

Iron status among under-five children with first febrile convulsion and subsequent febrile convulsion

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ABSTRACT

Objective: The objective of this study is to estimate the iron status using hemoglobin (Hb), red cell indices, serum iron, plasma ferritin, total iron binding capacity (TIBC), and transferrin saturation (TSAT) in children with first febrile convulsion (FFC) and subsequent FC (SFC). **Methods:** The study was conducted in a tertiary care teaching hospital among children aged 6 months–5 years with first and subsequent episodes of the simple FC taking cases and controls in a ratio of 2:2:1. Consecutive cases and concurrent controls were selected for the study. Controls were children of the same age group with short febrile illness but without any seizures. After informed consent from parents, detailed history was taken; clinical examination and blood investigations were done to estimate iron status in both cases and controls. Laboratory tests included Hb, hematocrit (Hct), red cell indices, peripheral smear, red cell distribution width (RDW), serum iron concentration, plasma ferritin, TIBC, and TSAT. The data were then analyzed statistically using SPSS software. **Results:** 44 cases with FFC, 44 with SFC, and 22 controls were included in the study. The mean Hb, Hct, red cell indices, and RDW between the three groups did not show any significant difference. The mean serum ferritin was significantly lower in the SFC group compared to the control group ($p=0.005$). The mean serum TIBC was significantly higher in the SFC group compared to the control group ($p=0.004$) and also the SFC group compared to the FFC group ($p=0.022$). **Conclusions:** Poor iron status in subsequent febrile seizures indicates that iron deficiency is associated with subsequent seizures. Hence, screening for iron status rather than Hb level estimation should be considered for children presenting with or at high risk for febrile seizures.

Key words: Anemia, Children, Iron deficiency, Subsequent febrile convulsion

Iron deficiency anemia (IDA) and febrile convulsions (FC) are the two common conditions in children worldwide as well as in our country. FC occurs in 2–5% of all children and IDA is to the tune of 30% [1,2]. ID is known to cause neurological symptoms such as behavioral changes, poor attention span, and learning deficits in children including decreased visual and auditory processing time [3-7]. FC has an excellent prognosis; however, many of them also have subsequent FCs (SFC). The probability of seizure recurrence after an initial febrile seizure in children remains uncertain. Population-based studies have indicated that three or more recurrent seizures occur in only 4.1–9% children. Children who have their FFC before the age of 1 year have 50% chances of further seizures. In addition to genetic predisposition, FCs are generally thought to be induced by ID as IDA has been reported in a significant proportion of children with FC. ID reduces the metabolism of some neurotransmitters, such as monoamine and aldehyde oxidase [8,9] and thus, it may alter the seizure threshold of a child [10,11]. It is postulated as a risk factor for febrile seizures in children and is an easily correctable condition [12,13]. It has also been suggested that fever aggravates the negative effects

of ID on the brain. ID may also influence the type, duration, or recurrence risk of seizures [14].

It is interesting to note that so far only very few studies have addressed the issue of recurrence of FC in the setting of ID. Considering the high prevalence of febrile seizure and ID in children, this study was conducted to assess the iron status in children with 1st episode FC and subsequent episodes of FC.

MATERIALS AND METHODS

This study was conducted in the pediatric department of a tertiary care teaching hospital during a 1-year period from March 2016 to February 2017. Institutional research committee and Ethics Committee Clearance obtained before conducting the study. The study subjects included consecutive cases 6 months–5-year-old attending the hospital with first and subsequent episodes of simple FC and controls taken in the ratio of 2:2:1. Controls were children of same age group presenting with short febrile illness but without any seizures. Children with complex febrile seizure, history of perinatal insult, developmental delay, neurological deficit, epilepsy, and central nervous system (CNS) infection were excluded from the study.

