasma ferritin level was significantly lower in children with first febrile seizure than in reference group, suggesting a possible role of iron insufficiency in first febrile seizures.[11]

Rehmaan N conducted a case control study to find the association between iron deficiency anemia and febrile convulsions among 60 children dividing them into 2 groups with children having febrile seizure as cases and while those with febrile illness without seizure comprised as controls.[14] He found that plasma ferritin was significantly lower in cases as compared to controls suggesting that iron deficient children are more prone to febrile seizure and suggested for a follow up study of patient found to be iron deficiency at the time of a first febrile seizure to determine the incidence of subsequent febrile seizure after treatment for iron deficiency.

Sherjil A et al conducted a multicentric study in which 310 children aged between 6 months to 6 years were included and concluded that patients with febrile seizures are 1.93 times more likely to have iron deficiency anemia compared to febrile patients without seizures.[22]

Kumari PL et al in 2009 did a study having 154 cases and 154 controls in children of age group 6 months to 3 years presenting with simple febrile seizures and concluded that iron deficiency is a significant risk factor for simple febrile seizures in children of age group 6 months to 3 years.[9]

Vaswani RK et al conducted study among 100 children, dividing equally children between 6 months and 6 years with first febrile seizure as cases and febrile illness without seizure as controls.[23] The results of this study showed the proportion of children with low ferritin (<25µg/L) was significantly higher in cases (34.68%) than in controls (15.30%) with value of $p < 0.0001$. This concluded that iron deficiency could be a potential risk factor for febrile seizure in children.

Fallah R et al in December 2011 did an analytic case-control study where iron status of 6 to 60 months old children with first febrile seizures from December 2011 to August 2012 was evaluated and compared with healthy age and sex matched control children.[13] Based on the result of this study, iron deficiency was found to be an important risk factor for development of febrile convulsion.

Sadeghzadeh M et al did a study to find the association between iron deficiency anemia and febrile seizures in children aged 6 months to 3 years.[24] The results of this study suggested that although anemia was not common among febrile seizure patients, iron deficiency was more frequent in these patients.

Pisacane A et al conducted a case control study in 156 children for less than 2 years to know the relationship of iron deficiency and febrile seizure.[8] He reported that fever can worsen the negative effects of anemia or of iron deficiency on brain and a seizure can occur as a consequence.

Subgroup analysis-association of iron deficiency anemia with simple febrile convulsion cases

Subgroup analysis for association of iron deficiency anemia with simple febrile convulsion cases showed OR of 1.11 (95% CI 0.298-4.138), which suggests there is poor association of iron deficiency anemia with simple febrile convulsions.

Subgroup analysis-association of iron deficiency anemia with complex febrile convulsion cases

Subgroup analysis for association of iron deficiency anemia with complex febrile convulsion cases showed OR of 2.809 (95% CI 0.521-15.041), which suggests there is poor association of iron deficiency anemia with complex febrile convulsions. Wide confidence interval indicates less sample size. Study with large sample size is required for reliable interpretation.

CONCLUSION

Onset of febrile convulsions is common below 2 years of age. In present study, majority (67.63%) (23 out of 34) of the children with febrile seizures had age of onset of convulsions below 2 years of age. The mean age of onset in present study was 24.62±13.77 months.

Febrile convulsion is more common problem in boys. In present study, there was preponderance of male, with male: female ratio of 1.8:1 (64.7% Versus 35.29%). Majority of cases of febrile convulsions present with generalized tonic clonic type of convulsions. In present study, 91.17% of patients had GTCS type of convulsions.

Presentation of febrile convulsions as status epilepticus is not common. In present study, all patients had duration of convulsions less than 5 minutes and none of them had convulsions lasting more than 5 minutes. Post ictal drowsiness after an episode of febrile convulsion is short lasting. In present study, all patients had postictal drowsiness lasting for less than 30 minutes.

Simple febrile convulsion is a more common problem than complex one. In present study, 76.45% had simple febrile seizures and only 23.52% had complex febrile seizures.

Onset of convulsion is common within 24 hours of onset of fever. In present study, 58.82% of children with febrile convulsion had convulsion within 24 hours of fever. 29.41% of children had convulsions within 24 to 48 hours of onset of fever. 11.76% of children had convulsions after 48 hours of onset of fever. Febrile convulsion is known for recurrences. Past history of febrile seizures was present in 26.5% (9/34) children and was absent in 73.52% (25/34) children.

Undifferentiated viral fever and acute upper respiratory infections are the common causes of fever. In present study, undifferentiated viral fever was present in 52.94% of children, and acute upper respiratory tract infection was present in 32.4% of children.

Iron deficiency anemia is not likely to have significant association with febrile convulsions. In present study, iron deficiency anemia was present in 23.52% of cases as compared to 17.64% in the control group. Odds ratio was 1.436 (95% CI 0.439-4.669, p value 0.549), which suggest there is no significant association of iron deficiency anemia with febrile convulsions. Subgroup analysis for association of iron deficiency anemia with simple febrile convulsion cases showed Odds ratio of 1.11 (95% CI 0.298-4.138), which suggests there is poor association of iron deficiency anemia with simple febrile convulsions. Subgroup analysis for association of iron deficiency anemia with complex febrile convulsion cases showed Odds ratio of 2.809 (95% CI 0.521-15.041), which suggests there is poor association of iron deficiency anemia with complex febrile convulsions. Wide confidence interval indicates less sample size. Study with large sample size is required for reliable interpretation.

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