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# Comparison of Iron Status Among Childrens with Simple Febrile Seizure and Control – A Hospital Based Observational Study in Eastern India

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## ABSTRACT

**Introduction:** Correlation between simple febrile seizures (FS) and iron deficiency anaemia (IDA) is not conclusive due to diversified results reported in numerous previous studies. Low serum ferritin levels have been shown to reduce the seizure threshold. Simple FS and IDA are particularly common in children aged 6 to 60 months. In India, around 60% of children's have nutritional anaemia predominantly due to iron.

**Objectives:** To find out any correlation between Febrile Seizure and Iron Deficiency Anemia.

**Method:** In this hospital-based observational study, we evaluated 90 children aged 6 to 60 months in two equal groups taking fever with seizures as cases and fever without seizures as controls. The study was conducted in the Department of Pediatrics', IMS & SUM Hospital Bhubaneswar from January to June 2019. Detection of IDA was based on complete blood count, serum iron, total iron-binding capacity and serum transferrin level, which were done in all participants as a part of the routine test for the evaluation of microcytic hypochromic anaemia.

**Results:** IDA was found in 64.4% among fever with the seizure group as compared to 28.8% in the group having a fever without a seizure. Boys outnumbered girls in the febrile seizure group. Upper respiratory tract infection mostly of viral aetiology was the most common cause of fever in both cases (51.1%) and controls (46.5%). We found 64.4% of children in the cases group had IDA as compared to 35.6% in the control group and this was statistically significant (adjusted odds ratio 4.4615, 95% CI 1.8363-10.8402, p=0.001). The Chi-Square test indicated a significant association between IDA and FS (p =0.0007). p <0.05 was considered significant.

**Conclusions:** In this study, there was a statistically significant correlation between IDA and simple FS.

**Keywords:** Seizure, Anaemia, Iron deficiency, Fever, IDA, Hypoglycaemia

## INTRODUCTION

Febrile seizures (FS) commonly occur in children aged 6-60 months, with an episode of fever more than 100.4°F, without any evidence of central nervous system (CNS) aetiology or metabolic abnormality, and that occurs without a previous history of unprovoked seizure.<sup>1,2</sup> S is considered to be a "syndrome" since it has several similar features in many of the affected children (a) FS typically occurs in a restricted age range; (b) Major proportion of children with FS depicts normal neurological outcome after the episode and (c) FS are not associated with developmental and structural anomalies

lies in the brain, although susceptibility to febrile seizures is mostly enhanced by the existence of such pathology.<sup>3,4</sup> Simple febrile seizures are generalised tonic-clonic seizures (GTCS) that persist less than 10-15 minutes and occurs once in 24 hours of fever in a child with normal neurological status. Approximately eighty per cent of fever-related seizures in this age group are simple FS.<sup>4</sup>

Iron deficiency is a very common micronutrient deficiency worldwide.<sup>5</sup> According to the World Health Organisation (WHO) iron deficiency contributes to a major proportion of anaemia and is preventable by proper nutritional supplementation.<sup>6</sup> In India iron deficiency anaemia (IDA) is the most

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common cause of nutritional anaemia (60%). Iron deficiency has been known to alter the threshold of seizures among children.<sup>7,8</sup> Research done by Daoud et al. (2002), Hartfield et al. (2009), Momen et al. (2010) and Tae N, et al. (2014) have documented that children with iron deficiency states have a higher incidence of FS than the control group.<sup>9,10,11,12</sup> In contrast, studies by Kobrinsky et al. (1995) and Talebian et al. (2006) showed that reduced iron level in the body has a beneficial role against simple FS by altering the level of seizure threshold.<sup>13,14</sup>

## Objectives

- To study the haematological parameters reflecting IDA among children aged 6 months to 5 years presenting with FS.
- To compare the status of iron deficiency among children presenting with febrile seizures with a control group.

