

# RESEARCH ARTICLE

## EVALUATION OF IRON STATUS IN 9-MONTH TO 5-YEAR-OLD CHILDREN WITH FEBRILE SEIZURES: A CASE-CONTROL STUDY IN THE SOUTH WEST OF IRAN

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### Abstract

#### Objective

Febrile convulsions are prevalent in children aged between 9 months and 5 years, with an incidence of 2-5%. On the other hand, iron deficiency anemia is the most common hematologic disease of infancy and childhood with a period of incidence that coincides with the time of developing febrile convulsions. Therefore, it is hypothesized that there is a possible association between these conditions. This study was designed to elucidate this association.

#### Materials & Methods

Two sex and age matched groups (n=50 in each) of 9-month to 5-year-old febrile children who were admitted to Abuzar Hospital between September 2003 and October 2004 were selected. The first group, or the case group, included children with the first attack of febrile seizure and the second group, or the control group, included febrile children without seizure. Blood samples were collected for measuring complete blood count (CBC) indices, serum Iron, ferritin and total iron binding capacity (TIBC) levels.

#### Results

Both groups were comparable for age, sex, and the type of febrile illness at admission, except for seizure. There was no significant difference in CBC, Iron and TIBC between two groups but a significant difference was seen in MCV (Mean Corpuscular Volume), especially in females (P= 0.017). The ferritin level in the case group was significantly lower (30.3 ±16.5 µg/dl) than the control group (84.2 ±28.5 µg/dl) (P= 0.000).

#### Conclusion

The findings of this study suggested a positive association between iron deficiency and the first febrile seizure in children. Supplemental iron may prevent the recurrence of febrile seizure. Prudently, further studies with larger sample sizes and longer follow-up periods need to be undertaken to substantiate this hypothesis.

**Keywords:** Febrile seizure, Iron, ferritin level, Anemia, Children

### Introduction

According to International League Against Epilepsy (ILAE), a febrile seizure is defined as a seizure attack associated with a febrile illness unrelated to brain infection or acute electrolyte imbalance in children older than one month without any previous history of afebrile seizure (1, 2). Febrile seizures are one of the most common neurologic problems during infancy and childhood

periods, occurring in 3-4% of the children, with an excellent prognosis. Its incidence in Japan and Mariana islands has been reported as 7% and 14%, respectively. They occur rarely before 9 months and after 5 years of age, with a peak incidence between 14 -18 months of age (3). Febrile seizures are classified to simple (typical) and complex (atypical) types. About 39 %of the emergency referrals with febrile seizures suffer from the complex type. On the other hand, the etiology of febrile seizures is not clear. Different factors have been considered including familial (genetic) factors, prenatal factors, present acute illness, the highest degree of fever and finally, anemia. (1) Iron deficiency anemia, as the most common type of anemia during infancy and childhood, occurs usually between 9-24 months of age and this period coincides with the peak incidence of febrile seizures (4). Iron has an important role in multiple physiological functions of neurotransmitters. Many of the nervous system enzymes are iron-dependent for their proper activities. It has been determined that iron depletion has negative effects on neurocognitive functions of children and supplemental iron can reduce breath-holding spells. On the other hand, fever can exaggerate the negative effects of anemia on brain (5).

Several studies with controversial results have attempted to evaluate the relationship between iron deficiency anemia and febrile convulsions in different areas of the world. Kobrinsky et al. found that iron deficiency anemia was less common in the febrile seizure group than the febrile seizure-free control group (6). Pisacane et al. also found that iron deficiency anemia was more common in the febrile seizure group than two groups of children suffering from febrile illnesses (7).

