

## Iron Status and Iron Deficiency Anemia in Patients with Febrile Seizure

Ghasem Miri-Aliabad,<sup>1</sup> Ali Khajeh,\*<sup>1</sup> Marziyeh Arefi<sup>2</sup>

1. Department of Pediatrics, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran
2. General Physician, Zahedan University of Medical Sciences, Zahedan, Iran

Article information	Abstract
<p>Article history: Received: 20 May 2012 Accepted: 18 Aug 201. Available online: 15 Feb 2012 ZJRMS 2013; 15(9): 14-17</p> <p>Keywords: Febrile Seizure Children Anemia Iron Deficiency</p> <p>*Corresponding author at: Department of pediatrics, Children and Adolescent Health Research Center, Zahedan University of Medical Sciences, Zahedan, Iran. E-mail: aliyavar2005@yahoo.com</p>	<p><b>Background:</b> Febrile seizure is the most common form of seizure and iron deficiency is the most prevalent nutritional deficiency in children. Pathogenesis of this type of seizure is not well known, but several factors including genetic predisposition, lack of elements such as zinc, magnesium and iron are implicated in its occurrence. The objective of this study is to determine the iron status and iron deficiency anemia in patients with febrile seizure referred to “Ali-Ebn-e-Abitaleb hospital” of Zahedan in 2010.</p> <p><b>Materials and Methods:</b> This case-control study was conducted on 50 children with febrile seizure and 50 children with febrile illness but not seizure as a control group with age range of 6-72 months. Both groups were identical in terms of age and gender. After obtaining demographic information based on clinical examination, history and information contained in the documents, complete blood cells count, red blood cell indices and serum ferritin were performed for all patients.</p> <p><b>Results:</b> The average age of patients in the case and control groups was <math>25.28 \pm 17.26</math> and <math>26.12 \pm 20.04</math> months, respectively. Mean values of hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, plasma ferritin and serum iron levels in patients with febrile seizure were lower than the control group, but this difference was not statistically significant. The number of patients suffered from iron deficiency anemia in the case and control groups, were 22 (44%) and 18 (36%), respectively.</p> <p><b>Conclusion:</b> Considering the lack of significant differences between the case and control groups in terms of iron status and anemia prevalence, it is suggested that careful evaluation of anemia and RBC indices in such patients should be done only based on clinical and nutritional history of each patient.</p> <p>Copyright © 2013 Zahedan University of Medical Sciences. All rights reserved.</p>

## Introduction

Febrile seizure is the most common type of seizure in children which occurs in 2-5% of children [1-3]. This type of seizure occurs in 6-60 month children who are otherwise healthy following rapid increase in body temperature and is often the first sign of fever. Its age peak is 18 months. Intracranial infections and other definite causes of seizure should be ruled out for febrile seizure [3, 4]. In some studies, the relationship between family history of seizure, smoking mothers, and alcohol consumption during pregnancy and febrile seizure have been mentioned, however the risk factors are largely unknown [5]. Iron deficiency is one of the most common nutritional disorders in children and anemia caused by iron deficiency is prevalent during the second and third years of life.

Iron plays important roles in many neurological functions, enzymatic reactions and in the metabolism of several neurotransmitters. Iron deficiency may lead to anemia, behavioral and cognitive changes, growth delay, immune function disorder, stroke, breath-holding attacks and pseudo tumor cerebri [6, 7]. Given the effect of iron deficiency on brain development in animal models, neurotransmitters normal activity disorder caused by iron

deficiency may lead to susceptibility of children toward febrile seizure [8].

Given the contradictory results about the prevalence of iron deficiency anemia and its possible relationship with febrile seizure in various studies, the objective of present study is to investigate this issue.

