DOI: 10.7860/JCDR/2023/61832.18148

Original Article

Paediatrics Section

Role of Iron Deficiency Anaemia in First Febrile Seizures in Six Months to Six Years of Age at a Tertiary Care Hospital, Southern India

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ABSTRACT

Introduction: Febrile Seizures (FS) are the most common neurological disorders among infants and young children, occurring in 2%-5% of children younger than five years of age. Iron deficiency is reported as a commonest micronutrient deficiency, that has been associated with FS.

Aim: To find out the cause of fever and the role of Iron Deficiency Anaemia (IDA) and its outcome in first FS in six months to six years of age.

Materials and Methods: This was a hospital-based prospective observational study, conducted in the Department of Paediatrics at King George Hospital, Visakhapatnam, Andhra Pradesh, India. The duration of the study was one year and seven months, from December 2019 to July 2021. A total of 130 children (six months-six years) were included in the study. A total of 65 cases had a febrile seizure and the rest 65 controls had a history of Febrile Illness (FI) without seizures. Anaemia was defined as the decrease of Haemoglobin (Hb) <11 gm%. Among the Red Blood Cells (RBC) indices Mean Corpuscular Volume (MCV) <70 femtolitres (fL), Mean Corpuscular Haemoglobin (MCH) <27 picograms (pg), plasma ferritin <12 µg/dL, and serum ferrous <60 µg/dL, Total Iron Binding Capacity (TIBC) >450 µg/dL, transferrin <250 mg. Discrete variables are expressed as counts (%) and compared using the Chi-square test, quantitative variables were expressed as mean and Standard Deviation (SD) and compared using t-test and Statistical significance was set at p-value <0.05. Analysis was done using Statistical Package for Social Sciences (SPSS) version 22.0.

Results: The mean age of the study participants (cases) was 2.57±1.5 years for cases and 2.56±1.35 years for controls. In the present study, male:female ratio was 1.24:1. In the present study, positive family history of seizures is an important risk factor for FS. The observations came 43 (66.2%) cases were IDA with FS 22 (33.8%) cases, were, with only FS 23 (35.4%) of controls were, with IDA and FI 42 (64.6%) of controls with the FI, which is statistically significant, p-value=0.001.

Conclusion: The IDA is one of the major risk factors for FS in the paediatric age group. Early identification and treatment of iron deficiency may prove helpful in preventing FS in paediatric patient.

Keywords: Febrile illness, Haemoglobin, Neurological disorders

INTRODUCTION

The FS are the most common neurological disorders among infants and young children. They occur in 2-5% of children, younger than five years of age. It is an age-dependent phenomenon with a strong genetic predisposition [1]. By definition, FS are the seizures that occur between the ages of six months to 60 months with a temperature of 38°C (100.4°F) or higher, that is not the result of Central Nervous System (CNS) infection or any metabolic imbalance, and that occurs in the absence of a history of prior afebrile seizure [1]. Iron deficiency has non haematological systemic effects. Both iron deficiency and IDA are associated with impaired neurocognitive function in infancy and also increased risk of seizures, strokes, breath-holding spells in children and exacerbation of restless leg syndrome [2]. Many of the nervous system enzymes are iron-dependent because of their activities. Iron deficiency inhibits the metabolism of certain neurotransmitters including monoamine and aldehyde oxidase [3,4]. And thus, it may alter the seizure threshold of a child [2].

It has been determined that, iron depletion has a negative effect on neurocognitive function and supplementing iron reduces breath-holding spells, on the other hand, fever can exaggerate the negative effect of anaemia on the brain. Considering the above features, IDA as a risk factor for FS is probable [5]. Therefore, the present study was conducted to find out the causes of fever and the role of IDA and its outcome in first FS in six months to six years of age.

