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IRON DEFICIENCY AS A POTENTIAL RISK FACTOR FOR FEBRILE SEIZURES

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ABSTRACT

Background: Febrile seizures are the most common type of seizure disorder in childhood, affecting approximately 2–5% of children between 6 and 60 months of age. Iron plays an essential role in brain energy metabolism, neurotransmitter synthesis, myelination, and neuronal function. Iron deficiency may alter seizure threshold and has been proposed as a potential risk factor for febrile seizures.

Objective: To evaluate iron deficiency in children with febrile seizures and to assess its association with first and recurrent febrile seizure episodes.

Methods: This prospective observational study was conducted at the Indira Gandhi Institute of Child Health, Bengaluru, over a period of 12 months from January 2019 to December 2019. Sixty children aged 6–60 months diagnosed with febrile seizures according to the American Academy of Pediatrics criteria were enrolled. Thirty children had a first febrile seizure episode and thirty had recurrent febrile seizures. Detailed clinical history, physical examination findings, hematological parameters, peripheral smear findings, and iron profile including serum ferritin, serum iron, total iron-binding capacity (TIBC), and transferrin saturation (TSAT) were recorded and analyzed.

Results: The mean age at presentation was 15.7 months in children with first febrile seizures and 27.9 months in those with recurrent febrile seizures. Serum ferritin, serum iron, and transferrin saturation levels were significantly lower in children with recurrent febrile seizures compared with first febrile seizure cases and controls. Mean serum iron levels were 34.9 µg/dL in first febrile seizures, 26.9 µg/dL in recurrent febrile seizures, and 154.2 µg/dL in controls ($p<0.001$). Similarly, transferrin saturation was significantly lower in recurrent febrile seizures (8.5%) than in first febrile seizures (9.7%) and controls (45.63%) ($p<0.001$). Hematological indices suggestive of iron deficiency, including MCH and MCHC, were also significantly reduced among children with febrile seizures.

Conclusion: Iron deficiency appears to be an important and potentially modifiable risk factor for febrile seizures, particularly recurrent febrile seizures. Routine evaluation of iron status in children presenting with febrile seizures may facilitate early identification and treatment of iron deficiency, potentially reducing the risk of recurrence.

KEYWORDS: Febrile seizures; Iron deficiency; Serum ferritin; Serum iron; Transferrin saturation; Recurrent febrile seizures.

INTRODUCTION

Febrile seizures are seizures that occurs between the age of 6months to 60 months with a temperature of 38 degree C or higher, that are not because of central nervous system infection or any metabolic imbalance, and that occurs in the absence of a
history of prior afebrile seizures [1].

A simple febrile seizure is a primary generalized, usually tonic-clonic, seizures associated with fever, lasting for a maximum of 15 min, and not recurrent within a 24-hr period [1].

A complex febrile seizure is more prolonged (>15min), focal and/or reoccurs within 24 hours [1]

Febrile status epilepticus is a febrile seizure lasting longer than 30 minutes Simple febrile seizure plus is the recurrent febrile seizure within 24 hours [1]

A number of reports suggest that iron-deficiency anemia, and even iron deficiency without significant anemia, affects attention span, alertness, and learning of both infants and adolescents.

Iron deficiency although a common entity is rarely considered as a primary etiology in frequently observed pediatric neurological disorders. There seems to be a flurry of studies recently relating iron deficiency to a variety of neurological problems. While the most obvious consequence of iron deficiency is anemia, at the cellular level, iron is involved in a variety of process and its deficiency virtually affects every organ system including the central nervous system. Iron and its role in the central and peripheral nervous system functioning has been investigated in animal models and in clinical human studies. Deficiency of iron in children has been implicated in developmental abnormalities, ischemic stroke, venous thrombosis, breath-holding spells and other neurological abnormalities. The most intriguing recent description relates to the association between febrile seizures and iron deficiency. Though the pathophysiology remains speculative iron is involved in the metabolism of several neurotransmitters.

In addition, monoamine oxidase and aldehyde oxidase are decreased in iron deficiency, which has been correlated with the neurological abnormalities. (2,3)

METHODS

The present study was a prospective observational study, conducted over a period of 12 months at Indira Gandhi Institute of Child Health, Bengaluru from January 2019 to December 2019.

Statistical Analysis

One Way ANOVA Power Analysis

Numeric Results

Power	n	k	N	Alpha	Beta	SD of mean	SD	Effect size
0.91180	24.00	3	72	0.05000	0.08820	12.811	29.300	0.4372
0.90247	30.00	3	90	0.05000	0.09753	12.811	33.440	0.3831
0.90273	77.00	3	231	0.05000	0.09727	12.811	54.130	0.2367

Inclusion criteria:

As per AAP guidelines of febrile seizures, children between the age group of 6 months to 60months fulfilling the diagnostic criteria formed the study group.

