

# Relationship of Iron Deficiency Anemia with Simple Febrile Seizure in Children

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## Summary:

**Background and objective:** Febrile Seizure (FS) is the commonest seizure disorder among under 5 children. Iron deficiency is a documented risk factor of FS and as the data about the relationship of iron deficiency with FS among Bangladeshi children is scanty, this study was undertaken to assess the association of Serum Ferritin to simple FS.

**Materials and Methods:** This case control study was conducted at the department of pediatrics of SSMC & Mitford Hospital during 7<sup>th</sup> May 2011 to 6<sup>th</sup> January 2012 on consecutive 120 children aged between five months to six years who fulfilled the inclusion criteria were considered as cases. Similar number of age and sex matched children admitted with fever without seizures were taken as controls. All candidates were gone through CBC with RBC indices and serum ferritin and iron deficiency anemia was diagnosed on the basis of mentioned tests.

**Results:** The results showed that majority of the cases were male (66.7%) and most of them were between 13-24 months

of age (51.7%). Mean duration of convulsion was less than 5 minutes in 70% of the cases. Level of Hb was low in both the cases and controls but the other RBC indices for anemia like MCV, MCH, MCHC and serum ferritin were significantly lower among the febrile seizures group in comparison to controls. The chi-square test is indicated as a significant difference between two groups and odds ratio is 6.0 which signifies that febrile seizure group were 6.0 times more likely to develop iron deficiency anemia compared to control group.

**Conclusion:** The findings suggest that children with febrile seizure have association with iron deficiency anemia (which is evident by microcytic hypochromic anemia and low serum ferritin level). This means low serum ferritin and presence of anemia can serve as a risk factor for febrile seizure in children.

**Key words:** Fever, simple febrile seizure, iron deficiency anemia.

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## Introduction:

Febrile Seizures (FS) are the commonest seizures in children and one of the most common cause of pediatric emergency, in 3-4% of children under the age of 5 years<sup>1</sup>. Global incidence of febrile seizure is 4.8/1000person/year<sup>2</sup>. The incidence is higher in developing countries because of their increased incidence of infection<sup>2</sup>. Owing to their association with epilepsy in future in some cases, various studies have attempted to identify the risk factors associated with FS like family history of FS or epilepsy, perinatal factors like maternal smoking & alcohol consumption<sup>3</sup>. Among several other risk factors iron deficiency has been found as a provoking factor of FS in different studies<sup>4,5</sup>. In iron deficiency, there is deficiency of several neurotransmitters like monoamine oxidase, aldehyde oxidase that seems to be responsible for FS<sup>6</sup>. Studies

reported that Low level of serum ferritin may lower the seizure threshold<sup>5</sup> and fever can worsen the negative effects of low serum ferritin on the brain and trigger seizure<sup>4</sup>. Several studies were conducted in different parts of the world to see the risk factor of febrile seizure and found a relationship of iron deficiency anemia and febrile seizure. Still in Bangladesh no study was conducted to see the risk factors of FS. Through this study we can explore the relationship of FS and then programs pertaining to prevention of FS can be undertaken to lower the risk of recurrence of FS and its consequences.

## Materials and Methods:

A case control study was conducted at pediatric department of SSMC & Mitford Hospital over one year following approval by ethical review committee of same institution. Sixty consecutive children aged 5 months to 6 years admitted to pediatric ward with simple febrile seizure (Case definition: Simple febrile seizure is defined as a primary generalized, usually tonic-clonic, attack associated with fever, lasting for a maximum 15 minutes

