

# The Relationship between Iron Deficiency Anemia and Simple Febrile Convulsion in Children Aged 6 Months to 5 years

Running title: Iron Deficiency Anemia and Simple Febrile Convulsion

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## Abstract

*This study aimed to evaluate the relationship between simple febrile convulsion and iron deficiency anemia in children. In this case-control study, 60 children aged 6 months to 5 years old with simple febrile convulsion hospitalized in the Pediatric Unit of Heshmatiyeh Hospital of Sabzevar. separately for case and control groups and the two groups were compared in terms of blood indexes and iron deficiency anemia. The significance level was considered P-value <0.05. The case and control groups were matched in terms of age and sex, and there was no significant difference between the two groups. The results showed the prevalence of iron deficiency anemia in the febrile convulsion group was somewhat lower than that of the control group. However, no significant difference was found between the two groups ( $p > 0.05$ ). The results of this study showed that the risk of convulsion is not higher in cases with anemia. However, iron can be prescribed with caution for high-risk patients with a history of previous convulsion or a positive family history of this condition, if they suffer from iron deficiency anemia. Moreover, according to the results of previous studies and the present study, conducting extensive research simultaneously in several centers is recommended.*

**Keywords:** Simple fever, Simple convulsion, Iron deficiency, Anemia

## **Introduction**

A febrile convulsion is the most common childhood neuropathic disorder that occurs in children aged 6 months to 5 years old (1). It is seen in 2 and 5% of all children. The occurrence of this disorder is associated with a temperature higher than 38 ° C, without evidence of central nervous system or other underlying diseases (2). Its main reason is the inadequacy of the non-mature brain system against the stress caused by high fever (3). Many studies have been conducted to explain the risk factors that predispose children to febrile convulsion. Based on these studies, the risk factors of this disorder are age (peak of its occurrence around the age of 14-18 months old), prematurity and race (Asian) (4), family history of fever and convulsion (5), delayed developmental and history of hospitalization in the neonatal intensive care units for more than 28 days (6), some vaccines such as influenza vaccine, measles, rubella, and mumps, or pertussis vaccine (7). Moreover, bacterial and viral infections (8-10), smoking and using alcohol by the mother (9, 11-13), and high fever (14) are among the risk factors that can be prevented and modified. In investigating the risk factors, despite the above-mentioned studies, limited studies have investigated the correlation between micronutrients and fever and convulsion and they have reported zinc (15) and iron deficiencies (16, 17) as possible causes of this disorder. Iron deficiency is the most common deficiency in micronutrients. The prevalence of iron deficiency and anemia associated with it is high in the world, especially in developing countries, so that WHO estimates that 27% of pre-school children suffer from iron deficiency anemia. This disorder can cause iron deficiency anemia by reducing the production of hemoglobin. It can be modified and treated. Iron is needed for brain metabolism, neurotransmitter metabolism, and myelination for neurons, which can change the threshold of stimulation of neurons. It has a high correlation with delay in permanent motor and cognitive development, even after treatment and modification (18-21). Studies conducted on the role of iron deficiency in febrile convulsion have provided completely contradictory results. In some of these studies, iron deficiency has been reported as a risk factor (22). Some studies have not reported iron deficiency as a risk factor. Some studies have reported that iron deficiency can have a protective effect on fever and convulsion (23). Due to the significant prevalence and the importance of prevention-based interventions in this disorder as well as the contradictory inconsistencies in the results of past studies, we decided to evaluate the relationship between iron deficiency and febrile convulsion in children hospitalized in Heshmatiyeh Hospital of Sabzevar.

## **Method and Materials**

### **Study design**

In this case-control study, 60 children aged 6 months to 6 years with simple febrile convulsion hospitalized in the pediatric unit of Heshmatiyeh Hospital of Sabzevar from October 2017 to mid-winter of the same year (case group) and the same number of children who had a fever but no convulsion (control group) were studied and two groups were compared in terms of iron deficiency anemia. The sample size according to the results of similar studies and the mean and standard deviation of ferritin, Hb, Hct, MCV, Fe and TIBC in case group with fever and convulsion, compared to the control group without fever and convulsion and error rate  $\alpha = 5\%$

and  $\beta = 80\%$ , was calculated 55 people in each group. Considering the probability of 5% dropout in samples, the final sample size was calculated by 60 people. Non-randomized and purposeful sampling was used in this study, in which 120 patients were studied. Accordingly, patients were selected as the sample of the study after their referring and hospitalization in the pediatric unit and after examining the inclusion criteria and obtaining their consent. In all children, body temperature was measured by the axillary method at the beginning of hospitalization and if their fever was above  $38^{\circ}\text{C}$ , they were included in the study. Acetaminophen (10-15 mg/kg of body weight) was used every 4 to 6 hours as a fever drug. A convulsion for less than 15 minutes along with fever, without local and focal symptoms, was considered as a simple febrile convulsion. Other inclusion criteria in the fever and convulsion (febrile convulsion) group included no previous episodes of febrile convulsion, lack of convulsion caused by known organic problems (complex convulsion, or delayed development and neurological defects, central nervous system infection, presence of *Shigella* gastroenteritis based on the presence of red blood cells and white blood cell in the fecal test or chronic diarrhea of *Shigella* gastroenteritis).

