

The Relationship Between Iron Deficiency Anemia And First Febrile Convulsion In Children

Mohammad Razaq, Sanjeev K. Digra, Sunil Dutt Sharma, Ghanshyam S. Saini

Abstract

Febrile convulsion (FC) is a common cause of seizure in young children, with an excellent Prognosis. There are hypothesis that iron deficiency may affect febrile convulsion and the threshold of neuron excitation. This study was planned to investigate the relationship of iron deficiency anemia with febrile convulsions in children aging between 6months and 60 months . In this case-control study, the authors assessed 200 children with a diagnosis of first Febrile convulsion ,aged between 6 months and 5 years; during December 2013 to November 2015. The control group consisted of 200 Febrile children without convulsion: Controls were matched to the cases by gender and age. Laboratory tests consisted of complete Blood count (CBC). Serum iron, plasma ferritin and Total Iron Binding Capacity (TIBC) analyses were done in each patient. It was observed that the patients and controls were 22.86 ± 12.86 and 21.91 ± 13.58 months of mean age respectively. The amount of Hb, Hct, MCV, MCH, MCHC, RBC count, and serum iron and plasma ferritin was significantly higher and TIBC was significantly lower among the cases with febrile convulsion than the controls. The incidence of iron deficiency anemia was significantly higher in controls compared with the cases (P less than 0.016). The mean of temperature peak on admission was significantly higher in the febrile convulsion group than controls.

Key Words

Iron deficiency , Anemia, Fever, Seizure

Introduction

Febrile convulsions (FC) refer to the convulsions that occur in children between the ages of 6 months and five years , with body temperature of 38°C or higher not resulting from central nervous system (CNS) infection or any metabolic imbalance without any prior afebrile seizures. In the United States and Western Europe, they occur 2-4% of all children.(1-2)

Febrile convulsions have been studied extensively over the past two decades, and with the available literature practitioner's can easily assess the risks associated with such presentations.(2,3) Independent risk factors for febrile convulsions were height of temperature, history of febrile convulsions in a first degree of relatives, the number of fever episodes per year .(4) Genetic factors contribute significantly, as the relatives of these patients

are at increased risk compared to the general population.(5) Most studies have supported a multifactorial model with an estimated heritability of 75%.(6) Risk factors associated with a complex first febrile convulsion were age of 15 months or less, birth weight of 2kg or less, and initial temperature 38°C or less.(7) Iron deficiency anemia is one of the most common nutritional deficiency in the world today, especially in developing countries, with an estimated 5 billion people so affected (7). Iron is an important micro nutrient which is used roughly by all the cells in the human body. It is well understood that iron is a cofactor for several enzymes in the human body and has a role in the neurotransmitters production and function, hormonal function and DNA duplication, myelin formation and brain energy

From the Dept. of Pediatrics, Govt. Medical College/SMGS Hospital, Jammu (J&K), India

Correspondence to : Dr. Mohammad Razaq, Asstt. Professor Dept. of Pediatrics, Govt. Medical College/SMGS Hospital, Jammu (J&K), India

metabolism.(8-9) The relationship between iron deficiency and febrile convulsion is unknown. While some studies have shown iron deficiency anemia as a risk factor for the development of febrile convulsion, this relationship has not been confirmed by other studies while in others it has been stated that iron deficiency increases the threshold of neuron excitation and thus can play a protective role against febrile convulsion.(9-12) By keeping in view these contradictory results, we planned to study the relationship between iron deficiency anemia and febrile convulsion among the hospitalized children in the Shri Maharaja Gulab Singh (SMGS) hospital Govt. Medical College Jammu ; (Jammu and Kashmir). Thus the current study was undertaken to study the relationship of iron deficiency anemia with febrile convulsions in children amongst 6months to 60 months age group.

Materials and Methods

The study group consisted of all children with a diagnosis of first febrile convulsion (FFC), aged between 6 months and 5 years, without history of previous convulsion, developmental delay, neurological deficit or CNS infection and Shigella gastroenteritis patients who were treated at Govt. Medical College- Shri Maharaja Gulab Singh (SMGS) hospital Jammu (J&K) India department of Paediatrics, during November 2013 to December 2015. This case-control study involved total 200 patients and 200 controls. During hospitalization the children underwent careful physical and nervous system examination by the medical team on emergency ward duty, especially focusing on symptoms of meningeal irritations. Axillary temperatures (when 0.5 degree was added to them) exceeded 38°C, they were included in the study. Acetaminophen 10-15mg/kg as an antipyretic was administered every 4-6 hours for children whose body temperature exceeded 38°C. The case and control groups were matched with respect to age, sex, body

