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Simple Febrile Convulsion and Iron Deficiency Anemia A Co-relation in Nepalese Children

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Abstract Simple febrile convulsion is the most common central nervous system disease seen in children. There are hypotheses that thresh hold of neuron excitation maybe affected by iron deficiency anemia. This study was done to find out a co-relation between iron deficiency anemia and simple febrile convulsion. The prospective comparative study was conducted at Manipal Teaching Hospital, Pokhara, Nepal 162 children admitted in the pediatric ward were selected and divided into two groups, febrile convulsion (Cases) and other causes of fever with no convulsion (Control). Blood was sent for each child for complete blood count, peripheral smear blood indices and iron profile. Statistical analysis was done using SPSS version 19. A p value <0.05 was considered statistically significant. The patients and controls were 22.55 ±10.220 and 21.64±12.959 months of mean age, respectively. The peak of mean temperature on admission was in the febrile convulsion group than controls. (57/92) 61.95 % of cases and 15/70) 21.42% of controls anemic (*P*< 0.001). Moreover, the group with febrile convulsion had significantly lower blood indices, such as Hb, MCV, MCH, MCHC and RDW, compared to control group (*P*< 0.001).Iron deficiency anemia was significantly higher in cases compared to controls(p<0.001) Iron supplementation can probably increase the threshold of neuron excitation in fever and help prevent febrile convulsion in children.

Keywords: *children, febrile convulsion, iron deficiency*

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1. Introduction

Febrile convulsion (FC) is defined as convulsion which occurs in children aged 6 months to 60 months and is accompanied by fever higher than 38°C (100.4°F), and does not involve symptoms of central nervous system infections [1]. It is the most common cause of convulsion in children, that affects 2-5% of children per year [1]. FC rarely leads to brain damage but still the convulsive episodes are stressful for the parents, and affects families' quality of life. Over that it also has relation to epilepsy in 2-4% cases in future [2]. Iron deficiency is the most common micronutrient deficiency which decreases the production of hemoglobin thus resulting in iron deficiency anemia [3] Iron is essential for the metabolism of brain and neurotransmitters, and in the production of myelin which is required for nerve cells and can change the amplitude and the threshold of neurons excitation [4]. Studies conducted on the role of iron deficiency in FC have shown conflicting results. In some studies, iron deficiency has been identified as a risk factor [5,6,7], while in others it has been stated that iron deficiency increases the threshold of neuron excitation and thus can play a protective role against FC [8,9]. To add on further information to these contradictory results, we carried out this study to see the relationship of iron deficiency anemia with simple febrile convulsion in Nepalese children.

2. Materials and Methods

2.1. Study Setting

A prospective comparative hospital based study conducted at Manipal Teaching Hospital from June 1013 to June 1015.

2.2. Sample Size Calculation

In a pilot study done prior to original study for power 95% and α error 5% with 95% level of confidence showed proportion of anemia in febrile convulsion was 0.7 and that in control 0.3 and required sample size in each arm were 38.

2.3. Ethical Committee Approval

The Ethics committee of the Manipal Teaching Hospital approved this study. All parents or guardians of the sick children gave their Witten consent before enrolling the case for study; they could withdraw from the study anytime they desired. The researchers were committed to the Declaration of Helsinki at all stages of the study [10].

2.4. Enrollment of Cases:

This study enrolled 92 cases of simple FC and 70 age and sex matched controls with fever but no convulsion. These children were of age 6 month to 60 months, the age at which FC occurs. Simple FC was defined in this study as - A convulsion accompanied by fever that lasted less than 15 minutes without local and focal symptoms.

2.5. Inclusion Criteria:

1. Children aged 6 months to 6 years presenting with simple febrile convulsion for cases and for controls children of same age with fever but no convulsion.
2. Both first and recurrent episodes of FC were included for cases.

2.6. Exclusion Criteria:

1. Atypical febrile convulsion.
2. Diagnosed organic cause of convulsion.
3. Delayed milestones, neurological defects.
4. Central nervous system infection- meningitis, encephalitis.
5. Anemia resulting from other causes - hemolysis bleeding, hemolytic anemia
6. Gastroenteritis and dysentery
7. On iron therapy.
8. Refusal of Consent.