MATERIALS AND METHODS

The present hospital-based prospective observational study was conducted in the Department of Paediatrics at King George Hospital, Visakhapatnam, Andhra Pradesh, India. The duration of the study was one year and seven months, from December 2019 to July 2021. The present study was done on the children aged six months to six years, admitted to Intensive Psychiatric Care Unit (IPCU) and children medical ward with the first episode of FS. Ethical clearance was obtained from the Institutional Ethics Committee at Andhra Medical College, with serial No: 27/IEC.

Inclusion criteria: Patients of either gender aged, six months to six years, patients whose guardian/representative were willing to give valid consent were included in the study.

Exclusion criteria: Patients with iron supplementation therapy, children with other haematological disorders such as, haemolytic anaemias, leukaemia, lymphoma, myeloma were excluded from the study. Children with chronic illness such as cystic fibrosis, mental retardation, children with a previous history of seizures, and children with neurological deficits were excluded from the study.

Sample size calculation: A total of 130 children were included in the study based on convenience sampling. Cases were defined as 65 consecutive children, admitted to the paediatric ward with the first episode of febrile seizure and the control group included 65 children, who got admitted to the hospital with FI without FS.

Study Procedure

After taking the informed written consent from the parent or guardian, the relevant information from the history, physical examination and investigation findings were recorded in a predesigned proforma. General details like name, age, sex, weight, address, presenting complaints, onset, duration, and progression were taken in detail. The average length of the seizure, types of seizure (focal and generalised seizures, typical and atypical seizures), number of episodes of seizure, and aetiology of fever were noted. Protein Energy Malnutrition (PEM) grade and history of FI was noted. Any episode of previous afebrile seizure was also noted. Family history of convulsions and systemic examination was done in detail. Vital data: Heart Rate (HR), Respiratory Rate (RR), Blood Pressure (BP), Oxygen Saturation (SpO_2), and temperature were recorded. Anthropometry (height, weight, mid upper arm circumflex) were recorded, any abnormalities like pallor, icterus, cyanosis, clubbing, generalised lymphadenopathy and pedal oedema were checked.

Routine investigations such as Complete Blood Count (CBC), which includes Hb, Total Leucocyte Count (TLC), Differential Count (DLC), Erythrocytic Sedimentation Rate (ESR), Packed Cell Volume (PCV) were carried out. RBC Indices: MCV, MCH, Mean Corpuscular Haemoglobin Concentration (MCHC), peripheral smear stool for ova cyst/pus cells/epithelial cells were noted. Iron profile was assessed by serum ferritin level, serum iron level, TIBC, serum transferrin levels. Radiographic examinations such as chest X-ray, Electroencephalography (EEG), Magnetic Resonance Imaging (MRI) brain was done for cases as needed. The diagnostic threshold, that was employed in the present study for iron deficiency was: Hb level <11 g/dL, among the RBC indices MCV <70 fL, MCH <27 pg, serum ferritin <12 µg/dL, and serum iron <60 µg/dL, TIBC >450 µg/dL, transferrin <250 mg/dL [6].

STATISTICAL ANALYSIS

Analysis was done using SPSS version 22.0, discrete variables were expressed as counts (%) and compared using the Chi-square test, quantitative variables were present as Mean±SD and compared using t-test. Statistical significance was set at p-value <0.05.

RESULTS

A total of 130 children were included in the study. A total of 65 cases had FS and the control group had 65 FI without seizure cases. A total of 14 (21.5%) cases were <1 year of age, 17 (26.2%) cases were 1-2 years, 11 (16.9%) cases were 2-3 years, 14 (21.5%) cases were 3-4 years and 9 (13.8%) were cases between 4-6 years of age. In control group, 10 (15.4%) controls were <1 year of age, 19 (29.2%) of controls were 1-2 years, 19 (29.2%) cases were 2-3 years, 9 (13.8%) cases were 3-4 years and 8 (12.3%) cases were between 4-6 years. The mean age of cases was 2.57±1.5 years and the mean age among controls was 2.56±1.35 years. In the present study, 29 (44.6%) were females in the case group and 30 (46.2%) in the control group. The male:female ratio in cases was 1.24:1 and in the control group was 1.16:1. The mean weight of cases was 11.14±2.45 kg and in the control group was 12.60±3.41 kg, (p-value=0.006*) mean weight was significantly less in cases compared to controls. This means malnourished children were having more chances of FS.