FC was defined as convulsion which occurs in children aged 6–60 months with a temperature of 38°C (100.4°F) or higher that is not the result of CNS infection or any metabolic imbalance and that occur in the absence of a history of prior afebrile seizures [1,15-17]. A single convulsion of <15-min duration in the presence of fever without focal features was defined as a simple FC. If they lasted >15 min, had focal features or occurred more than once in 24 h, they were defined as complex FC [18]. Anemia was defined as decrease of hemoglobin (Hb) <11.0 g dl [19]. A hematocrit (Hct) <33%, mean corpuscular volume (MCV) <70 fl, mean corpuscular Hb (MCH) <23 pg, and mean corpuscular Hb concentration (MCHC) <30 g% were taken as abnormal. Serum iron concentration <40 µg/dl, plasma ferritin (PF) <12 µg/l, transferrin saturation (TSAT) <16%, and total iron binding capacity (TIBC) >430 mcg/dl were taken as indicators of ID. TSAT is the ratio of serum iron and total iron-binding capacity multiplied by 100.

A total of 44 cases with FFC, 44 cases with SFCs, and 22 controls were included in the study. After informed consent from parents, detailed history was taken; clinical examination and blood investigations were done to estimate iron status in both cases and controls. Laboratory tests included Hb, Hct, MCV, MCH, MCHC, peripheral smear, red cell distribution width (RDW), serum iron concentration, PF, TIBC, and TSAT. Peripheral smear, RDW, MCV, MCH, and MCHC were done for exclusion of other types of anemia such as thalassemia. Hospital records were also examined for relevant data. Other variables such as age of the child, sex, socioeconomic status (SES), family history of febrile seizure, family history of epilepsy, prematurity (<37 weeks gestational), low birth weight, nutritional status, and head circumference were also included in the study and considered for the analysis.

Data were entered in MS Excel, cleaned and checked for completeness. Data were statistically analyzed using SPSS version 16. Descriptive statistics were reported at baseline, with continuous data expressed as a mean±standard deviation and categorical data expressed as counts. Children with FFC, SFC, and controls were compared and all continuous explanatory variables were presented as means, with differences between the three groups compared by means of one-way ANOVA test and Tukey *post hoc* test. Categorical explanatory variables were summarized as frequencies and percentages, with differences between the three groups analyzed using Kruskal–Wallis H test when appropriate. A $p < 0.05$ was considered statistically significant, unless otherwise specified.

RESULTS

Among the 44 cases with SFCs, 40 (90.9%) had 2–3 recurrences, whereas 4 (9.1%) had 4–5 recurrences. Recurrence of febrile seizure was not seen in the <1 year age group, but it was seen in equal distribution in 1–2 year and >2 years age group. Majority of the patients in the FFC group were male (81.8%), whereas majority in the SFC group were female (75%) and the controls also had a female preponderance (63.6%). There was

a significant association between FFC and male sex ($p=0.000$). Majority of the patients in the FFC group were from lower-middle class (63.64%) and SFC group were from upper-lower class (54.55%) and a majority of controls were from upper-lower class (72.73%). Statistical significance was noted between FFC and socioeconomic status with the majority belonging to lower-middle class ($p=0.010$). The majority of cases and controls had respiratory infection as the presenting complaint.

There was a significant association between children with febrile seizures and family history of febrile seizures ($p=0.000$). First-degree relative was affected in 8 out of 25 cases with FFC and 18 out of 26 with SFCs. 11.4% of children with the first episode of febrile seizure had family history of epilepsy whereas 22.7% of recurrent febrile seizure had family history. Significant association was noted between subsequent febrile seizure and family history of epilepsy ($p=0.034$). A total of 4 (9.1%) cases with the first episode and 9 (20.5%) with recurrent episodes were preterm. A Kruskal–Wallis H-test showed that there was a difference between the three groups ($p=0.041$) (Table 1).

Maximum number of children with grade 1 PEM and first-degree stunting were noted in the subsequent febrile seizure group. 38.6% of children with first febrile seizures, 54.5% of subsequent febrile seizures, and 59.1% of controls had anemia (Fig. 1). The mean Hb, packed cell volume (PCV), red cell indices, and RDW between the three groups did not show any significant difference. The mean serum iron level is lowest for the group with subsequent febrile fits, but no significant difference was noted between the three groups (Table 2).

