

Association Between Iron Deficiency Anemia And Febrile Seizure In Children-A Case-Control Study

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Abstract:

Background: Febrile convulsion (FC) is a common cause of seizure in young children, with an excellent prognosis. In addition to genetic predisposition, FCs are generally thought to be induced by elemental changes such as iron deficiency. Regarding the high prevalence of febrile seizure and iron deficiency anemia in children, the aim was to investigate the role of iron deficiency anemia in FC patients. **Objective:** To find out the Association between Iron Deficiency Anemia and Febrile Seizure in Children. **Methods:** This was a case-control study conducted in the Dept. Of Prediatice, Shaheed Tajuddin Ahmad Medical College Hospital, Gazipur, Bangladesh between January 2019-December 2019. 60 consecutive children who fulfilled the inclusion criteria were considered in this study. All children were aged between 6-60 months. The groups were matched in age and gender and use of supplemental iron. Laboratory tests consisted of Complete Blood Count (CBC). Serum iron, plasma ferritin and Total Iron Binding Capacity (TIBC) analyses were done in each patient. **Results:** During the study, grading of anemia was moderate to severe in majority of cases (60%). Most of the patients belong to <7 ng/ml group, 88%. Low serum ferritin has association with the occurrence of simple febrile Convulsion, also, febrile Convulsion was 6 times vulnerable to develop in moderate to severe anemia. **Conclusion:** The results of this study suggest that the risk of febrile seizure occurrence in anemic children is less common as compared to non-anemic ones.

Keywords—FC, fever, childhood, Complete Blood Count (CBC).

I Introduction

Febrile seizures are the most common convulsive disorders in children aged between 6 months and 5 years, with a prevalence of 2-14% in different societies.¹⁻⁴ Febrile seizures are a relatively common childhood condition referring to a child having a seizure when he/she has a high temperature of 38.5°C or above by rectal measurement,¹⁻⁴ with no previous history of afebrile seizures or without acute systemic metabolic abnormality that may produce convulsions or nervous system infection.^{1,2} The exact cause of febrile convulsion is unknown, but genetic and environmental factors have influence on its occurrence.⁵ Age for peak incidence of febrile seizure is 14 to 18 months, which overlaps with that of iron deficiency anemia which is from 6 to 24 months.⁶ The World Health Organization estimates that anemia, largely caused by iron deficiency, affected between 500 million and two billion people worldwide.^{6,7} Iron deficiency is the most common nutritional deficiency and hematological disease of infancy and childhood,⁸ especially between 6 and 24 months of age.^{9,10} Iron deficiency (IDA) is the most common nutritional deficiency in the world. Iron is an important micronutrient which is used by roughly all the cells in the human body. It is well understood that iron is a cofactor for several enzymes in the body and has a role in the neurotransmitters production and function, hormonal function and DNA duplication.⁹ There are no accurate statistics of prevalence of iron deficiency anemia in Iranian children, however it is estimated to be about 20%.^{11,12} Supplemental iron in the form of ferrous sulfate is recommended for all full term infants, from 6 months to 2 years old according to Iran's regulations. Iron is a nutritional element not only needed for the synthesis of hemoglobin, but also essential for enzymes involved in neurochemical reactions,^{8,13} such as myelin formation,¹⁴ brain energy

metabolism,¹⁵ some neurotransmitters and enzymes metabolism such as monoaminoxidase and aldehydoxidase.^{6, 16, 17} Neurological symptoms like poor attention span, learning deficits, weak memory, delayed motor development and behavioral disturbance caused by iron deficiency are well-known.⁶ Despite these facts, some studies show that antipyretics do not affect prevention of seizures caused by fever,^{18,19} so other variables that affect this process have special circumstances and considering that fever can intensify the anemia symptoms by increasing body metabolism,¹⁷ there is a need to explore relation between febrile seizures and iron deficiency anemia. Many studies have investigated the etiology and natural history of febrile seizures and evaluated various management strategies, but very little information is available about iron deficiency as a risk factor. Previous studies examining the relationship between iron deficiency anemia and febrile convulsions have been conflicting.^{17,20-22} Some of them concluded that iron deprivation plays a role in the pathogenesis of febrile seizures.^{17, 21, 23, 24} In contrast, there are some studies that reported that iron deficiency raises the threshold for seizures.²⁰ Also, recently some reports have shown that although iron deficiency anemia is less frequent among the cases with febrile seizures, but there is no protective effect of iron deficiency against febrile convulsion.²⁵

II Methods

This was a case-control study conducted in the Dept. Of Prediaticce, Shaheed Tajuddin Ahmad Medical College Hospital, Gazipur, Bangladesh between January 2019-December 2019. 60 consecutive children who fulfilled the inclusion criteria were considered in this study. Samples with atypical febrile seizure, unconsciousness, electrolyte imbalance, having developmental anomaly, neurological deficit or with CNS manifestations were excluded from the study. Patient details such as age, gender, socioeconomic status was noted. A detailed history was taken regarding the duration and type of symptoms, systemic associations taken. Initial evaluation of the patients by history and clinical examination was performed and recorded in patients' data collection sheet. In all patients who did not have a history of any iron supplement therapies for previous 3 days, 5 mL of 6hr fasting blood sample was collected at 8:00 am. Then routine hematological investigations were performed. Red blood cell count (RBC), hemoglobin (Hb), Hematocrite (Hct), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), serum iron concentration, total iron binding capacity (TIBC) and plasma ferritin (PF) were collected for all patients separately.