## Materials and Methods

In this prospective case-control study, 50 children with febrile seizure diagnosis (case group) and 50 febrile children without convulsion (control group) referred to “Ali-Ebn-e-Abitaleb hospital” of Zahedan in 2010, were studied. The age range was 6 to 72 months. The control group was selected among hospitalized febrile children without febrile seizures and no previous history of seizures. Both groups were similar in terms of gender and age. Febrile seizure had occurred along with febrile illness in the absence of central nervous system infection and other known causes of seizures. No patient had developmental and neurological disorders. Children with a history of epilepsy, cerebral palsy, neurological defects, a history of severe head trauma, history of meningitis,

encephalitis and brain tumor, severe malnutrition, anemia, hemoglobinopathies, and known hematologic disorder, diabetes, renal failure and chronic diseases with multiple organ involvement were excluded. The required information was obtained based on history, clinical examination and the information contained in documents, including age, gender, and rectal temperature at the time of admission and the type of febrile seizure (simple or complex). After obtaining informed consent from parents, a citrated blood sample was taken from case and control groups for hemoglobin, hematocrit, mean cell volume (MCV) and mean cell hemoglobin (MCH). A serum sample was taken for determination of plasma ferritin (Ferritin), iron and total iron binding capacity (TIBC). The samples were kept in good condition and delivered to the laboratory. RBC parameters were measured using Sysmex KX-21N cell counter device. Plasma ferritin was measured by ELISA method. Serum iron and total iron binding capacity (TIBC) were measured by colorimetric and sedimentary methods, respectively.

Simple febrile seizure is referred to generalized tonic-clonic seizure without focal signs and without seizure repeat in the next 24 hours with less than 10 minutes duration whereas for the complex type, focal signs, repeated seizures in the next 24 hours with more than 10-15 minutes seizure duration occur [9-11]. Anemia is referred to hemoglobin <11 gr/dl in the age range of 6-48 months and <11.5 gr/dl in the age range of 48-72 months [12]. Iron deficiency is defined as ferritin <12 ng/ml in non-inflammatory conditions and without fever [13]. Average plasma ferritin, total iron binding capacity (TIBC), transferrin saturation, hemoglobin, hematocrit, MCV, MCH, MCHC and RDW was calculated for each group. The Chi-square and Independent *t*-tests were used to compare qualitative and quantitative variables, respectively. The obtained data were analyzed using SPSS-16. The significant relationship between data was evaluated with *p*-value <0.05.

## Results

The average age and male to female ratio was similar in both groups. The average age of patients in the case and control groups was 25.28±17.26 and 26.12±20.04 months, respectively. The number of boys and girls in both groups was 31 (62%) and 19 (38%) respectively (*p*=1.00). The average rectal temperature of patients in the case and control groups was 39.26±0.47 and 39.25±0.44°C, respectively. There were no significant differences between the two groups in terms of gender, age and mean temperature at admission. Table 1 shows the frequency distribution of the age range and table 2 represents the fever causes. The most common cause of fever was gastroenteritis in both groups. In the case group, 43 children (86%) suffered from simple seizure and 7 children (14%) suffered from complex seizure. Fourteen patients (28%) had positive family history of febrile seizure in the case group. Table 3 shows the hematologic parameters in both groups. Mean values of hemoglobin,

hematocrit, mean cell volume, mean cell hemoglobin, plasma ferritin and serum iron levels in patients with febrile seizure was lower than the control group, but the difference was not statistically significant (Table 3). Twenty two patients (44%) in the case group and 18 patients (36%) in the control group suffered from anemia. Eight patients (16%) in the case group and 4 patients (8%) in the control group suffered from microcytosis. The mean plasma ferritin in the groups with simple and complex febrile seizure was 74.06±55.63 and 34.85±12.74 mg/dl, respectively. Fifteen patients with simple febrile seizure (35%, among 43 patients) and all patients with complex febrile seizure (100%) suffered from anemia (*p*=0.001).

**Table 1.** Frequency distribution age of case and control groups

Age(mo)	6-12	13-24	25-48	49-72
	N (%)	N (%)	N (%)	N (%)
Case group	12(24)	23(46)	9(18)	6(12)
Control group	16(32)	15(30)	8(16)	11(22)
Total	28(56)	38(76)	17(34)	17(34)

**Table 2.** Underlying causes of illness in case and control group

Cause of fever	Case group	Control group
	N (%)	N (%)
Gastroenteritis	26(52)	30(60)
Acute otitis media	2(4)	2(4)
Upper respiratory infection	20(40)	6(12)
Urinary tract infection	2(4)	4(8)
Other causes	0(0)	8(16)
Total	50(100)	50(100)