Table 1. Normal Values: Hb, Indices, RDW [11]

	Age	Normal Levels
S Iron (µg/dl)	All ages	22-184
TIBC (µg/dl)	Infants Thereafter	100-400 250-400
S Ferritin (ng/ml)	0-6wks 7wks-1year 1-9yrs 10-18 yrs Male Female	0-400 10-95 10-60 10-300 10-70
TLC (cells/mm3)	0-30days 1-23mo 2-9 yrs	9100-34000 6000-14000 4500-12000
Neutrophil (%)	All age	54-62
Hemoglobin (g/dl)	1-23mo 2-9yrs	10.5-14 11.5-14.5
MCH(pg/cell)	1-23mo 2-9yrs	24-30 25-31
MCHC(%)	All age	32-36%
MCV(fl)	1-23mo 2-9yrs	72-88 76-90
RDW(%)	1mo-24mo 25-60mo	<16.5 <15

At hospitalization all children underwent a careful physical and nervous system examination, especially with respect to symptoms of meningeal irritation. Axillary temperature at hospitalization (0.5 degree was added to them) was taken and when the temperature exceeded 38°C, they were included in the study. The case and control groups were matched with respect to age, sex, body temperature and history of treatment with iron supplements. The high temperature was first treated with antipyretics 10-15 mg/kg administered every 4-6 hours. After normalization of body temperature 5 ml of blood was taken from each child complete blood count (CBC), hemoglobin, blood indices [MCV, MCH, MCHC] and iron profile [S.iron, TIBC, S.Ferritin]. The normal values of these parameters are listed in Table 1. Children with values less than those presented in Table 1 (taking the age of the child into consideration) were considered to be suffering from anemia and iron deficient. In cases where meningitis was suspected, cerebrospinal fluid analysis was done.

2.7. Dependent Variable/Exposure Variable:

Febrile convulsion.

2.8. Independent Variables/Outcome Variables:

Anemia - Anemia is diagnosed when the hemoglobin level falls more than two standard

deviations below the normal level for the related age and sex.

Iron deficiency anemia - In iron deficiency anemia, S iron, serum ferritin decline but TIBC

rises. Under these conditions, red blood cell indices also fall.

2.9 Determination of Complete Blood Parameters and hemoglobin estimation

Using automated hematology analyzer at Clinical laboratory of Manipal Teaching Hospital. The system calculates Hemoglobin as:

Hb (g/L) = Constant X Log_{10} (Blank Photocurrent/ Sample Photocurrent)

2.10. Estimation of iron profile: [12,13]

Serum iron estimation in µg/dl:

Done using R2 reagent- Reagent composition is as follows

Hydroxllamine hydrochloride 220mmol/L

Ferrozine ≥ 3.0mmol/L

Total iron binding capacityin µg/dl:

Calculated as follows:

UIBC (United Iron biding capacity) + Serum Iron

Serum ferritin in ng/ml:

Circulation Ferritin concentration in serum was estimated by a microplatechemiilluminescence immunoassay (CLIA).

2.11. Statistical Analysis

The data were entered into the SPSS version -19 and Chi-square and t- test was performed to compare the parameters and P values less than 0.05 were considered statistically significant.

3. Results

Out of 162 children 92 were cases (febrile convulsion) and 70 were controls (fever without convulsion). Age, sex, ethnic group, temperature on admission, duration of breast feeding, nutritional status, weight in the two groups were similar (were not significantly different from each other) [Table 2 & Table 3]. The cases and controls were 22.55 ±10.220 and 21.64±12.959 months of mean age, respectively. Febrile convulsion was noticed more in the males (59/92) than in females (33/92) with ratio 1.79:1. [Table 2] The mean peak temperature on admission was more in cases [101.25±1.427] than controls [100.83±1.541] but this was statistical insignificant ($p<0.071$).