There was a significant difference of mean serum ferritin value between the three groups as determined by one-way ANOVA ($p=0.008$). A Tukey *post hoc* test revealed that the mean serum ferritin was significantly lower in the subsequent febrile seizure group ($p=0.005$) compared to the control group. There was no significant difference between the first episode seizure and control group ($p=0.084$) and first episode and subsequent episode group ($p=0.423$).

There was a significant difference of mean serum TIBC value between the three groups as determined by one-way ANOVA ($F(2,107) = 6.401, p=0.002$). A Tukey's *post hoc* test revealed that the mean serum TIBC was significantly higher in the subsequent

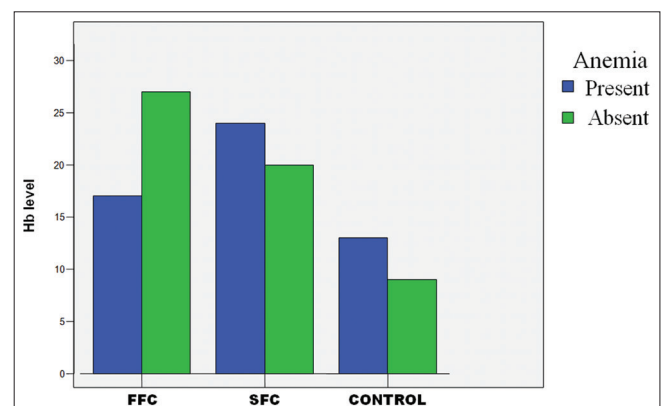


Figure 1: Bar chart showing anemia among children with first febrile convulsion, subsequent febrile convulsion, and controls

Table 1: Baseline characteristics of the three groups, FFC, SFC and controls

Parameters	First FC (%)	Subsequent FC (%)	Control (%)	p value
Age (years)				
<1	25	0	18.2	-
1–2	13.6	50	40.9	
>2	61.4	50	40.9	
Sex ratio				
Male:Female	4.5:1	1:3	1:1.7	0.000
Recurrences				
≤3 Episodes	-	40 (90.9)	-	-
>3 Episodes		4 (9.1)		
SES				
Upper middle	1 (2.3)	1 (2.3)	0	0.010
Upper lower	15 (34.1)	19 (43.2)	6 (27.3)	
Lower middle	28 (63.6)	24 (54.5)	16 (72.7)	
Family history				
FCs	25 (56.8)	26 (59.1)	0	0.000
Epilepsy	5 (11.4)	10 (22.7)	0	0.034
Preterm	4 (9.1)	9 (20.5)	0	0.041
Low birth weight	6 (13.6)	9 (20.5)	0	0.074
Malnutrition				
Grade 1	15 (34.1)	26 (59.1)	7 (31.8)	0.003
Grade 2	6 (13.6)	5 (11.4)		
Grade 3	1 (2.3)	2 (4.5)	0	
Stunting				
First degree	7 (15.9)	21 (47.7)	7 (31.8)	0.018
Second degree	1 (2.3)	0	0	
Wasting				
First degree	7 (15.9)	8 (18.2)	7 (31.8) 0	0.419
Second degree	1 (2.3)	4 (9.1)		
Anemia	17 (38.6)	24 (54.5)	13 (59.1)	0.192

Table 2: Comparison of Hb, iron status, red cell indices in the three groups, FFC, SFC, and controls

Laboratory parameters	First episode	Subsequent seizures	Control	p value
Mean Hb	10.81 (0.85)	10.71 (0.87)	10.73 (0.47)	0.823
Serum Ferritin	78.57 (33.44)	68.66 (29.3)	99.40 (54.13)	0.008
TIBC (µg/dl)	357.77 (86.53)	410.52 (95.59)	332.68 (94.23)	0.002
Serum iron (µg/dl)	71.18 (56.36)	57.27 (26.38)	71.55 (40.78)	0.255
TSAT (µg/dl)	21.71 (21.71)	14.94 (8.77)	21.92 (11.65)	0.090
PCV	32.32 (2.38)	31.90 (2.49)	32.31 (0.86)	0.630
RDW	15.22 (2.29)	16.16 (2.45)	14.97 (1.74)	0.067
MCV	79.27 (4.82)	78.14 (4.89)	80.48 (5.99)	0.205
MCH	29.7 (2.79)	33.47 (14.56)	28.07 (1.35)	0.055
MCHC	32.99 (3.23)	33.28 (2.24)	33.46 (1.33)	0.749