temperature, developmental curve and history of treatment with iron supplements. The family histories of children with respect to febrile convulsion and anemia were also checked and the related information was recorded. A convulsion accompanied by fever that lasted less than 15 minutes without focal symptoms was considered as a simple febrile convulsion. In suspected cases of meningitis and Shigella gastroenteritis (based on the presence of white blood cells in faeces or a history of bloody diarrhea), lumbar puncture was done for cerebro spinal fluid analysis and if meningitis was diagnosed, the child was excluded from the study. After normalization of body temperature of all the affected children, 5ml of blood sample was taken from each child for complete blood count (CBC) and to measure the levels of serum Iron, plasma ferritin, and TIBC (Total Iron Binding Capacity), in order to assess the Iron deficiency anemia. In *Table 1*, the normal values of blood indices are listed. Children with blood indices less than those presented in *Table 1* were considered to be suffering from iron deficiency anemia. Anemia is diagnosed when the hemoglobin levels falls more than two standard deviations below the normal level of the related age group and sex, as presence of Hb < 10.5g% for 6-24 months and < 11.5g% for 24-60 months old, Hct < 33% for 6-24 months and < 34% for 24-60 months old, MCV < 70 fl for 6-24 months and < 75 fl for 24-60 months old, MCH < 23pg for 6-24 months and < 24pg for 24-60 months old, MCHC < 30g% for 6-24 months and < 31g% for 24-60 months old, RBC < 3.7x10⁶ for 6-24 months and < 3.9x10⁶ for 24-60 months old, serum iron concentration < 40µg/dl before 1 year old and < 50µg/dl after 1 year old, plasma ferritin < 7µg/l and TIBC > 430 µg/dl. Complete blood counts, the levels of serum iron, plasma ferritin and TIBC were done to differentiate iron deficiency from other causes of anemia. In iron

Table 1. Normal Values of Blood Indices in Various Age Groups of The Children

Age	Hemoglobin (g/dl)	Hematocrit %	MVC	MCH	MCHC	RBC	Sr. Iron Conc.	Plasma ferritin	TIBC
6-24 months	<10.5g%	<33%	<70 fl	<23pg	<30g%	<3.7x10 ⁶	<40µg/dl before 1 year of age and <50µg/dl after 1 year of age	<7µg per litre	More than 430 µg per dl.
24-60 months	<11.5%	<34%	<75fl	<24pg	<31g%	<3.9x10 ⁶			

Table 2. Baseline Characteristics of two Groups

Age/ Sex	The febrile convulsion group (n=200)		The control group (n=200)	
	Number	Percentage	Number	Percentage
Age (months)				
6-12	41	21.5	56	29.3
12-36	121	60.5	86	43
36-60	18	9.4	46	24.1
More than 60	20	10.5	12	6.3
Sex				
Girls	80	40	87	43
Boys	120	62.8	113	59.2

Table 3. Age and duration wise distribution of two Groups

Age group (months)	Simple febrile convulsion (n=132-66%)	Complex febrile convulsion (n=68-34%)
	6-12	23(17.4%)
12-24	65(49.2%)	29 (42.6%)
24-36	22(16.7%)	10 (14.7%)
36-48	15(11.4%)	7 (10.3%)
48-60	7(5.3%)	8 (11.8%)
Duration:		
<1h	20 (15.1%)	18 (26.5%)
1-24h	96 (72.7%)	34 (50%)
>24h	16 (12.1%)	16 (23.5%)

Table 4. Hematological Findings of two Groups

Index	The febrile convulsion group(n=200)	The control group(n=200)	P value
WBC	10746.07 ± 3804.77	11905.75 ± 5323.27	0.001
RBC	4.2853 x 10 ⁶ ± 4.68968 x 10 ⁵	4.3252x10 ⁶ ± 4.3252x10 ⁵	0.437
Hb	11.28 ± 0.94	10.97 ± 1.45	<0.001
Hct	34.85 ± 2.29	33.5 ± 3.88	<0.001
MCV	81.19 ± 4.66	75.94 ± 5.99	0.036
MCH	27.07 ± 2.63	27.00 ± 4.35	0.004
MCHC	33.54 ± 1.73	31.92 ± 2.32	0.031
Platelet	197701.57 ± 64285.54	334490 ± 39322.8	<0.0001
Fe	63.72 ± 24.63	63.23 ± 26.91	0.112
TIBC	338.65 ± 76.85	342.07 ± 74.99	0.956
Ferritin	87.50 ± 37.04	80.78 ± 35.43	0.205