Table 2. Baseline Characteristics of Case and Control Groups:

	Case (FC)	Control	Chi-square	P value
Ethnic group :				
Brahmin	29(56.9%)	22(43.1%)		
Chettri	11(68.8%)	5(31.3%)		
Mongol	30(62.5%)	18(37.5%)	10.631	0.100
Dalit	16(59.3%)	11(40.7%)		
Newar	6(42.9%)	8(57.5%)		
Others	0	6(100%)		
Sex : Male	59(61.5%	37(38.5%)	2.09	0.099
Female	33(50%)	33(50%)		
Age : 6mo-23mo	46(56.8%)	35(43.2)	0.000	0.563
24mo-60mo	46(56.8%)	35(43.2)		
Weight /age : Low	52(58.4%)	37(41.6%)	0.216	0.380
Normal	40(54.8%)	33(45.2%)		
Main diet: Vegetarian	26(51%)	25(49%)	1.024	0.200
Nonveg	66(59.5%)	45(40.5%)		
Duration of fever at presentation:				
1-2Day	88(80.7%)	21(19.3%)	77.839	0.001
≥3Day	4(7.5%)	49(92.5%)		
Clinical Presentation				
Irritability :Yes	42(65.6%)	22(34.4%)	4.437	0.109
Vomiting :Yes	13(33.3%)	26(66.7%)	11.517	0.001
Cough :Yes	48(54.5%)	40(45.5%)	1.075	0.584
Urine symptom: Yes	1(8.3%)	11(91.7%)	12.401	0.001
Pain abdomen: Yes	1(5%)	19(95%)	24.94	0.001
PICA: Yes	10(71.4%)	4(28.6%)	1.338	0.192
Pallor :Yes	31(86.1%)	5(13.9%)	16.216	0.001
Walking bare foot	42(82.4%)	9(17.6%)	19.821	0.001
Anemia :Yes	57(79.2%)	15(20.8%)	26.444	0.001
No	35(38.9%)	55(61.1%)		

Table 3. T test for Equality of Means for Matched Parameters in Two Groups

Variables	Mean ±SD [Case= 92]	Mean ±SD[control=70]	T test	P value
Age	22.55 ±10.220	21.64±12.959	0.501	0.617
Weight	11.15 ±2.262	11.31±3.226	-0.372	0.711
Mean duration of exclusive BF	4.84 ±1.823	5.20 ±1.830	-1.253	0.212
Temp on admission	101.25±1.427	100.83±1.541	1.799	0.074

3.1. Anemia and Iron Profile in Febrile Convulsion

61.95% of children in febrile convulsion group and 21.42 % in the control group had anemia ($P< 0.001$) [Table 5]. The mean hemoglobin for cases was 9.98 ±1.678 and for controls 11.58±1.722 with p<0.001 [Table 4].

Means of the blood indices of the febrile convulsion group, and their comparison with the corresponding means of the control group are listed in Table 4. The group with febrile convulsion had significantly lower blood indices, such MCV, MCH, MCHC compared to control group ($P< 0.001$).

Table 4. T test for Equality of Means for Lab Parameters in Case and Controls

Parameters	Group: Grp1=92 Grp2= 70	Mean ±SD	Test	P value
TLC	1 2	12666 ±6200.891 11407 ±4464.02	1.439	0.152
Neutrophil	1 2	67 ±17.937 52 ±20.461	5.041	0.001
CRP	1 2	9.36±19.162 14.44±25.788	-1.440	0.152
Hb	1 2	9.98 ±1.678 11.58±1.722	-5.939	0.001
MCV	1 2	66.21±8.578 75.81±11.941	- 5.562	0.001
MCH	1 2	21.89±3.338 24.94±3.666	-5.522	0.001
MCHC	1 2	32±2.744 32.7±1.624	-1.168	0.051
RDW	1 2	16.65±5.080 14.20±1.804	3.846	0.001
S. Iron	1 2	29.01±19.265 43.96±17.382	-5.102	0.001
TIBC	1 2	409±118.92 365±113.73	2.394	0.018
S.Ferritin	1 2	37.02±35.483 50.48±45.191	-2.125	0.035

Iron deficiency anemia was significantly higher in cases compared to controls (p<0.001).The mean iron and ferritin was significantly low (p<001 & p <0.035) and TIBC significantly high (p<0.018) in cases than controls. [Table 4].