Hb: Hemoglobin, FFC: First febrile convulsion, SFC: Subsequent febrile convulsion TIBC: Total iron binding capacity, TSAT: Transferrin saturation, PCV: Packed cell volume, RDW: Red cell distribution width, MCV: Mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration

febrile seizure group ($p=0.004$) compared to the control group and also the subsequent febrile seizure group ($p=0.022$) compared to the first febrile seizure group (Fig. 2). There was no significant difference between the first episode seizure and control group ($p=0.549$). The mean serum TSAT value was lowest in the subsequent febrile seizure group, but it was not statistically significant ($p=0.090$).

DISCUSSION

Numerous studies have addressed the association between febrile seizures and IDA. However, most of them have studied the relation of ID with febrile seizures in general but have not studied the iron status of subsequent febrile seizures. In our study, we have assessed the iron status of the first episode of febrile

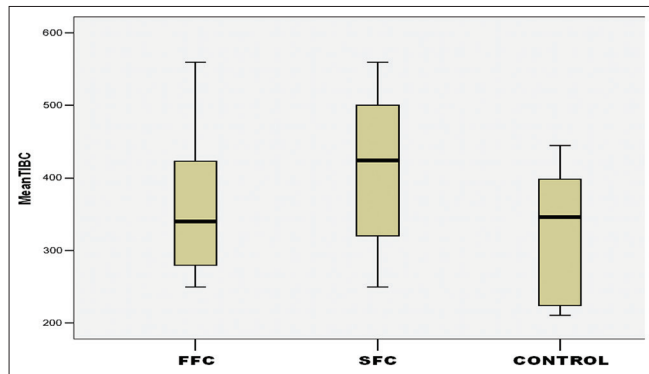


Figure 2: Box plot of total iron binding capacity values of first febrile convulsion, subsequent febrile convulsion, and controls

seizures, subsequent episode of febrile seizures and controls. A total of 38.6% of children with first febrile seizures, 54.5% of subsequent febrile seizures, and 59.1% of controls had anemia. The mean Hb level, PCV, red cell indices and RDW between the three groups did not show any significant difference.

The most important observation made in the present study is the significantly low mean serum ferritin level in the subsequent febrile seizure group (68.66 ± 29.3 , $p=0.005$) compared to the control group (99.4 ± 54.1). The mean serum TIBC was significantly higher in the subsequent febrile seizure group compared to the control group ($p=0.004$). It was also higher in the subsequent febrile seizure group compared to the first febrile seizure group ($p=0.022$).

In a prospective case-control study from Europe by Papageorgiou *et al.* [20], similar observation was noted. Ferritin was lower and TIBC was higher in 18 children with previous seizures than in 32 children with the first seizure; although, Hb and MCHC were higher. In another study from Bhopal [21] by Gupta *et al.*, statistically significant association was noted between recurrence of febrile seizures and ID ($p=0.0143$) which is similar to our study.

In a study from Nepal [22] among 92 cases and 70 controls, it has been found that the mean Hb for cases was 9.98 ± 1.678 and for controls 11.58 ± 1.722 with $p < 0.001$. The group with FC had significantly lower blood indices, compared to control group ($p < 0.001$). The mean iron and ferritin were significantly low ($p < 0.001$ and $p < 0.035$) and TIBC significantly high ($p < 0.018$) in cases than controls. However, in our study, the mean Hb level, PCV, red cell indices, and RDW between the three groups did not show any significant difference ($p=0.189$).