In the present study, average length of seizure in 62 (95.4%) cases lasted for <5 minutes and 3 (4.6%) cases of seizures lasted for five-10 minutes. In cases (FS) group 63 (96.9%) of cases, the seizure was generalised and 2 (3.1%) cases had focal seizures. In the study, it was observed that, 100% of children with complex FS had IDA. Children with complex FS have more chances of IDA, therefore, screening must be done [Table/Fig-1].

In the present study, 80% of cases and 86% of controls had no PEM, 16.9% of cases and 7.7% of controls grade I PEM, 3.1% of cases and 6.2% of controls had grade II PEM. No cases and controls in grade III and IV PEM and the association were not statistically significant. Chi-square=3.065, p-value=0.216. The mean temperature in cases group was 102.16 with a standard deviation of 1.07°F, whereas, in control it was 101.98° with a standard deviation of 0.95°F and the difference was statistically not significant (p-value=0.316). In the present study, family history of seizures was more in cases compared to controls. A total of 5 (7.7%) of cases had a positive family history. The p-value is statistically significant which gives information that, positive family history of seizures is a risk factor for FS [Table/Fig-2]. The most common etiological cause for fever in both the groups was Upper Respiratory Tract Infection (URTI). A total of 61.5% of cases and 61.5% of controls had URTI. The next common infection was acute Gastroenteritis (GE) 18.4% of cases had acute GE 21.5% of controls had acute GE. A 20.1% of cases and 17% of controls had fever followed by other causes like vaccination, enteric fever, viral fevers, and Lower Respiratory Tract Infection (LRTI).

S. No.	Type of seizures	Cases (FS)	IDA	Without IDA	Percentage (%)
1	Simple febrile	55	33	22	60
2	Complex febrile	10	10	0	100
Total		65	43	22	

[Table/Fig-1]: Typical Febrile Seizures (FS) vs atypical FS with Iron Deficiency Anaemia (IDA).

Family history			Groups		Total
			Cases	Controls	
FS	No	Count	60	65	125
		%	92.3	100	96.2
	Yes	Count	5	0	5
		%	7.7	0	3.8
Total		Count	65	65	130
		%	100	100	100

[Table/Fig-2]: Family history of FS.
Chi-square=5.200, p-value=0.023*; FS: Febrile seizures; *: Significant

In the present study, the mean value for Hb in cases was 8.712±1.64 g/dL and in controls was 9.974±2.0770 g/dL. Hb was significantly lower in cases compared to controls with a p-value<0.001*. The mean value for MCV in cases was 66.57±16.53 fL and in controls was 82.90±16.72 fL. The mean value of MCV is significantly low in cases compared to controls with a p-value<0.001**. The mean value for MCH in cases was 25.451±6.132 pg and in controls was 30.769±4.343 pg which is statistically significant (p-value=0.001**). Mean serum ferritin in cases 36.83±49.01 µg/dL mean serum ferritin controls 72.41±54.26 µg/dL, p-value=0.01 which was statistically significant. The mean serum iron in cases was 70.97±4136 µg/dL mean serum iron in controls was 93.84±38.5 µg/dL which is statistically significant (p-value=0.001**). Mean TIBC levels cases 459.46±131.52 µg/dL, and mean TIBC in controls 344.32±152.45 µg/dL which is statistically significant (p-value=0.001**) [Table/Fig-3]. Mean serum transferrin in cases was 254.35±78.08 mg/dL.