3.2. Regression Analysis for Anemia and Iron Profile

All lab parameters were statistically significant and the OR with CI 95% for all parameters are shown in Table 5.

Table 5. Relation of Variables in Case and Control by Regression Analysis

Variables	FC		P value	Odds ratio (95% CI)
	Yes (n=92) CASE	No (n=70) CONTROL		
Hb (N=162)				
Low (n=72)	57(61.95%)	15(21.42%)	0.001	5.971(2.938,12.137)
Normal (n=90)	35(38 %	55(78.57%)		1
MCV (N =162)				
Low (n=92	76(82.6%)	16(22.85%)	0.001	16.031(7.380,34.825)
Normal (n=70)	16(17.39%)	54(77.1%)		1
MCH (N=162)				
Low (n=79)	64(69.56%)	15(21.42%	0.001	8.381(4.066,17.275)
Normal (n=83)	28(30.43%)	55(78.57%)		1
MCHC (N= 162)				
Low (n=55)	43(46.73%)	12(17.14%	0.001	4.241(2.015,8.921)
Normal (n=107)	49 (53.26%)	58 (82.85%)		1
RDW (N=162)				
High (n=117)	71(77.1%	46(65.71%	0.024	2.338 (1.116, 4.899)
Normal (n= 45)	21(22.82%	24(34.28%)		1
TIBC (N=162)				
High (n=62)	49(53.26%)	13(18.57%)	0.001	4.996(2.412,10.352)
Normal (n=100)	43(46.73%)	57(81.42%)		1
Iron (N= 162)				
Low (n= 63)	50(54.34%)	13(18.57%)	0.001	5.220 (2.518,10.819)
Normal (99)	42(45.65%)	57(81.42%)		1
Ferritin (N=162)				
Low (n= 127)	31 (33.69%)	9(12.85%)	0.003	3.444(1.513,7.841)
Normal /high(n= 35)	61(66.30)	61(87.14%)		1

4. Discussions

FC is the most common type of seizure in children which has excellent prognosis. Many risk factors like genetic factors, age, gender type and duration of seizure, family and developmental history, multiple seizures, perinatal exposure to antiretroviral drugs, history of maternal smoking and alcohol consumption during pregnancy have been studied as potential predictors of recurrent febrile seizures [14,15,16]. However, iron as risk factor for FC has contradictory results [5,6,7,8,9]. This study showed that patients with FC were more frequently anemic with iron deficiency than controls. One of the most common micronutrient deficiency is Iron deficiency affect at least one third of population in the world. The most common clinical presentation of iron deficiency is anemia, but other systems may also be affected. Central system manifestations like Behavioral impairments, Cognitive dysfunction, psychomotor retardation, are noticed. Other manifestations like pica, breath holding spells, restless leg syndrome may also be associated with iron deficiency. Effect of iron deficiency in the developing brain and mechanism like altered development of hippocampus neurons, delayed maturation of myelin and alterations in synaptic neurotransmitter systems which include Glutamate, Gamma – Amino Butyric Acid(GABA) Norepinephrine, Dopamine and serotonin may be responsible for these symptoms. [17,18]. Hence Iron deficiency reduces the metabolism of these neurotransmitters and may lead to onset of a convulsion. In this study 79.2 % of children in FC group and 20.8 % children in control group had anemia (p<0.001). Similar to our findings Pisacane et al, [7] also found higher frequency of anemia in FC cases (30%) than controls (14 %). They concluded that fever can deteriorate the negative effect of anemia on the brain and, hence, can cause convulsion. Contradicting these findings, Kobrinski et al [8]reported iron deficiency anemia in 25.1% FC group and 26.6% control but this study was conducted in small number of patients. In our study there were significant differences between the FC group and the control group regarding blood indices Hb, MCV, MCH, MCHC, all these parameters were lower in FC group. The mean of serum ironferritin was lower and TIBC was higher and statistically significant in FC group. Other studies had also found similar results like ours. [5,6,19,20] Daoud et al. [5] found that the average values of Hb, Hct and the mean level of ferritin were significantly lower in the FC group compared to the control group, and attributed this difference to the probable role played by iron deficiency in the occurrence of febrile convulsion. These results have been repeated in other studies [6,19,20].