In the study from Iran [23], patients with febrile seizures were more frequently iron deficient as defined by a serum ferritin level below 20 ng/dl (56.6% vs. 24.8%, $p=0.0001$). Mean Hb concentration was 10.8 g/dl in the control and 11.7 g/dl in the case group ($p < 0.05$). The difference between groups in MCV was not statistically significant (75.5 fl vs. 74.4 fl, $p < 0.130$). This observation was similar to ours where no difference was noted with respect to Hb, red cell indices, and peripheral smear.

In the present study, certain other observations were also made regarding the patient characteristics. Recurrence of febrile seizure was seen in equal distribution in 1–2 years and >2 yr age

group, while it was not seen in <1 year age group. In a study by Berg *et al.*, the risk of recurrence was 14% at 6 months, 27% at 18 months, and 30% at 24 months after the first episode of febrile seizures [24]. Regarding sex distribution, majority of the patients in the FFC group were males with a male-to-female ratio of 4.5:1 which is similar to other studies in the literature [22,25,26]. In our study, among children in the SFC group, 75% were females and controls also had a female preponderance (63.6%). In the literature, male sex has been described as a risk factor for recurrence [1] which is against our observation.

On correlating prevalence of FC with socioeconomic status, the present study showed that the majority of children of FFC belong to lower-middle SES (63.64%) and SFC and control group belong to upper-lower SES (54.55% and 72.73%, respectively). Kumari *et al.* [27] also found similar results where 74.7% cases and 70.8% control belonged to lower SES ($p=0.443$). This does not coincide with results of previous studies where lower SES has been a risk factor for febrile seizures. In a study from Bhopal [25], the majority of children of FC belong to lower SES in contrast to control group where maximum children belong to middle SES (odds ratio [OR] 3.16 [$p=0.008$]).

There is a significant association between children with febrile seizures and family history of febrile seizures in our study. Other studies by Kumari *et al.* [27] ($p=0.004$) and Berg *et al.* [24] also shows that children with family history of febrile seizure are more prone to develop febrile seizures. In our study, 11.4% of children with the first episode of febrile seizure had family history of seizure disorder whereas 22.7% of recurrent seizure had family history. Thus, significant association was noted between recurrence of febrile seizure and family history of epilepsy. Both family history of febrile seizure and family history of epilepsy are minor risk factors for recurrence of febrile seizures according to the literature [1].

A total of 9.1% of first-episode cases and 20.5% of recurrent episode group were born preterm in our study. Recurrence of febrile seizure was associated with prematurity in our study ($p=0.041$). In the study by Kumari *et al.* [27], prematurity was found to be associated with febrile seizure (adjusted OR 2.58, 95% CI: 1.19–5.62, $p=0.01$). In our study, 59.1% children in the SFC group had grade 1 PEM against 34.1% in the FFC and 31.8% in the control group ($p=0.003$). In the study by Kumari *et al.* [27], malnutrition was not found to be significant cause of febrile seizure.

Limitation of the present study is that comparatively less number of controls was taken due to financial constraints. Furthermore, we have not compared the different groups with respect to duration of fever and degree of temperature before the onset of seizure. This study did not take the history of whether the first seizures in subsequent seizure group was evaluated for anemia or supplemented with iron. Serum ferritin, a non-specific acute phase reactant can rise in any inflammatory condition. However, serum iron and TIBC values were observed in the study which would have not altered by infection. Hb level, red cell indices, and peripheral smear were not affected in our studied population which indicates the importance of detection of early ID and supplementation of iron which can reduce the incidence

of febrile seizures, among both, first episode and subsequent episodes.

CONCLUSION

In this study, we found significantly lower serum ferritin and serum TIBC levels in the subsequent febrile seizure group than in the control group. Even though mean Hb levels were not different, poor iron status (low ferritin, elevated TIBC, and low TSAT) in subsequent seizures indicate that ID is associated with subsequent seizures. Hence, iron status screening rather than Hb estimation should be considered for children presenting either with or at high risk for febrile seizures.

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