S. No.	Parameters	Mean±SD	p-value
1	**Serum iron (µg/dL)**		
	Cases (FS)	70.97±41.36	<0.001**
	Controls (FI)	93.84±38.52	
2	**TIBC (µg/dL)**		
	Cases (FS	459.46±131.529	<0.001**
	Controls (FI)	344.32±152.458	

[Table/Fig-3]: Comparison of serum iron and Total Iron Binding Capacity (TIBC) levels between cases and controls.
SD: Standard deviation; *=statistically significant

The mean serum transferrin in controls was 283.18±68.8 mg/dL which is statistically significant (p-value=0.027*).

In the present study, the final observation outcomes were 66.2% of cases had FS with IDA, 33.8% of cases had FS without IDA, 35.4% of controls had FI with IDA, 64.6% of controls had FI without IDA [Table/Fig-4].

Final observations	Groups		Total n (%)
	Cases (n=65) n (%)	Controls (n=65) n (%)	
FS without IDA	22 (33.8)	0	22 (16.9)
FI without IDA	0	42 (64.6)	42 (32.3)
FI with IDA	0	23 (35.4)	23 (17.7)
FS with IDA	43 (66.2)	0	43 (33.1)
Total	65 (100)	65 (100)	130 (100)

[Table/Fig-4]: Final observations cases vs controls.

DISCUSSION

In the present study, the mean age of presentation of FS was 30 months, which is comparable to other studies done by Sharif MR et al., found mean age of 25 months [7]. Another study done by Vaswani RK et al., found a mean age of 18 months [8]. Studies done by Ghasemi F et al., and Jang HN et al., found the mean age to be 27 months [9,10]. Naveed-ur-Rehman and Billoo AG found mean age was 22.97±9.5 months [11]. Amirsalari S et al., found an average age of 39±15.92 months [12]. In a study done in Kenya by Idro R et al., mean age was found to be 30.3±19 months [13]. It is generally noted that, the febrile convulsion and the first febrile convulsion are more common in the second year. There was a preponderance of males in the present study for the febrile seizure group which was statistically not significant (p-value=0.860). Another study conducted by Sharif MR et al., showed male preponderance [7]. The mean weight of cases, was significantly less in cases compared to controls (p-value=0.006). This signifies children in cases are having more chances of malnutrition and anaemia most common IDA compared to cases. This means malnourished children are having more chances of FS.

RK et al., Amirsalari S et al., Daoud AS et al., and Khalid N and Akrem M, failed to find any significant difference between the two groups [8,12,16,18]. In the present study, mean serum ferritin in cases 36.83±49.01 and serum ferritin controls was 72.41±54.26 (p-value=0.01) which was statistically significant. In the present study, IDA in children with FS was more frequent than those with FI, thus, suggesting iron deficiency is a risk factor for FS. Daoud AS et al., observed a significantly lower serum ferritin level in the FS group than in the reference group, proving that, serum ferritin is a sensitive, specific and reliable measurement for determining iron deficiency at an early stage, and it may be the best indicator of total body iron status [16]. Vaswani RK et al., observed significantly low serum ferritin levels in children with FS than in controls [8]. Kumari PL et al., found a highly significant association between iron deficiency and simple FS p<0.05* [17]. Similarly, Naveed-ur-Rehman and Billoo AG found plasma ferritin level was significantly lower in cases as compared to controls suggesting that, iron-deficient children are more prone to FS [11]. Whereas, a study done by Amirsalari S et al., Idro R et al., Sadeghzadeh M et al., and Bidabadi E and Mashouf M found no significant difference in serum ferritin levels between the two groups [12,13,19,20].