Exclusion criteria:

1. Children with afebrile seizures
2. CNS infection
3. Neurodevelopmental disorder
4. On iron supplements (longer than 1 month)

The study was approved by the institutional ethical committee.

Informed written consent was obtained from parents of each patient before enrolment.

A total number of 60 children between the age group of 6 months to 60 months presenting with first and subsequent episode of febrile seizures formed the study group.

Detailed clinical history including demographic data, fever – type and duration;

convulsions – semiology, frequency and duration; family history of convulsions, general physical examination anthropometry and cns examination were recorded in a standard predesigned proforma.

These children were subjected to relevant investigations which included hemogram with peripheral smear, RBC indices and iron profile including TIBC, serum iron, serum ferritin, transferrin saturation levels.

They were treated as per standard treatment protocol.

Children with febrile illness without febrile seizures with age and sex matched were taken as controls and samples of 2cc blood in EDTA tube (purple cap) were collected for hemogram and peripheral smear and 2cc blood were collected in gel tube (yellow cap) for iron profile analysis.

RESULTS

Table 1 Baseline characteristics

Parameters	First episode	Subsequent episode	Controls
AGE (years) <1 1-2 >2	 13 14 03	 02 16 12	 17 6 7
SEX RATIO Male : Female	 1:1.14	 4:1	 1.3:1
Family history FCs Epilepsy	 5 2	 3 3	 2 0
Recurrences <3 >3		 26 4	 -
Socioeconomic history Upper middle Upper lower	 4	 5	 4

Lower	21 5	20 5	22 4
Anaemia	18	22	15

Table 2

Laboratory parameters	First episode	Subsequent seizures	Control	P value
Mean Hb	9.52	9.76	10.4	0.134
Serum Ferritin	39.49	28.3	79.9	0.015
TIBC	341	346	337	0.33
Serum iron	34.9	26.9	154.2	<0.001
TSAT	9.7	8.5	45.63	<0.001
PCV	31.95	30.74	31.5	0.875
MCV	73.38	71.90	75.5	0.171
MCH	22.49	22.40	25.3	0.032
MCHC	30.37	30.78	32.29	<0.001

DISCUSSION

There are many studies with the association of iron status and febrile seizures with conflicting results. Therefore, in this study iron status of first episode of febrile seizure and subsequent episodes of febrile seizures were studied. In this study a total number of 60 cases of febrile seizure children were included in the study. Out of which 30 children had first episode of febrile convulsions 30 had subsequent episode of febrile convulsions

In FFS the commonest age group of presentation was <24 months -90%.

In SFS group, the commonest age group of presentation was 13-60 months- 93.3%. Incidence of subsequent episodes of febrile seizures was low in <12 months.

The present study was in par with the studies by Krishnan R et al[4] that showed low incidence of subsequent febrile seizures in 6m-12months and 100% incidence in 13-60 months of age group.

In children less than 5 years the myelination is still developing, hence the lower seizure threshold making them susceptible for febrile seizures.

Sex distribution in present study,

Presenting with FFS the sex ratio was 1.1:1 and in SFS was 4:1 and in controls 1.3:1. Thus a male preponderance was seen in population presenting with subsequent episode of febrile seizures in contrast with the study conducted by Rekha Krishnan et al showed male preponderance in first episode of febrile seizures and female preponderance in subsequent episode of febrile seizures.

In our study population, 8(13.3%) out of 60 cases were having a positive correlation with family history febrile convulsions and 3(10%) of subsequent cases had positive correlation..

Iron status in the study

In present study, mean S.Ferritin levels was 33.8(26.4) similar to the studies done by Tajesh Malla et al, Duod et al, and Soheila Zareifar et al.(5,6,7)

The mean Serum ferritin levels was low (28.3) in subsequent febrile seizures as compared with first episode of febrile seizures (39.49) and controls , thus being a potential risk factor for febrile seizures.

However it was statistically insignificant probable as the S. ferrtin being an acute phase reactant in the setting of fever.

The mean Serum iron levels in cases were 34.9 and 26.9 in first and subsequent episodes of febrile seizures but in controls was 154.2 which was statistically significant with p value of <0.001.which was in par with study conducted by Rekha krishna et al which was 71.18 and 57.27 in first and subsequent episodes of febrile seizures respectively.

The mean value of TSAT were 9.7 and 8.5 in first and subsequent episode of febrile seizures however in controls it was 45.63 which was statistically significant with p value <0.001.