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and not recurrent within a 24 hour period<sup>7</sup>) were enrolled as cases (Age 5 months-6 years of both sexes, single generalized tonic clonic convulsion within 24-48 hours of onset of fever, first and subsequent febrile seizure, no CNS manifestation, with or without positive family history). A reference group of 60 children of age and sex matched having febrile illness without seizures were selected as controls. Samples with age <5 months or >6 years, atypical febrile seizure, unconsciousness, electrolyte imbalance, having developmental anomaly, neurological deficit or with CNS manifestations were excluded from the study. Informed written consents were obtained from parents or care-givers after explaining the objective of this study. After thorough history and physical examination, the following investigations hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and serum ferritin were done and the findings were recorded on a preset questionnaire. In this study iron deficiency anemia was defined as Hb <12 gm/dl, MCV <80 fl, MCH <27pg, MCHC <33gm/dl and S. ferritin <7ng/dl. S. Ferritin was estimated by CMIA (chemiluminescent microparticle immunoassay). Then all collected data were recorded, compiled and were analyzed by SPSS 12.

### Results:

A reference group of 60 children of age and sex matched having febrile illness without seizures were selected as controls. The above table shows that majority of cases and controls were between 13 to 24 months age group and out of 60 cases 24(41.7%) had family history of febrile seizure.

Table shows the severity of anemia among the cases and controls. Grading of anemia was moderate to severe in majority of cases (60%) whereas that was mild among the controls (80%). A significant number of cases had low serum ferritin level in comparison to controls and the mean difference of blood MCV ( $p < 0.001$ ), MCH ( $p < 0.001$ ) and MCHC ( $p < 0.001$ ) which are statistically significant i.e. all the parameters (except Hb level) related to RBC indicating anemia were significantly lower among the cases in comparison to controls.

This table shows low serum ferritin has association with the occurrence of simple febrile seizure (odds ratio 1.95%CI 14.96-173.5). This table shows that the febrile seizures was 6 times vulnerable to develop in moderate to severe anaemia (CI = 2.47-14.85). It also shows an association with serum ferritin level among cases and control. It has been found that cases having serum ferritin

**Table-I**

Demographic characteristics	<i>Demographic characteristics</i>				P value
	Cases (No=60)		Controls (No=60)		
	No	%	No	%	
Age (in months)					
< 12	24	40.0	23	38.3	0.07 <sup>ns</sup>
13-24	31	51.7	24	40.0	
> 25	5	8.3	13	21.7	
Sex					
Male	40	66.67	38	63.33	0.7 <sup>ns</sup>
Female	20	33.33	22	35.67	
Family history of febrile seizure					
Yes	25	41.7			
Sib	4	6.7			
Parents	10	16.7			
Others	11	18.3			
Non	35	58.3			

ns = Not significant; P value reached from unpaired t-test

**Table-II**

<i>Clinical profile and investigation results</i>			
Anaemia	Cases No (%)	Controls No (%)	P value
Present	56 (93.3)	59 (98.3)	0.17 <sup>NS</sup>
Absent	4 (6.7)	1 (1.7)	
Severity of anemia			
Severe (3-6 gm/dl)	07 (11.7)	01	<0.001 <sup>S</sup>
Moderate (6-9 gm/dl)	29 (48.3)	12 (20.0)	
Mild (9-12 gm/dl)	24 (40.0)	47 (80.0)	
Investigation			
Hb (g/dl)	10.32±8.7	9.92±1.18	0.72 <sup>NS</sup>
MCV (fl)	69.39±5.90	77.38±3.70	<0.001 <sup>S</sup>
MCH (pg)	23.74±2.65	29.0±2.49	<0.001 <sup>S</sup>
MCHC (gm/dl)	28.69±3.66	31.35±3.41	<0.001 <sup>S</sup>
Serum Ferritin (ng/ml)			
<7	52 (86.7%)	7 (11.7%)	<0.001 <sup>S</sup>
>7	8 (13.3%)	53 (83.3%)	

NS=nonsignificant, s = significant; P value reached from chi-square test

**Table-III**

<i>Association of and anemia and serum ferritin between febrile seizure and fever without seizure (n=120)</i>					
Determinants	Febrile seizure	Fever without seizure	Odds ratio	95% CI	P value
Anemia					
Moderate to severe	36	12	6.00	2.47-14.85	<0.001 <sup>s</sup>
Mild	24	48			
Serum ferritin					
<7ng/ml	52	7	49.21	14.96-173.5	<0.001 <sup>s</sup>
>7ng/ml	8	53			

s = significant; P value reached from chi-square test

level < 7 ng/ml has 49 times more chance of having febrile seizure than control (CI = 14.96-173.5).

