

**TO EVALUATE THE RELATIONSHIP BETWEEN IRON DEFICIENCY AND FEBRILE SEIZURES**

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**ABSTRACT****BACKGROUND**

Febrile seizures [FS] are convulsions brought on by a fever in infants or small children. Most common age group affected is between 6 months to 60 months. Studies showed that there is a variable association between febrile seizures and iron deficiency anaemia [IDA] in children. This study compared various haematological indices with febrile seizures to detect iron deficiency anaemia among children.

**METHODS**

This is a comparative observational study. 200 children were recruited, among which 100 children aged between 6 months and 6 years, with febrile seizures, were taken as cases, and another 100 children in similar age group, only with fever and without seizures, were taken as controls. Various blood parameters were analysed between these two groups to detect iron deficiency.

**RESULTS**

Haematological parameters like Hb % and serum ferritin were significantly lower, and RDW was significantly increased in cases as compared to controls. This signifies a definite correlation between iron deficiency and febrile seizures.

**CONCLUSIONS**

There is a strong association between children with FS and iron deficiency anaemia. This suggests that IDA maybe be a risk factor for FS and all children with FS require iron indices and iron supplementation.

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**BACKGROUND**

Febrile seizure [FS] is most common in children with an incidence of 3-4% under the age of 5 years<sup>1</sup>. Most of the studies suggested that iron deficiency is a predisposing factor for febrile seizures.<sup>2</sup> FS episodes are excruciating to the parent and child and can cause psychological trauma to the both. The relationship between fever and convulsion in children had been documented by Hippocrates as early as the 5<sup>th</sup> century B.C, but it was not noticed as a separate clinical entity till 1980.<sup>3,4</sup>

A Febrile Seizure is defined by the International League Against Epilepsy (ILAE) as a "Seizure occurring in childhood after 1 month of age associated with a febrile illness not caused by an infection of central nervous system, without previous neonatal seizure or a previous unprovoked seizure and not meeting the criteria for other acute symptomatic seizure".<sup>5</sup>

Iron deficiency anaemia, as the most common type of anaemia during infancy and childhood, occurs usually

between 9-24 months of age and this period matches with febrile seizure period<sup>6</sup>. Iron deficiency [ID] reduces the metabolism of some neurotransmitters, such as mono amine and aldehyde oxidase <sup>7, 8</sup>. In India as per NFHS-3 70% of under-fives are anaemic.

Many studies have highlighted the correlation between iron deficiency and febrile seizures in children. While some studies have shown that iron deficiency children will increase the seizure threshold, others suggest that iron deficiency will decrease the threshold in children.

Hence this comparative observational study was carried out to evaluate the association, if any, between iron deficiency and febrile seizures.

**METHODS**

Children with febrile seizures as inpatients, in tertiary care centre were enrolled in the study between November 2012 to April 2014. Sample size was taken based on period sample. A total of 200 cases between 6 months and 5 years of age with febrile seizures were enrolled and 200 children were selected who got admitted in the hospital for febrile illness but without seizures. Controls were grouped –cases and controls were matched on age basis [Within 1 month for children younger than 1 year, and 2 months children older than 1 year]. An informed verbal consent was obtained from parents or legal guardians.

Children with history of afebrile seizures, central nervous system infection, developmental delay and neurological deficit were excluded.

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A pre-designed proforma was used to collect relevant information. Blood samples were collected from both cases and controls and estimated for iron deficiency. RBC indices and haemoglobin estimation were detected. Serum ferritin was measured by chemiluminescent method. Statistical data was analysed using SPSS package and Z-test was used for checking the significance with P<0.05 considered as statistically significant. Iron deficiency anaemia was defined as HB <11 gm/dl, MCV< 70 fl, MCH < 23 pg, ferritin < 7, RDW >14.5%. In case of fever a higher cut-off value of ferritin between 7.1- 40 was considered as Iron deficiency anaemia.

**RESULTS**

Among total of 200 children, 100 were cases with febrile seizure and other 100 were controls. The mean age in months was 23.2 among cases and 23.8 among controls. The mean maximum temperature recorded was 101F among cases and 101.12 F among the control group. With regards to family history of febrile seizures, 29 had positive family history among cases and 29 had past history of febrile seizures.

Demographic Details		Febrile Seizures Cases [N=100]	Controls [N=100]
Mean Age [Months]		23.2	23.8
Mean Maximum Temperature [F]		101	101.12
Mean Duration of Fever [Days]		1.65	3.24
Family H/O Febrile Seizures	Yes	29	0
	No	71	100
Febrile Seizures Past H/O	Yes	29	0
	No	71	100
Gender	Male	68	63
	Female	32	37
Nutritional Status	Normal	85	82
	Malnutrition-Grade -1	11	15
	Grade -2	2	3
	Grade -3	2	0
<b>Underlying Cause of Illness</b>			
Acute Dysentery		1	1
Age		29	39
LRI		4	16
URTI		13	20
UTI		6	3

**Table 1**

Two children among the cases group had grade -3 malnutrition. Whereas 11 had grade 1-2 malnutrition among cases and 18 among controls had malnutrition. The disease causing the fever in both groups were Acute gastroenteritis, URTI and LRI.