Statistical Analysis: Data were processed and analyzed using computer-based software SPSS (Statistical Package for Social Sciences) for windows version 22. Unpaired ttest was used to compare quantitative variables. Variables were expressed as range and mean \pm SD. p value < 0.05 were taken

significant. Students't test, Pearson's correlation coefficient test, multivariate logistic regression analysis and Fisher's exact test as applicable.

III Results

In Table-1 shows age distribution of the patients where most of the patients (51.7%) belongs to age group 13 months -36 months than 40% belongs to 6 months - 12 months than 8.3% patients belongs to 37 months to 60 months. In figure-1 shows gender distribution of the Male patients were 58% higher than female. The patients where male was 79% and female was 21%. In Figure-2 shows residential area distribution of the patients where 80% patients belong to urban area. In Table-2 shows clinical profile of the patients where grading of anemia was moderate to severe in majority of cases (60%).

Table-1: Age distribution of the patients.

Variable	Distribution	Percentage (%)
Age group	6 months-12 months	40
	13 months-36 months	51.7
	37 months-60 months	8.3

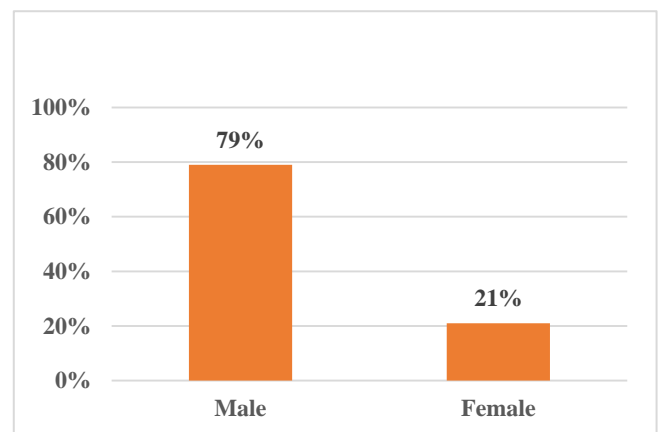


Fig-1: Gender distribution of the patients.

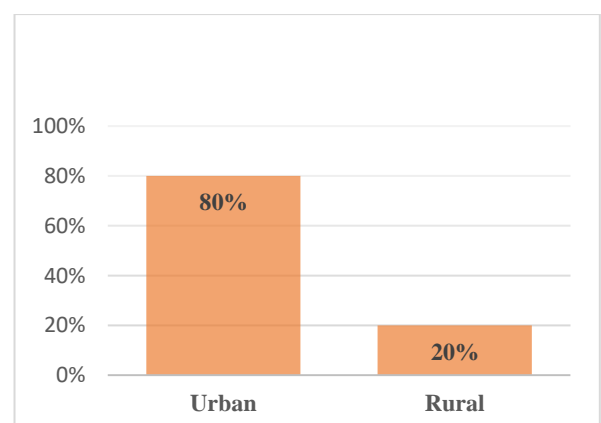


Fig-2: Residential area distribution of the patients.

Table-2: Clinical profile of the patients.

Clinical profile	%
Family history of febrile seizure:	
Yes No	41.7 5.3
Anemia:	
Yes No	93.3 6.7
Severity of anemia:	
Severe (3-6 gm/dl):	11.7
Moderate (6-9 gm/dl):	40.0
Mild (9-12 gm/dl):	48.3
Investigation:	
Hb (g/dl):	10.32±8.7
MCV (fl):	69.39±5.90
MCH (pg):	23.74±2.65
MCHC (gm/dl):	28.69±3.66

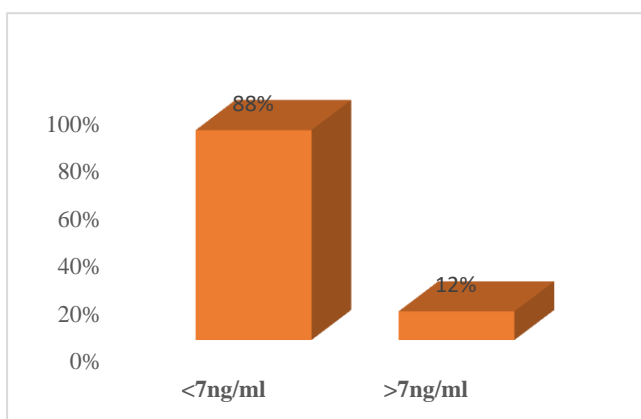


Fig-3: Serum Ferritin level of the patients.