#### **Discussion:**

This hospital based case-control study was carried out to see the iron status of under 5 children with febrile seizure children aged 5 to 60 months taking age and sex matched non febrile seizure peers as control.

The relevant findings of this study were discussed and compared with those of previously and recent published studies.

In our study the mean haemoglobin concentration of the cases and that of controls were low and the difference was nonsignificant (p=0.72). Vaswani et al<sup>6</sup> showed both cases & controls group had anemia (defined by Hb less than 11 gm/dl) but did not mention the severity of anemia in both groups. Daoud et al<sup>8</sup> also showed low Hb level in both groups but proportion were higher among cases.

In the present study the mean MCH, MCHC, MCV and serum ferritin (ng/ml) were significantly (p<0.05) less in children having febrile seizure than those in controls.

Daoud et al<sup>8</sup> mentioned that Hb, MCV and MCH levels were also lower in the cases than controls. However, the differences were not statistically significant in their study. Hartfield et al<sup>9</sup> found the Hb level was almost similar between two groups, MCH was significantly low in case group. Modaresi<sup>10</sup> et al, Gancer et al<sup>11</sup> and Mall et al<sup>12</sup> also noticed the mean Hb, HCT, MCH, serum iron level significantly lower in case group than in control group.

In this study majority cases had low serum ferritin level (<7 ng/ml) comprising 86.7% on the other hand, in control group serum ferritin level >7 ng/ml in the most of children (88.3%). So, the difference is statistically significant i.e significant number of the cases had low serum ferritin level in comparison to controls. Daoud et al.<sup>8</sup> mentioned that mean ferritin level were lower in children who had a seizure with fever, suggesting a possible risk factors in febrile seizures. They have shown that the mean plasma ferritin level was significantly lower ( $p < 0.0001$ ) in the first febrile seizure group compared to the reference group. Vaswani et al.<sup>6</sup> observed significantly low serum ferritin value in case than that of control. However Yousefichaijan et al<sup>13</sup>

observed that only 22.5% child with febrile seizure had iron deficiency anaemia and 34% of control group exhibit anaemia ( $p < 0.001$ ). Febrile seizure group had significantly high RBC indices (MCV, MCH, MCHC) compared to control group.

In this current study we found low serum ferritin has association with the occurrence of simple febrile seizure (odds ratio 1; 95% CI 14.96-173.5). Saeed et al<sup>14</sup> showed positive association of Iron Deficiency Anemia with febrile seizure. In their study mean serum ferritin level in case 6.9  $\mu\text{g/L}$  & in control 7.9  $\mu\text{g/L}$ . Nasehi et al<sup>15</sup> observed odds ratio of Iron Deficiency Anaemia in children with febrile seizure in comparison to the control group was 1.27 (CI 95%-1.03- 1.56). Here ferritin level was not significant between the two groups ( $p = 0.08$ ) but the iron level in two groups was significant ( $p = 0.00$ ). Habibian<sup>16</sup> et al, Ghasemi<sup>17</sup> et al and Srinivasa<sup>18</sup> et al also found odds ratio 1.52, 1.89 and 1.84 respectively for iron deficiency anemia in patient with febrile seizure compared to febrile children without seizure. The main limitation was the potential confounding effect of serum ferritin as an acute phase reactant which can interfere with the influence of iron status on febrile seizures. This limitation could be overcome by predicting the time when

serum ferritin level returned to its baseline value after acute phase reaction and by estimation of Total Iron Binding Capacity.

### Conclusion:

It is concluded that the febrile seizures are associated with low MCH and serum ferritin level. To ascertain the significance of this finding and its role in the development of febrile seizures large and multicenter studies are required.

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