deficiency, serum iron and plasma ferritin decline but TIBC rises. In addition to this CBC also shows a fall in red blood cells indices (the number and the volume of the red blood cells and the mean hemoglobin conc.) in iron deficiency anemia. Children with anemia resulting due to other causes (hemolysis, bleeding diathesis, thalassemia, etc.) were excluded from the study. The Ethics Committee of Govt. Medical College/University of Jammu approved this study. All the parents or guardians of the sick children

gave their written consent to their children taking part in the study; they could withdraw from the study anytime they desired.

Statistical Analysis

Results of the experiments concerning the case and control groups were separately entered into SPSS-19. Descriptive distribution and chi-square tests were performed for the qualitative variables and the independent t-student test was carried out and p-values

less than 0.05 were considered significant.

Results (Table 1-4)

There were a total of 200 patients and 200 controls. The patients and controls were 22.86 ± 12.86 and 21.91 ± 13.58 months of mean age, respectively. Both patients and the controls had a similar proportion of males (57.5% vs. 59%) and females (42.5% vs. 41%). Upper respiratory tract infections and gastroenteritis were the most frequent underlying illnesses for fever in cases and controls respectively.

The mean of temperature peak on admission was significantly higher in the FFC group ($38.74 \pm 0.76^\circ\text{C}$) compared with the controls ($38.2 \pm 0.67^\circ\text{C}$) ($P < 0.0001$). Table 2 shows the time interval between initiation of the fever and the seizure attack in the patients with FFC.

Simple seizures were the most frequent type of seizures in all age groups, and the relationship between duration of initiation of fever and type of convulsion attacks for cases with FFC was statistically significant ($p = 0.014$).

Data on the patient's hematologic status are provided in Table 4 as shown in the table, the amount of RBC, serum iron, and PF were significantly higher, and TIBC was significantly lower among the cases with FFC than in the controls. The amount of Hb, Hct, MCV, MCH, and MCHC were also higher among cases than controls, but differences were not statistically significant.

Family history of febrile convulsion or epilepsy, iron supplement therapy, and presence of iron deficiency anemia among cases and controls are detailed in Table 4. Iron deficiency anemia was less frequent among the cases with FFC, as compared to the controls, and its difference was not statistically significant. A significantly higher proportion of children from the FFC group had a family history of epilepsy ($P < 0.0001$).

Discussion

As dietary habits of children would have an important influence on iron intake, all of our participants had breast or formula feeding until 6 months of age; solid foods such as cereals, rice and vegetable soup added on at 6 months of age. However, 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 the families of the two groups of children studied. Most children naturally adapted themselves to

the program of three meals in a day by the time they were 1 year old. Moreover, the differences between the two groups regarding iron supplements were not significant. Taking the studies conducted into account, it can be said that there is a considerable difference of opinion concerning the relationship of anemia (particularly iron deficiency anemia) and febrile convulsion in children. Results of our study showed that the prevalence of anemia in the febrile convulsion group was considerably lower than that of control group so that 22.5% of the children in the febrile convulsion group suffered from anemia, while 34.0% of the children in the control group afflicted with it ($P < 0.001$). There were significant differences between the febrile convulsion group and the control group regarding blood indices such as Hb, Hct, MCV, MCH, and MCHC as well, so that all these indices were higher in febrile convulsion group as compared to the control group. The means of serum iron and serum ferritin in the febrile convulsion group were higher than the means of the control group, but these differences were not significant. The results of our study confirm those obtained by Talebian *et al.* (13) and Derakhshanfar *et al.* (16). We tried to select a suitable sample and to match factors that may influence the result as well. Talebian *et al.* (13) concluded a case-control study in Kashan in 2006 on 120 children less than 5 years of age. They reported that the probability of the occurrence of convulsion in children afflicted with anemia not only does not increase but it apparently decreases significantly, and that anemia may have a protective role against the occurrence of febrile convulsion. The sample volume in their research seems to be sufficient for a case-control study, although they give few details about matching of the studied groups. As we know, ferritin is an acute phase reactor that nonspecifically increases in response to any febrile illness (14). Given that blood samples were taken to measure the levels of Fe, TIBC, and ferritin after the body temperature of the patients had been brought down to the normal level, the differences in ferritin levels between the two groups cannot be attributed to fever. (15) In a study carried out on a sizable sample consisting of 1000 children (500 in the case group and 500 in the control group), Derakhshanfar *et al.* (16) studied the relationship between iron deficiency anemia and febrile convulsion. They found that the level of iron deficiency and iron