Another study found that the incidence of FC in patients with thalassemia was much lower than among children in the general population [21]. Thus, iron overload may be a major factor in the brain metabolism that prevents febrile seizures. Hemolytic anemias were excluded in this study.

In contrast, Momen and Hakimzadeh found no relationship between iron-deficiency anemia with first febrile convulsion in children younger than 5 years of age in Iran [22]. In other studies, iron-deficiency anemia was less frequent among patients with febrile seizure than in controls. [8,9,23,24] Talebian et al [9] in 2006 reported that the probability of the occurrence of convulsion in children with anemia significantly decreases and anemia may have protective role against occurrence of FC. In their study blood samples for iron profile was drawn after

the body temperature of patient was brought down to normal level as ferritin is acute phase reactor that nonspecifically increases in response to any febrile illness [25]. We also had sent blood for iron profile after fever subsided. Derakhshanfar et al [26] attributed the probable reason for the protective role of iron deficiency to the role iron plays in the activity of exciting neurotransmitters such as monoamine oxidase and aldehyde oxidase. They also added that the lack of iron leads to a reduction in excitation power of the neurons and to a decline in the probability of excitation and convulsion in iron deficiency anemia. The differences between these studies and ours could be due to the difference in sample sizes and age groups of patients used in different studies; they could be as well due to unsuitable standardization and failure to consider intervening factors such as the factors causing fever.

Gastroenteritis was excluded from this study because dehydration in gastroenteritis can concentrate blood and mask anemia. Furthermore, if a person has bloody diarrhea they may develop anemia due to blood loss. Habits and diets of children play an important role in the absorption and storage of iron and in preventing iron deficiency anemia there were no significant differences in the economic conditions of families of two groups of children. All children were breast fed till 5-6 months and received solid food as cereals, beans, pulses, vegetables, carrot egg yolk, khichadi, fruits, meat, after this age. Most children naturally adapted themselves to the program of three meals in a day and were in family diet by the time they were 1 year old.

FC was 1.847 times more likely to have iron deficiency anemia [OR 1.847] in one study [27] and it was OR 3.3 with 95% CI1.7-6.5) in another study [7] In this study also risk of anemia was 5.971 times higher [OR 5.971 with 95% CI 2.938- 12.137] and risk of iron deficiency was 5.22 times higher [OR 5.220 with 95% CI 2.518-10.819], in FC than control by regression analysis.

5. Conclusion

In conclusions, iron deficiency anemia was significantly noted in children with FC in comparison with the control group. Therefore a possible role of low body iron status should be considered as risk factorfor development of FC As contradictory results have been reported regarding the role of iron insufficiency in FC further studies in larger population is recommended

List of Abbreviations

SD: Standard deviation
SPSS: Statistical Package for the Social Sciences
Hb: Hemoglobin
MCV: Mean corpuscular Volume
MCH: Mean corpuscular hemoglobin
MCHC: Mean corpuscular Hb concentration
RDW: red cell distribution width
FC: Febrile convulsion
CBC; Complete blood count
TIBC: Total iron binding capacity
TLC: Total leukocyte count
OR: Odds ratio
µg/dl: microgram per deciliter
>: More than
>: Less than
≤: Equal and less than
≥: Equal and more than

Authors' contributions

TM responsible for concept of article, designing article, collecting data and analysis, review of literature and write up of manuscript. KM responsible for concept of article, designing of article,, critical analysis and writing up of manuscript. BS responsible for statistical analysis and writing of manuscript. PC, SKS and AG responsible for review of literature and revision of the manuscript. The final document was approved by all authors.

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Limitations

The main limitation of this study was that this was a hospital based study so the results could not be generalized.

What this study adds

Various studies on relationship between FC and iron deficiency anemia have given contradictory results. This study adds on the information that iron deficiency anemia is a risk factor for FC and that iron supplementation may help prevent the convulsion.

Declaration of Conflicting Interests

The authors declare that there are noconflicts of interest with respect to the research, authorship and /or publication of this article

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