In the present study, IDA was a potential risk factor for first FS which is statistically proven. The final observatory outcomes were 66.2% cases were IDA with FS 33.8% cases are with only FS 35.4% controls are with IDA with FI 64.6% controls with FI. [Table/Fig-5] shows a comparison of present study findings with similar previously published studies [7,8,10,11,16]. Vaswani RK et al., from KEM Hospital Mumbai, found that, mean serum ferritin level was significantly low in cases with FS as compared to controls with FI with p=0.003 suggesting iron deficiency could be a potential risk factor for FS in children [8]. In a study conducted by Sharif MR et al., the incidence of iron deficiency anaemia in the febrile convulsion group was higher than in the control group [7]. Fever can lead to worsening the effects of anaemia or iron deficiency on the brain, thereby, causing convulsions. A possible reason for the same might be because of the higher levels and the role of iron in brain metabolism, which leads to less occurrence of febrile

Studies	Age (in months)	Haemoglobin	MCV	MCH	Serum ferritin	Serum iron	TIBC	Serum transferrin
Sharif MR et al., [7] (2015)	25	11.45				70.62	393	235
Jang HN et al., [10] (2019)	27	12	77	26	35	18	326	5.7 %
Naveed-ur-Rehman and Billoo AG [11] (2005)	26	10	70	24	10			
Vaswani RK et al., [8] (2010)	26	9.4	73.4	21.4	31.9			
Daoud AS et al., [16] (2002)	27	11	72	24	30			
Present study	30	8.71	66.57	25.45	36.83	70.97	459.46	254.35

[Table/Fig-5]: Present study compared with other studies [7,8,10,11,16].
MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; TIBC: Total iron binding capacity

The URTI, was the most common aetiology of fever in the present study. A 61.5% of cases and 61.5% of controls have URTI. This is similar to other studies like Sharif MR et al., 64% URTI in cases and 60% URTI in control groups, Calvindoroputro C et al., 90% URTI in cases and 25% URTI controls, Kumar BT et al., 82% in cases and 77.8% in controls, Dauod AS et al., URTI 43% in cases and 45% in controls [7,14-16]. In the present study, 7.7% of cases had a positive family history. The difference was statistically significant, p-value=0.023. Therefore, positive family history can be considered as a risk factor for FS. Similar results were found in studies done by Sharif MR et al., Ghasemi F et al., and Calvindoroputro C et al., [7,9,14]. In the present study, all the three parameters Hb, MCV, and MCH were low in cases as compared to controls and the difference was statistically significant. Screening helps in the early identification of cases. Mean Hb, MCV and MCH were 8.71 gm%, 66.57 fL, and 25.45 pg, respectively in cases.

Naveed-ur-Rehman and Billoo AG; and Kumari PL et al., had results similar to the present study [11,17]. Whereas, Vaswani convulsion in those children [21], whereas, some studies have reported findings contrary to the present study. Hartfield DS et al., reported that, a total of 9% of cases had iron deficiency and 6% had IDA, compared to 5% and 4% of controls, respectively [22]. Bidabadi E and Mashouf M reported that, iron deficiency in the febrile convulsion group (44%) was less than in the control group (48%), but as there was no statistically significant difference, the protective effect of iron deficiency against febrile convulsions could not be ascertained [20].

Limitation(s)

The study was done in a limited number of subjects and study subjects were selected by convenience sampling. The results may vary if, done in a large number of subjects.

CONCLUSION(S)

In the present study, IDA was found to be more among the cases as compared to controls. The results suggest that, IDA may

be the potential risk factor for a febrile seizure. All the laboratory parameters done in cases of IDA were significantly lower than controls suggesting that, children with iron deficiency show a greater propensity to FS. Future studies should be designed to study the iron deficiency status, at the time of first seizure and to determine the occurrence of further seizures after treatment of iron deficiency.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Nov 26, 2022
- Manual Googling: Feb 16, 2023
- iThenticate Software: Mar 10, 2023 (20%)

ETYMOLOGY: Author Origin

EMENDATIONS: 9

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Nov 23, 2022**
Date of Peer Review: **Feb 04, 2023**
Date of Acceptance: **Mar 24, 2023**
Date of Publishing: **Jul 01, 2023**