Table 3

	Present study Mean (SD)	Rekha krishna et al Mean (SD)	Mean (SD)

S.Ferritin CASES FFS SFS S.Iron CASES FFS SFS TSAT CASES FFS SFS TIBC CASES FFS SFS	 33.8 39.49 28.3 30.9 34.9 26.9 (p-<0-001) 9.1 9.7 8.5 (p-<0-001) 343.5 341 346	 78.57 68.66 71.18 57.27 21.71 14.94 357.77 410.52	

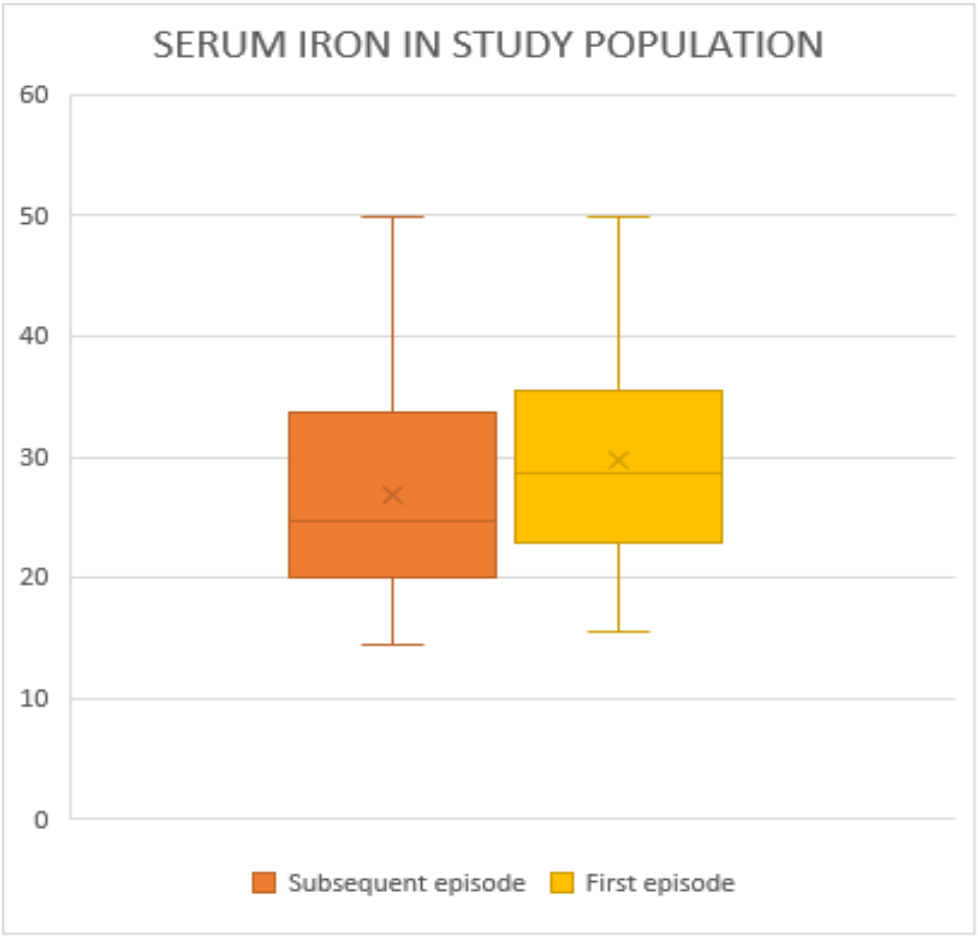

Fig no: 1

Fig no: 2

Haematological parameters of the study

There were low levels of MCV, MCH, MCHC of first and subsequent episode of febrile seizures. In the study done by Krishnan etal there was significant correlation of MCH. Peripheral smear showing microcytic hypochromic RBC's suggestive of iron deficiency anemia was found in 36(60%) of cases similar to study done by Bharath et al.

CONCLUSION

Iron deficiency was significantly associated with febrile seizures, particularly recurrent febrile seizures, in children aged 6–60 months. Children with recurrent febrile seizures demonstrated lower serum iron and transferrin saturation levels compared with those experiencing a first febrile seizure and healthy controls. Hematological indices indicative of iron deficiency were also more prevalent among affected children. These findings support the hypothesis that iron deficiency may contribute to lowering the seizure threshold in susceptible children. Routine screening for iron deficiency should be considered in children presenting with febrile seizures, especially those with recurrent episodes. Early diagnosis and appropriate iron supplementation may represent a simple and cost-effective strategy to reduce recurrence and improve neurological outcomes. Further multicenter studies with larger sample sizes are warranted to confirm these findings and evaluate the long-term impact of iron therapy on seizure recurrence.

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Ethics Approval and Consent to Participate

The study was approved by the Institutional Ethics Committee of the Indira Gandhi Institute of Child Health, Bengaluru. Written informed consent was obtained from the parents or legal guardians of all enrolled children prior to participation in the study.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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