Blood Indices	Cases [N=100]		Controls [N=100]		p Value
	Mean	SD	Mean	SD	
HB%	10.92	1.27	11.31	1.46	0.032
MCV	73.19	4.60	73.84	3.57	0.120
MCH	22.44	1.74	22.68	1.52	0.506
RDW	14.38	1.09	13.73	0.85	0.000
Ferritin	45.35	26.71	82.13	25.05	0.000

**Table 2**

Haematological parameters including HB, MCV, MCH, RDW and Ferritin were measured among cases and controls. The mean and SD values of Hb%, Ferritin was found to be less among cases when compared to controls. The difference between cases and controls was statistically significant [p<0.05] among the parameters HB%, RDW and Ferritin.

Blood Indices	Cases	%	Controls	%	p Value
HB<11	51	51%	33	33%	0.010
MCV<70	32	32%	17	17%	0.014
MCH<23	62	62%	60	60%	0.772
Ferritin <7	1	1%	0	0%	0.316
Ferritin >7.1-40	43	43%	4	4%	0.000
RDW>14.5%	41	41%	13	13%	0.000

**Table 3**

The total number of children with low levels of haematological parameters are measured separately. Hb% less than 11 gm% in 55% of the cases and only 33% among controls. MCV was less than 70 among 32% cases and 17 % controls. 62% of the cases and 60% of the controls had MCH less than 23. Serum ferritin was less than 7 in only one case and less than 40 among 43 cases and 4 controls. RDW >14.5% among 41 % cases and 13 % controls. The differences between cases and controls was statistically significant among Hb%, MCV, Ferritin between 7.1-40 and RDW values.

**DISCUSSION**

In this study, 68% of the children among the FS group were males and almost similar 63% of the children among controls were males. The mean age in months was 23.2 months among cases and 23.8 months among controls. Acute Gastroenteritis was found to be the most common underlying cause among cases and controls. The mean duration of fever was 1.65 days among cases and 3.24 days in controls, which is significantly less. The obvious explanation for this is that unless there are complications like seizures, children with fever are usually evaluated and treated on an outpatient basis. Increase in brain temperature may alter neuronal function and ion channels.<sup>9,10</sup> This might have influenced neuronal firing and probability of generating massive synchronised neuronal activity i.e. seizures. Fever, in addition to increase in brain temperature, also leads to inflammatory process which includes secretion of cytokines in their peripheral brain.<sup>11,12</sup>

In the present study family history of febrile seizures were noticed among 29% of the cases. Daoud AS et al<sup>13</sup> found positive family history of seizures in 18% of his patients and Kumari PL et al<sup>14</sup> noticed that 26% of his patients and positive family history. Family history of febrile seizures is associated with an increased risk of recurrence.<sup>15,16</sup>

Past history of febrile seizures was noticed among 29%. Gautam Shah et al<sup>17</sup> noticed that 26.5% of the children had previous history of febrile seizures which is almost similar to our study.

The mean and SD values of the haematological parameters like HB%, Ferritin values were lower among cases when compared to controls which was statistically significant. Whereas, the RDW value was high among cases compared to controls. Similar results were noticed in a study done by Chandrasekhar R.V et al<sup>18</sup>, which showed that the mean and SD values of the haematological parameters [HB%, Ferritin] among cases was less compared to controls which was statistically significant. Studies done by Piscane et al<sup>19</sup>

showed results similar to our study. Furthermore, few more studies done by Naveedur et al,<sup>20</sup> Daoud et al also stated that iron deficiency anaemia was more common among children with febrile seizures when compared with controls. This signifies a definite correlation between iron deficiency and febrile seizures. Some studies done to find the relationship between iron deficiency and febrile seizure have shown various results. In contrast to our finding, Korbinsky et al<sup>21</sup> from North Dakota [USA], comparatively evaluated by a observational study, which includes 26 cases of febrile seizures and 25 controls. He concluded that children with febrile seizures were less likely to be iron deficient. This may be due to small sample size.

Abnormalities in brain iron metabolism, myelination, and neurotransmitter activity have been demonstrated in iron deficiency. We hypothesize that disruption of normal neurotransmitter activity, caused by iron deficiency predisposes to febrile seizure. Further work using animal models may help to elucidate the exact mechanism.

### CONCLUSIONS

Iron deficiency is a definite risk factor for febrile seizures. Children with febrile seizures are 2.12 times more likely to have iron deficiency than other children of the same age group. A follow up study of patients found to be iron-deficient at the time of a first febrile seizure, to determine the incidence of subsequent febrile seizures after treatment for iron deficiency would be of great interest.

### Recommendations

- All children aged between 6 months to 6 years with febrile seizures should be evaluated for iron deficiency anaemia.
- Children aged between 6 months to 6 years with iron deficiency, and family history of febrile seizures should be supplemented with iron to reduce the incidence of seizures episodes.
- In centres where no facilities are available to evaluate iron deficiency, iron supplementation should be given for all children.

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