deficiency anemia in the control group were significantly higher than those in the case group, and concluded that the risk of febrile convulsion in children suffering from iron deficiency was less than the risk in other children. In their study, the criteria for excluding children from the study were only epilepsy, neuro-developmental disorders, other types of anemia, and current treatment with iron supplements. We also dealt with the factors causing fever because these factors can affect blood cell profiles. Results of our research, compared to those of Talebian *et al* (13) were achieved using more suitable risk factors and standardization, and a larger sample size was employed as well. Moreover, our results, compared to those obtained by Derakhshanfar *et al* (15) are more reliable given our more suitable standardization and our more limiting criteria for including and excluding participants. In the study conducted by Derakhshanfar *et al* (15) they attributed the probable reason for the protective role of iron deficiency to the role iron play in the activity of exciting neurotransmitters such as monoamine oxidase and aldehyde oxidase. They added that the lack of iron leads to a reduction in the excitation power of the neuron 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 fact that these researchers used different sample sizes and age groups of patients; they could be as well due to unsuitable standardization and failure to consider intervening factors such as the factors causing fever. Of course, the fact that we only studied hospitalized patients could be one of the limitations of our study.

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.

References

1. Shinnar S. Febrile Seizures In: Swaiman KF, Ashwal Ferriero DM, editors. Paediatric neurology principals and practice. 4th ed. Mosby Elsevier; 2006 .pp. 1079-89.
2. Hampers LC, Thompson DA, Bajaj L, Tseng BS, Rudolph JR. Febrile Seizure: measuring adherence to AAP guidelines among Community ED physicians. *Paediatric Emerg Care* 2006; 22 (7): 465-69.
3. Warden CR, Zibulewsky J, Mac S. Evaluation and management of febrile seizures in the out of hospital and emergency department settings. *Ann Emerg Med* 2003; 41: 215-22.
4. Huag CC, Wang ST, Chang YC, Tsai JJ. Risk factors for a first febrile convulsion in children: a population study in Southern Taiwan. *Epilepsia* 1999; 40(6): 719-25.
5. Tsuboi T. Genetic aspects of febrile convulsions. *Hum Genet* 1977; 38: 169-73.
6. Johnson WG, Kgler SL, Stenroos ES, Meulener MC, Rangwalla I, Johnson TW. etal Pedigree analysis in families with febrile seizures. *Am J Med Genet* 1996; 61: 345-52.
7. Ling SG, clinic characteristics and risk factors for a complex first febrile convulsion. *Singapore Med J* 2001; 42(6) : 264-7.
8. Hart field D. Iron deficiency is a public health problem in Canadian infants and children. *Paediatr Child Health* 2010; 15: 347-50.
9. Erikson KM, Jones BC, Hess EJ, Zhang Q ,Beard JL. Iron deficiency decreases dopamine D1 and D2 receptors in rat brain. *Pharmacol Biochem Behav* 2001; 69: 409-18.
10. Kumari PL, Nair MK, Nair SM, Kailash L, Geetha S. Iron deficiency as a risk factor for simple febrile seizures: A case control study. *Indian Pediatr* 2012; 49: 17-9.
11. Heydarian F, Vatankhah H. The role anemia in first simple febrile seizure in children aged 6 months to 5 years old. *Neurosciences (Riyadh)* 2012; 17:226-9.
12. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case control study. *Seizure* 2009; 18: 347-51.
13. Talebian NM, Mosavi GA, Khojasteh MR. Relationship between febrile seizure and anemia. *Iran J Pediatr* 2006; 16:79-82.
14. Mahdavi MR, Makhloogh A, Kosaryan M, Roshan P. credibility of the measurement of serum ferritin and transferrin receptor as indicators of iron deficiency anemia in haemodialysis patients. *Eur Rev Med Phamacol Sci* 2011; 15:1158-62.
15. Derakhshanfar H, Abas Khanian A, Alimohammadi H, Modanlookordi M. Association between iron deficiency anemia and febrile seizure in children. *Med Glas (Zenica)* 2012;9: 239-42