Momen et al. compared 100 children suffering from febrile seizures with 100 febrile children affected by acute febrile illnesses without seizure including upper and lower respiratory, gastrointestinal and urinary tracts infections. There was no significant

difference between the two groups regarding anemia (8). Batieha et al. compared 75 children suffering from febrile seizures with 75 children affected by acute febrile illnesses without convulsion. Both groups were matched for sex and age distribution. The febrile seizure group had a lower mean serum ferritin level than the control group (9). Similar results were observed by Rehman et al. who performed a study similar to Batieha et al., but with 30 children in each group. (10). Hartfield et al. conducted a retrospective case control study in Canada and compared 361 children aged 6 to 36 months who presented with febrile seizures with 390 otherwise healthy controls who presented with a febrile illness and determined iron status using MCV, RDW, and hemoglobin. They found that 9% of the cases had iron deficiency and 6% had iron deficiency anemia, compared to 5% and 4% of controls, respectively (11).

Vaswani et al. studied fifty children between 6 months and 6 years with the first episode of febrile seizure (Cases) and 50 children with febrile illnesses but without convulsions (Controls). Iron deficiency was determined by measuring hemoglobin, red blood cell indices and serum ferritin. Serum ferritin level was significantly low in children with the first episode of febrile seizure (12).

Bidabadi et al. assessed 200 children with the first episode of febrile convulsion, aged between 6 months and 5 years, and an age-matched and sex-matched control group. The results of their study suggest that iron deficiency anemia was less frequent in cases with febrile convulsions, as compared to controls, and no a protective effect of iron deficiency was seen against febrile convulsions (13).

Because of the controversies regarding the positive or negative effect of iron on the occurrence of febrile seizures, we decided to study the relationship between febrile seizures and iron deficiency anemia in 9-month to 5-year-old children, the common age for the occurrence of febrile seizures.

## Materials & Methods

In this case-control cross-sectional prospective study, 100 children who were admitted to Ahvaz Abuzar Children's Hospital between September 2003 and October 2004 were evaluated. The study was approved by the University Hospital and Ahvaz Jundishapur University of Medical Sciences Ethics Committees, and all subjects signed informed written consents before participation. The patients were divided into two equal groups of 50. This number was based on coincidence quotient power of 99% and 90%. Our case group consisted of 50 children aged between 6 months and 5 years who suffered from a single episode of simple febrile convulsion which was not due to brain infection, electrolyte imbalance or drug toxicity. They had a rectal temperature of 39°C or more but had no previous history of seizure attacks.

Fifty febrile, age- and sex-matched children suffering from acute febrile illnesses with a rectal temperature of 39°C or more and no history of seizure or any other problems were selected as the control group. Upon arrival to the emergency room, the history was taken and physical examination was performed. Following parents' consent, blood samples were taken for evaluating CBC (Complete Blood Count), Iron, TIBC (Total Iron Binding Capacity), ferritin and other necessary laboratory tests. All necessary information was recorded in previously prepared

questionnaires.

In this study, all requested laboratory tests were performed by the same Abuzar Hospital laboratory expert. Serum ferritin level was measured with ELISA (Enzyme Linked Immunosorbent Assay) method using the Immonotech measuring kit made in Germany. Hb <110 g/L, MCV <72 fl, ferritin <20 µg/dL and TIBC <440 µg/dL were considered as iron deficiency anemia indices (5).

For comparing the continuous quantity and quality variables between two groups, T-test was used. Cramer and Phi test was used to compare the quality variables between two groups. The confidence interval was calculated and a P value less than 0.05 was considered significant.

## Results

T-test showed no significant difference between the two groups regarding age, serum Hb level, RBC (Red Blood Cell) mass count, serum iron and TIBC levels (P= 0.649, 0.9, 0.9, 0.4 and 0.3, respectively) but a significant difference was seen in the serum ferritin level (P= 0.000) and blood RBC-MCV, especially in females (P= 0.017). However, the serum ferritin level in the case group was significantly lower (30.3 ±16.5 µg/dl) than the control group (84.2 ±28.5 µg/dl) (P= 0.000) (Table 1). Comparing Pearson chi-Square test showed no significant difference in sex distribution between two groups (P= 0.685) (Table 2).