Table-3: association of and anemia of simple febrile Convulsion.

Clinical profile	Febrile Convulsion	95% CI
Anemia:		
Moderate to severe	41.7	2.47-14.85
Mild	5.3	
Serum ferritin		
<7ng/ml	93.3	14.96-173.5
>7ng/ml	6.7	

In Figure-3 shows Serum Ferritin level of the patients where most of the patients belong to <7ng/ml, 88%. In Table-3 shows association of and anemia of simple febrile Convulsion, also, febrile Convulsion and serum ferritin between febrile Convulsion where was 6 times vulnerable to develop in moderate to severe low serum ferritin has association with the occurrence anemia.

IV Discussion

In the present study, febrile convulsion was extremely high in the 6-60 months old cases, which makes them a population at risk, and a prime target for prevention. In our study the mean haemoglobin concentration of the cases were low. The children were matched in age and gender and the history of iron supplement taking. One study showed their cases group had anemia (defined by Hb less than 11gm/dl)

but did not mentioned the severity of anemia.²⁹ Another study also showed similar result.³⁰ In the present study the mean MCH, MCHC, MCV and serum ferritin (ng/ml) were significantly less in patients which is supported by one report.³¹ One study reported that, MCH was significantly low in case group. Also, several studies also noticed the mean Hb, HCT, MCH, serum iron level significantly lower in case group. In this study majority cases had low serum ferritin level (<7 ng/ml) comprising 88%. One study mentioned that mean ferritin level was lower in children who had a convulsion with fever suggesting a possible risk factors in febrile convulsion. They have shown that the mean plasma ferritin level was significantly lower ($p < 0.0001$) in the first febrile convulsion group compared to the control group.³² This is consistent with some other studies.²⁵ In one study observed that only 22.5% child with febrile convulsion had iron deficiency anemia. Febrile convulsion group had significantly high RBC indices (MCV, MCH, MCHC).³³ In this current study we found low serum ferritin has association with the occurrence of simple febrile convulsion (CI 14.96-173.5). One report showed positive association of Iron Deficiency Anemia with febrile convulsion. In their study mean serum ferritin level in case 6.9 $\mu\text{g/L}$ & in control 7.9 $\mu\text{g/L}$. children having febrile convulsion.³⁴ Another study reported that, the ferritin level is affected by the severity of fever and increases with fever.²⁹ Nonetheless, when groups with similar fever severity (temperature) were compared, ferritin level was found to be lower in the FC children compared with the healthy ones.³⁰ Similar to Ala et al., and Bidabadi et al.^{25, 27} higher mean peak rectal temperature was a risk factor for febrile convulsion occurrence. As in Kobrin's study, the incidence rate of iron deficiency anemia was significantly higher in the febrile convulsion.²⁰ Kobrin thought that iron deficiency anemia may have a protective role against convulsion caused by fever.²⁰ On the contrary, in many other studies, the results were different.^{17,21, 23-25} Also some similar results were shown in some other studies^{21, 24}, which found that children with febrile seizures had significantly lower serum ferritin levels than febrile children without seizures. On the other hand, Bidabadi and Mashouf in a study in Iran have found that iron deficiency was less frequent in children with febrile convulsion, but they denied any role of iron insufficiency in febrile seizures.²⁵ This is consistent with other findings from our metaanalysis.^{31,32} The role of iron has also been documented in the production of serotonin, dopamine, and Gamma-Butyric Acid (GABA). One of the advantages of our study in comparison with other studies was the large sample size. As we noted, iron is an essential element in some neurotransmitters, so maybe its amount of monoaminoxidase and aldehydoxidase is reduced in iron deficiency anemia.^{17,28} Considering the monoaminoxidase as a stimulating neurotransmitter, it might be that its amount and function reduction occurs during iron deficiency anemia. That may cause a decrease of the neurons over provocation and so

decline the incidence of seizure.²⁸ According to the one finding, iron deficiency leads to dysfunction of myelination as well as tyrosine and tryptophan hydroxylase synthesis, which are necessary for neurotransmitter production as well as the release of neurotransmitters from vesicles.³³

V Conclusion

In conclusion, due to high prevalence of iron deficiency anemia in this study population. From our study we can conclude that, IDA was associated with a moderate increased risk of FC in children, particularly in the areas with low and moderate prevalence of anemia. We also recommend that, in future studies, IDA and FC should be defined more precisely and the role of the important factors, such as socio-economic status and the serum levels of zinc, manganese, lead, etc., should be controlled to determine whether the association between IDA and FC is causal or not. However, more prospectively designed metacentric studies are essential in order to confirm or decline this finding. Considering our findings, administration of supplemental iron should be considered carefully in high risk children for seizures or febrile seizures, like previous seizures or positive family history.

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