Exclusion criteria also included other causes of anemia (hemolysis, hemorrhage, thalassemia, etc.), as well as the lack of parental collaboration for the continuation of the study. After normalizing the body temperature, five ml of peripheral blood samples were taken from all patients and placed in heparin and non-heparin test tubes to conduct the complete blood count (CBC), serum iron, and ferritin plasma and TIBC tests and they transferred to Heshmatiyeh Hospital laboratory. In this study, the results of the requested blood tests were recorded quantitatively to determine the presence of iron deficiency anemia.

#### **Data collection and analysis**

Data needed for this study were recorded in a checklist containing demographic characteristics of the patients, clinical symptoms at baseline (body temperature), and other medical (24, 25) and drug information and medical records, and the level of blood indices of hemoglobin, hematocrit, ferritin, serum iron, and TIBC. All patients were examined until the end of the study and no patient was excluded due to the reasons such as death or non-follow-up. After receiving the answer of the relevant tests from Heshmatiyeh Hospital, iron deficiency anemia in the studied children based on the main criteria of iron deficiency anemia (Ferritin  $<12\text{ ng / mL}$ ,  $\text{Fe / TIBC} <15\%$ ) and other findings as a reduction of hemoglobin and the MCV less than 2 standard deviations from the normal mean for the child's age and a reduction in MCHC ( $<30\%$ ) and MCH ( $<27\text{ pg}$ ). Then, the data separately for two groups of case and control were entered to the SPSS 18 software and descriptive tests were used to describe the data and Chi-square test was used for the qualitative variables and an independent t-test was used for the quantitative variables.

#### **Ethical clearance**

The study was approved by Ethics Committee, Sabzevar University of Medical Sciences, Sabzevar, Iran.

## Results

In this study, 60 children with fever and simple convulsion were considered as case groups and 60 children with fever and without convulsion were considered as the control group and they were evaluated in terms of age and sex to determine the homogeneity. In terms of age, the highest frequency was observed in children aged between 12 and 23 months in both groups, and 15 patients in the control group (25%) and 26 patients in the case group were in this age range (43.3%) (Table 1).

**Table 1.** Frequency distribution of age range in terms of month in the case and control groups

Age range (in terms of month)	Control group %	Case group %
6 – 11	% 23.33	%15
12 – 23	% 25	%43.3
24 – 35	% 13.33	%10
36 – 47	% 10	%5
48 – 59	% 11.66	%8.3
60 – 72	% 18.33	% 18.33

The most common cause of fever and hospitalization in the control group was gastroenteritis (25%) and the most common cause of fever in febrile convulsion group was upper respiratory infection (35%) (Table 2). There were no significant differences between the two groups (P-value> 0.05) (Table 3).

**Table 2.** Comparison of the frequency of hospitalization causes in the case and control groups

Cause of hospitalization	Control children	Case group
Urinary tract Infection	66.11%	10%
Upper respiratory infection	13.33%	35%
Gastroenteritis	25%	23.33%
FUO	20%	10%

<b>Fever after vaccination</b>	6.66%	6.66%
<b>Pharyngitis</b>	5%	3.33%
<b>Other causes</b>	21.66%	11.66%
<b>TOTAL</b>	100%	100%

**Table 3.** Distribution of patients in terms of sex and age in both case and control groups

<b>Demographic variables</b>		<b>Control group</b>	<b>Case group</b>	<b>P value</b>	<b>Test</b>
Age (mean± standard deviation)		30.43±(22.41)	28.33±(22.21)	0.6	t-test
Sex	femal e	43.3 %	%41.7	0.85	Chi square
	male	% 56.7	%58.3		

There was no significant difference between two groups in the blood indices, including Hb, HCT, Ferritin, Iron, TIBC (P-value> 0.05), indicating that the incidence of convulsion was significantly correlated with the increase or decrease of the mean of blood indices in patients studied (Table 4). Based on the diagnostic criteria of iron deficiency anemia in children (Fe / TIBC <15%), 33 (55%) patients in the case group and 35 (58.33%) patients in the control group had iron deficiency anemia and no significant difference was found between the two groups (p = 0.71) (Table 5).