**Table 3.** Mean value of hematologic parameter among cases and control group

laboratory variable	Case group	Control group	<i>P</i> -Value
White blood cell(WBC)	11700±6240	11810±5793	0.97
Red blood cell(RBC)	4.50±0.48	4.38±0.48	0.20
Hemoglobin (g/dl)	10.94±1.21	11.10±1.08	0.50
Hematocrit (%)	34.67±2.87	34.72±2.72	0.92
MCV(fl)	78.14±7.35	79.63±5.40	0.25
MCH(pg)	24.70±3.32	25.31±2.10	0.27
MCHC(g/dl)	31.46±1.76	31.78±1.24	0.29
RDW	14.76±2.09	14.29±1.51	0.20
Platelet	271000±91000	291000±98000	0.29
Serum ferritin (ng/ml)	68.57±53.49	89.16±59.07	0.07
Serum iron (mcg/dl)	40.88±22.16	43.18±23.35	0.61
TIBC (mcg/dl)	296±101	271±57	0.13
Transferrin saturation(%)	0.14±0.06	0.15±0.05	0.41
Anemia (%)	44	36	0.27

## Discussion

Febrile seizure is the most common type of seizure in children which is seen as simple and complex febrile convulsion. A large percentage of febrile seizures are simple (70-75%) and 9-35 % of them are complex. Although febrile seizure in children is benign, seizure occurrence in children may cause parents to worry and fear [14, 15]. It can potentially affect the quality of family life and parents. These effects appear as physical, psychological and behavioral manifestations. It may have a series of negative outcomes in life which are due to lack of sufficient information of parents about febrile seizure [16]. Iron deficiency anemia in young children is one of

the most common micronutrient deficiencies worldwide which can lead to developmental and cognitive disorders. It has been revealed that disorders such as restless legs syndrome, attention deficit hyperactivity disorder (ADHD) and febrile seizure are related to iron deficiency [17].

Contradictory results have been reported about iron deficiency anemia and febrile seizure. Daoud et al. conducted a study on 75 children with first febrile seizure. They compared the case group with 75 children with febrile illness in the control group. The results showed that the mean serum ferritin level in the patient group was significantly lower than the control group indicating the possible role of iron deficiency in occurrence of febrile seizure. The mean hemoglobin, mean cell volume and mean cell hemoglobin were lower in the patient group, but it was not statistically significant [18].

The results of a study conducted by Pisacane et al. showed that iron deficiency anemia in patients with febrile seizure (30%) was more prevalent than control groups (14%) and healthy children (11.6%) [19]. Naveed-Ur-Rehman and Billoo AG found that iron deficiency anemia in patients with febrile seizure was significantly more common than in the control group and the plasma ferritin level was significantly lower than control group [20]. The results of a study conducted by Hartfield et al. showed that patients with febrile seizure suffering from iron deficiency approximately two times higher than control group (9% vs. 5%) [8]. Sherjil A et al. found that the iron deficiency anemia in patients with febrile seizure was almost two times more prevalent. Iron deficiency was considered as a risk factor for seizures in these patients [21]. Although our results also showed lower plasma ferritin levels and a higher incidence of anemia in the case group than control group, it was not statistically significant.

In a case-control study, Kobrinsky et al. showed that the iron deficiency in patients with febrile seizure was less common than the control group. It was assumed that iron deficiency may increase the seizure threshold in these patients and it may have a protective role against seizure [22]. Bidabadi et al. found that 44% of children with febrile seizure suffered from iron deficiency which was lower than the control group but iron deficiency anemia had no protective effect against seizure [23]. The results of latter studies are not consistent with the results of our study.

## References

1. Fallah R, Golestan M. Role of laboratory diagnostic tests in first febrile seizure. *J pediatr Neurol* 2008; 6(2): 129-132.
2. AL Zwaini EJ. Epidemiological and clinical features of hospitalized patients with febrile seizures in Ramadi, West of Iraq. *J Pediatr Neurol* 2007; 5(4): 311-315.
3. AL khathlan NA, Mohammed M J. Clinical profile of admitted children with febrile seizures. *Neurosciences* 2005; 10(1): 30-33.
4. Wanigasinghe J. Febrile seizures. *Sri Lanka J Child Health* 2009; 38(3): 93-7.