## Method

A hospital-based observational study was conducted in the paediatric department of the Institute of Medical Science & SUM hospital Bhubaneswar. The study period was 6 months from January to June 2019. A total of 90 children between 6-60 months of age was taken in two groups of 45 each taking febrile seizure as the study group and fever without seizure as the control group. The study population consisted of children between six to sixty months with normal developmental milestones admitted to our hospital for FS. The control group consisted of age-matched hospitalised children selected randomly with acute febrile illness (<7 days) for various causes like acute gastroenteritis, acute otitis media, acute respiratory tract infections without any evidence of seizures. In our study, both groups were taken in a one to one ratio. Study participants in both groups were similar regarding age, sex, temperature, developmental index and history of iron supplementations. Children among both groups were either exclusively breast-fed or given formula feeding until they were 6 months old and received solid complementary feeding without any significant dietary difference regarding nutritional iron intake. Basic haematological investigations were done on the day of hospitalisation. Required haematological investigations regarding blood parameters and iron profiles like blood cell count, red cell indices, serum iron profile, level of serum ferritin and iron-binding capacity were analysed and compared between the two groups. Ethical clearance of the research was obtained from the Ethical Committee of IMS & SUM hospital with Ref. Ethical clearance No. DMR/IMS-SH/SOA/170062. In all cases, the nature of the study was explained in detail in their language to the guardians and the consent for the present study was taken in a printed format.

*Inclusion criteria:* Children aged 6 to 60 months with the first episode of simple FS having no other causes of seizure.

*Exclusion criteria:* Children aged <6 months or > 5years, children with other causes of symptomatic seizures (meningitis, dyselectrolytaemia, hypoglycaemia), presence of chronic illness, known case of haematological disorder, children on haematinics, children with organic neurological abnormality and children who were known cases of seizure disorders.

A structured questionnaire was prepared and information regarding age, sex and history of any seizure among family members was collected from parents. According to WHO guidelines, anaemia is described as a haemoglobin level less than two standard deviations (SD) below the normal level for age, i.e. for ages 6–24 months Hb<10.5 g/dL and for 2–5 years Hb<11.5 g/dL. As per definition anaemia of iron deficiency was described as the level of serum iron below 22µg/dL, serum ferritin below 30 ng/mL.<sup>24,25</sup> Iron deficiency status was diagnosed by the above-mentioned parameters.

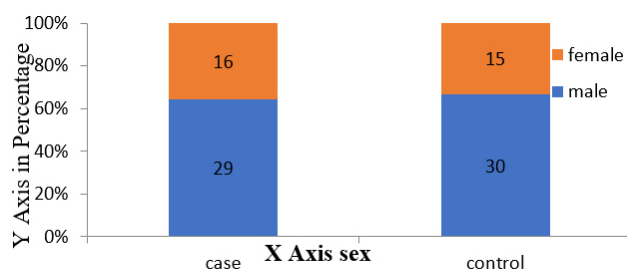
The data were collected and analysed using descriptive statistics (IBM SPSS version 2.0) taking into consideration of percentage, frequency, standard deviation, mean, and Chi-Square.

## RESULTS

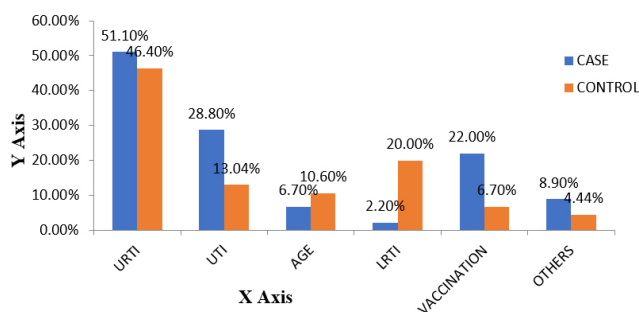
Our study consisted of an almost similar age and sex-matched study population. In our study, 1-2-year-old children were mostly affected. Males outnumbered females. The male to female ratio was found to be 1.8:1 vs 2.1:1 among cases and control groups respectively (Table; 1).

**Table 1: Distribution of cases according to age and sex**

Age	Case		Control	
	Male	Female	Male	Female
6 Month-1 Year	8	4	7	4
1 Year -2 Year	16	8	15	6
2 Year – 5 Year	5	4	8	5
Male : Female	1.81	1	2	1



**Figure 1:** Distribution of cases according to sex.



**Figure 2:** Cases of Fever among cases and controls. URTI; Upper respiratory Tract Infection UTI; urinary Tract Infection Age; Acute Gastro Enteritis LRTI; Lower respiratory Tract Infection

As shown in Figure 2, the most common cause of fever in the study group (51.1%) as well as the control group (46.4%) was found to be upper respiratory tract infection.