**Table 4.** Comparison of the mean blood indices in the febrile convulsion group (case group) and control group

<b>variable</b>	<b>group</b>	<b>mean</b>	<b>SD</b>	<b>P-value/T-test</b>
<b>Hb</b>	case	11.05	1.007	0.37
	control	11.22	1.016	
<b>HCT</b>	case	33.70	2.17	0.39
	control	34.08	2.66	
<b>Ferritin</b>	case	127.54	101.64	0.2
	control	106.54	75.58	
<b>Iron</b>	case	48.82	16.76	0.86
	control	48.28	17.80	
<b>TIBC</b>	case	326.98	34.06	0.97

control	327.25	45.17
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**Table 5.** Comparison of the frequency distribution of iron deficiency anemia in case and control groups

Anemia	Frequency (%)			P-value
	Yes	No	Total	
<b>Case</b>	35 (58.33%)	25 (41.66%)	%100	0.71
<b>Control</b>	33 (55%)	27 (45%)	%100	

### Discussion

The present study was conducted to determine the relationship between iron deficiency anemia and fever and convulsion in children aged 6 months to 5 years old. Iron deficiency anemia is the most common blood disease in neonates and children and is commonly associated with nutritional deficiencies (26). In this study conducted on 120 children admitted to the hospital, the highest febrile convulsion was seen in the age group of 12 to 23 months. The most common causes of fever and hospitalization in the control group were gastroenteritis (25%) and the most common cause of fever in the febrile convulsion group was upper respiratory tract infection (35%). Blood indices tests showed that the mean serum iron and ferritin were high in the febrile convulsion group than that in the control group, but these differences were not significant and the mean TIBC level was not significantly different between the two groups (P-value > 0.05).

Moreover, the mean of hemoglobin and hematocrit was 11.05 and 33.7 in the case group and 11.22 and 34.08, respectively, in the control group. Therefore, the prevalence of iron deficiency anemia in the febrile convulsion group was somewhat lower than that of the control group (58% versus 55%), but there was no statistically significant difference between the two groups ( $p = 0.71$ ). In reviewing the literature, the predictions on the relationship between iron deficiency anemia and fever and convulsion were very contradictory, for example, in contrast to the results of the present study, some evidence was found as follows: the study conducted by Papageorgiou et al (26) since March 2009 to 2011 in a case-control study on 100 children (age range of 6 months to 6 years) ( 50 children in case group and 50 children in the control group, the level of blood indices including Hct, Hb, ferritin, serum iron TIBC, was measured. It suggested that in febrile convulsion children, plasma ferritin levels were lower than normal and TIBC levels were higher than normal. In the study conducted by Sharif et al (27), the incidence of iron deficiency anemia was 45% in the control group and 22% in the case group and they concluded that the low level of blood iron and iron deficiency anemia could be an exacerbating factor for the development of convulsion in children with fever. In a review of a meta-analysis, in which pooled data of 17 studies with 2387 cases were, results showed that the presence of iron

deficiency anemia in children with a 1.98 odds ratio was significantly associated with febrile convulsion ( $P = 0.003$ ) (28). However, before the meta-analysis mentioned, studies conducted in Iran (29), Pakistan (29), and India (30) confirmed this relationship.

The main causes that lead to the different results among the studies mentioned above and our study may be the difference in the number of samples. Also, all samples of the case group in the present study experienced the first febrile convulsion, but in many of the studies mentioned, some of the samples had a history of febrile convulsion. Considering the type of convulsion, including simple convulsion and complex convulsion might be also involved in these differences, which was considered in some studies, while only simple convulsion was considered in this study. However, consistent with the present study, in the study conducted by Yusefchian et al to evaluate the relationship between iron deficiency anemia and simple febrile convulsion in children, it was found that the prevalence of anemia in the febrile convulsion group was lower than that of the control group, so that 22.5% of children in febrile convulsion group and 34% in the control group showed anemia ( $P < 0.001$ ). Also, the febrile convulsion group had high blood indices such as Hb, Hct, MCV, MCH, and MCHC compared to the control group ( $P < 0.001$ ) (31). However, these differences were not significant in the present study. Amirsalari et al (32) also did not report a significant relationship between iron deficiency anemia and febrile convulsion. If the present study or the studies that did not confirm this relationship were conducted on a larger population, they would have reported more reliable results. Also, our patients were matched only in terms of age and sex and if samples were matched in terms of other variables, such as social, economic, and nutritional status, more accurate results would be achieved. Another important point is that our study was conducted only on hospitalized children, which can be considered as a limitation and reduce the generalizability of the results. According to the present study, it may be argued that although iron deficiency is fluctuating in these patients, we cannot state with certainty that iron deficiency plays a significant role in the febrile convulsion. However, iron can be prescribed with caution for high-risk patients with a history of previous convulsion or a positive family history of this condition, if they suffer from iron deficiency anemia. Moreover, according to the results of the previous studies and the present study, conducting extensive research simultaneously in several centers is recommended.

### **Conflict of interest**

The authors declare that there is no conflict of interest.

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