**Table 1.** Comparison of different indices between case and control groups

Group	RBC <sup>1</sup> mass (average)	Hemoglobin (average)	MCV <sup>2</sup> (average)	Ferritin (average)	Iron (average)	TIBC <sup>3</sup> (average)
Case	4.4892	11.292	72.56	30.312	79.50	297.24
Control	4.4990	11.458	74.40	96.390	81.88	291.62
P value	0.919(NS*)	0.232 (NS*)	0.017 (Significant)	0.000 (Significant)	0.467 (NS*)	0.366 (NS*)

1: RBC: Red Blood Cell, 2: MCV: Mean Corpuscular Volume, 3: TIBC: Total Iron Binding Capacity

\*: NS: Not Significant

**Table2.** Comparison of case and control groups regarding number, age and sex

Group (Number)	Male (%)	Female (%)	Total number (age distribution)	P value (age , sex)
Case	30(60%)	20(40%)	50(6-60 months)	Age: 0.649 (NS*)
Control	30(60%)	20(40%)	50(6-60 months)	Sex: 0.685 (NS*)
Total	60(60%)	40(40%)	100	

\* NS: Not Significant

### Discussion

Febrile seizures are the most common type of childhood seizure disorders. It has been hypothesized that many factors are involved in febrile convulsions including familial (genetic) and prenatal factors, present acute illness, highest degree of fever and finally, iron deficiency anemia (5). Our study revealed that serum ferritin level, as an important indicator of body iron store situation, was significantly lower in children suffering from febrile seizures than children in the control group ( $P = 0.001$ ). This finding comes in agreement with other studies; Pisacane et al. (Italy, 1996), Batiha et al. (Jordan, 2002), Rehman et al. (Pakistan, 2005), Hartfield et al. (Canada) and Vaswani et al. (India, 2006) found the same results as the present study. They proposed that iron deficiency anemia was more common in children with febrile seizures than control groups (6, 8, 9, 10, 11, 12).

On the other hand, in 1995, Kobrinsky et al suggested that iron deficiency anemia raised the seizure threshold (6). In 2006, Bidabadi et al suggested that iron deficiency anemia was less frequent in cases with febrile convulsions compared to the controls, and stated that iron deficiency was not protective

against febrile convulsions (13).

This contrasting finding, along with our findings, may explain what Kobrinsky et al. reported in their study: the low number of children enrolled in their study (25 children with febrile seizures against 25 febrile children without seizures) and their criteria for assessing anemia were only based on blood Hb level, MCV and MCH (Mean Corpuscular Hemoglobin), without measuring serum ferritin level. These parameters do not reveal the real bone marrow iron storage status. Ferritin is a protein carrier for iron and is the iron storage source in the body. Measuring serum ferritin level is a specific, sensitive and a reliable test for detecting iron depletion in the early stages of the disease and the best standard for determining the total body iron storage (4).

The findings of six studies suggest that reduction in serum ferritin level decreases seizure threshold because iron has an important role in proper functioning of many central nervous system enzymes and neurotransmitters. Fever may exaggerate the negative effects of ferritin on brain, and so stimulates seizure (4). Although it is clear that ferritin, as an acute phase reactant, is increased during any febrile illness, fever was equally present in our both groups.

Therefore, different serum ferritin levels between these groups cannot be attributed to fever alone. Differences of Hb, MCV and MCH between two groups of studied children, although not statistically significant, point out the chronic status of iron and cannot be regarded as acute phase reactants.

In conclusion, the present study showed that serum ferritin level was significantly lower in children suffering from febrile seizures than febrile children in the control group, suggesting that a low ferritin level may have an important role in children with febrile seizures. Therefore, prescribing supplementary iron in children may prevent the recurrence of febrile convulsion attacks. However, the sample size in this study was not enough for a definite conclusion and therefore, a multicentric study with more cases and a sufficient follow-up period is needed. Until a definite conclusion is reached, the present study suggests that oral supplemental iron therapy be given to children with febrile seizures who have a low serum ferritin level after recovery from their acute stage and subsiding of their fever to prevent the recurrence of febrile seizure attacks.

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