Table 2 shows the temperature on admission among cases and controls. In our study, admission temperature and subsequent temperature recording were measured from axillary temperature using a digital thermometer

**Table 2: Temperature on admission among cases and controls**

Temperature	Cases	Controls
98-99.9 °F	24%	31%
100-101.9 °F	39%	34%
102-103.9 °F	29%	30%
>104 °F	08%	05%
Total	100%	100%

In this study, we did not found any significant difference in the amplitude of temperature among cases and controls. The mean duration of fever was 3.7 ± 1.9 days in cases and 4.0 ± 2.0 days in controls. This was not statistically significant. Table 3 shows the iron status among cases and controls.

**Table 3: Iron status among cases and controls**

Iron status	Cases n (%)	Controls n (%)	p-value* Adjusted Odds ratio (95% CI)
Iron deficiency anaemia	29 (64.4)	13 (28.8)	0.0010 4.4615[1.8363 to 10.8402]
No iron deficiency anaemia	16 (35.6)	32 (71.2)	

In our study as shown in Table 3, 64.4% of Cases had IDA compared to 28.8% Controls and this is statistically significant. Table 4 shows the distribution of serum iron among children with FS.

**Table 4: Distribution of serum iron level in children having febrile seizures**

Serum iron	Number of patients (%)	p-value
Low	33 (73.3)	<0.005
Normal	12 (26.7)	
Total	45 (100.0)	

In our study low serum, iron levels occurred in 73.3% of children with FS compared to 26.7% of children with normal iron status which is statistically significant (p<0.005). Table 5 compares important parameters for iron status in children with simple FS (Cases) and Controls.

**Table 5: Comparison of important parameters for iron status in Cases and Controls**

Indices	Cases (n=45)		Controls (n=45)		p-value*
	Mean	SD	Mean	SD	
Haemoglobin (g/dL)	10.27	0.30	12.16	0.33	0.07
Haematocrit (%)	36.96	2.09	35.31	2.12	0.045
Mean corpuscular volume (fl)	76.34	3.27	79.41	3.99	0.038
Mean corpuscular haemoglobin concentration (g/dL)	32.25	0.89	34.92	1.89	0.09
Mean corpuscular haemoglobin (pg/cell)	25.43	1.73	27.55	2.37	0.04
Total iron binding capacity	326	2.34	289	2.46	0.06
Serum ferritin (ng/mL)	33.78	18.33	61.71	43.41	<0.001
Red cell distribution width (%)	16.15	0.71	14.24	1.37	0.078
Platelet count	212.97	79.34	278.4327	126.23	0.097

\*Analysis using student t-test

As shown in Table 5, the serum ferritin level is significantly lower in the FS group compared to the control group.

## DISCUSSION

In the present study, the age and sex distribution of both cases and controls were similar avoiding age and gender bias. The common age of presentation in our study among cases and controls was 1-2 years of age. Pisacane A et al.<sup>5</sup> had a mean age of 5.6 months, Ali A, et al.<sup>16</sup> a mean age of 18.8 months, Saeed T, et al.<sup>17</sup> a mean age of 17.4 months, Waheed N, et al.<sup>18</sup> a mean age of 23.4 months, Srinivasa S, et al.<sup>19</sup> a mean

age of 24 months and Thomas S, et al.<sup>20</sup> a mean age of 36 months. The comparison with previous studies suggests that the occurrence of FS ranges from 15 to 30 months, which is the common age of presentation of IDA among children in a developing country like India.

In this study, male to female ratio among cases was 1.8:1 as compared to 2:1 among controls. In previous studies,<sup>21</sup> FS was found to be more common in boys, which agrees with the findings of our research (47.9% girls and 52.1% boys). However, a study by Waheed N, et al. in Serbia found no gender difference in FS. The male preponderance of our study could not establish the biological or genetic basis of FS in males, as both cases and controls showed a predominance of males. As ours is a hospital-based observational study male predominance in FS is probably due to more number male children being admitted with simple FS.

In our study, the majority of both cases and controls had temperatures between 100°F-104°F. This lack of temperature difference among cases and controls avoids confusion regarding the amplitude of fever with episodes of seizure. Thus it was observed that amplitude of temperature does not directly correlate with FS being more common during the rising phase of body temperature but also occurring during the fall of temperature in a few cases. However, Millar JS<sup>22</sup> and Berg AT<sup>23</sup> observed that the amplitude of temperature has a strong association with FS and that at most times it occurred in the initial part of the illness. Accordingly, in another case-control study, risk factors for developing the first episode of FS have been investigated; the amplitude of the temperature as a characteristic of the acute illness was found to be an independent risk factor.<sup>23,24</sup> These studies suggest that a temperature threshold exists and that a higher risk of FS is associated with a lower threshold of fever. However, our study results do not support this hypothesis. In our study, iron deficiency as a risk factor for FS does not show much difference between study and control groups in terms of sex, age group and amplitude of temperature.

Among the aetiology of fever in both cases and controls were upper respiratory tract infection, urinary tract infection, acute gastroenteritis and lower respiratory tract infection as major contributors. The commonest aetiology of febrile illness in both cases and controls was upper respiratory tract infection, 51.1% and 46.4% respectively, followed by urinary tract infection. Similar findings were reported in various studies which suggest that respiratory infection, gastroenteritis and urinary infections were the common causes of fever.<sup>25,26</sup> In our study we observed that IDA was more common in the group with seizures. The study by Pisacane A, et al.<sup>15</sup> showed similar results. The study by Vaswani RK, et al.<sup>27</sup> found that 68% of FS were iron deficient as compared to 30% of the acute febrile illness in the normal group. A study by Ur-Rahman N, et al.<sup>28</sup> on 30 children each in both simple FS group

and febrile illness group without seizure indicated that IDA was common in the FS group.

Fever worsens the iron status in our body, which affects our brain nutrient metabolism leading to seizures. Further, chronic febrile illness leads to anaemia and patients with more severe symptoms have more convulsions. In many of the acute febrile episodes, there will be altered iron stores and serum ferritin may show false high values as a marker of inflammation. Most of the children have a loss of appetite during illness leading to nutritional deprivation and this can create a transitional iron-deficient condition. However, as we know, FS usually occurs at the onset of febrile disease, long before the development of anaemia and iron-deficient state sets in the course of the disease process. This indicates that iron deficiency is not a consequence of the disease but rather that IDA may provoke simple FS.<sup>28</sup> A study done in Thailand found that the rate of thalassaemic children with simple FS was 4 times lesser than the general child population. It was concluded from that study that it might be due to the higher iron load in the body in thalassaemic children and the role of brain iron metabolism leading to less occurrence of FS.<sup>29</sup> Studies conducted by Hartfield DS, et al.<sup>11</sup> and Kobrinsky NL, et al.<sup>14</sup> pointed out that state of iron deficiency showed a protective role against simple FS, which contradicts our study. Studies by Bidabadi E, et al.<sup>21</sup> and Amirsalari S, et al.<sup>30</sup> concluded that the iron-deficient status among cases (44%) was less than in the control group (48%), but this was not statistically significant so that the protecting role of iron-deficient conditions for combating FS could not be established.

In our study, we observed that the incidence of Iron deficiency anaemia (IDA) in children having simple FS was more than in the control group. Our results infer that anaemia and low serum iron levels act as a precipitating factor for simple FS among children 6 to 60 months of age. Thus, IDA must be considered while describing the risk factors for FS. Children with the first episode of simple FS and have other risk factors for FS must be monitored for IDA and treated accordingly. As this is a hospital-based observational study, further large scale multicentric-observation studies are needed to confirm the significant correlation between IDA and simple FS in children.

## CONCLUSION

- The correlations between Iron deficiency anaemia with simple febrile seizure demand intervention to minimise the disease burden due to iron deficiency anaemia.
- Awareness, improved feeding practices and active intervention by the implementation of national health programs (e.g.-NIPI) will aid to prevent both Iron deficiency anaemia and febrile seizure.

- Children with febrile seizures and having other risks factors must be monitored carefully for IDA and treated accordingly to prevent further occurrence of the disease.

**Limitation of the study-** As this is a hospital-based observational original research study needs further large scale multicentric- observation to find out the significant co-relation between IDA and simple febrile seizure in children.

Conflict of Interest

There are no conflicts of interest in the present study.

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