The present study showed that the prevalence of anemia and lower plasma ferritin level in patients with febrile seizure was higher, but the difference between the two groups was not statistically significant. The results showed that the mean values of hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, plasma ferritin, serum iron and transferrin saturation in patients with febrile seizure were lower than the control group, but the difference was not statistically significant. Also, the prevalence of iron deficiency anemia and the number of patients who suffered from microcytosis in the case group was more than control group, but the difference was not significant. Possible factors that may cause contradictory of the results of various studies include different diagnostic criteria for the diagnosis of iron deficiency, sample size, age of patients in each study, nutritional status and retrospective nature of many studies. However, even with greater frequency of iron deficiency in patients, causal relationship cannot be assumed between iron deficiency and febrile seizure. More prospective studies with larger sample size should be conducted.

Based on the results of current study, iron deficiency and its relevant anemia cannot be considered as a risk factor for febrile seizure. Therefore, it is recommended that the complete blood count, erythrocyte indices and careful investigation of anemia in these patients should be conducted based on clinical conditions and accurate nutritional history of each patient.

## Acknowledgements

The authors wish to thank laboratory personnel especially Mrs. Hejazi and Jahantigh. All personnel of pediatric emergency, children ward and the Archive of "Ali-Ebn-e-Abitaleb hospital" of Zahedan are kindly acknowledged. Deputy Research of Zahedan University of Medical Sciences is sincerely appreciated for funding this research project No: 2114-89.

## Authors' Contributions

All authors had equal role in design, work, statistical analysis and manuscript writing.

## Conflict of Interest

The authors declare no conflict of interest.

## Funding/Support

Zahedan University of Medical Sciences.

9. Tonia J, Steven JJ. Childhood febrile seizures: Overview and implication. *Int J Med Sci* 2007; 4(2): 110-114.
10. Waruiru C, Appleton R. Febrile Seizures: An update. *Arch Dis Child* 2004; 89(8): 751-756.
11. Donaldson D, Trotman H, Barton M, et al. Routine laboratory investigations in infants and children presenting with fever and Seizures at the university hospital of the West Indies. *West Indian Med J* 2008; 57(4): 369-72.
12. Oski FA, Brugnara C, Nathan DG. Diagnostic approach to the anemic patient. In: Nathan DG, Orkin SH. *Nathan and Oski's hematology of infancy and childhood*. 7<sup>th</sup> ed. Philadelphia: Saunders; 2009: 455-466.
13. Lanzkowski P. *Manual of pediatric hematology and oncology*. 5<sup>th</sup> ed. San Diego: Academic Press; 2011: 38-57.
14. Peiffer A, Thompson J, Charlier C, et al. A locus for febrile seizures (FEB3) maps to chromosome 2q 23-24. *Ann Neurol* 1999; 46(4): 671-8.
15. Kugler SL, Stenroos ES, Mandelbaum DE, et al. Hereditary febrile seizures: Phenotype and evidence for a chromosome 19 P locus. *Am J Med Genet* 1998; 79(5): 354-61.
16. Tanja F, Christine A, Filippo D. Febrile seizures and parental anxiety: Does information help? *Swiss Med Wkly* 2001; 131(37-38): 556-560.
17. Johnston MV. Iron deficiency, febrile seizures and brain development. *Indian Pediatr* 2012; 49(1):13-14.
18. Daoud AS, Batieha A, Ekteish A, et al. Iron status: A possible risk factor for the first febrile seizure. *Epilepsia* 2002; 43(7): 740-3.
19. Pisacane A, Sansone R, Impagliazzo N, et al. Iron deficiency anemia and febrile convulsions : Case-control study in children under 2 years. *BMJ* 1996; 313(7053): 343.
20. Naveed-ur-Rehman, Billoo AG. Association between iron deficiency anemia and febrile seizures. *J Coll Phys Surg Pak* 2005; 15(6): 338-40.
21. Sherjil A, Saeed ZU, Shehzad S and Amjad R. Iron deficiency anemia-a risk factor for febrile seizures in children. *J Ayub Med Coll Abbottabad* 2010; 22(3): 71-73.
22. Kobrinsky NL, Yager JY, Cheang MS, et al. Does iron deficiency raise the seizure threshold? *J Child Neurol* 1995; 10(2): 105-109.
23. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. *Seizure* 2009; 18(5): 347-51.

*Please cite this article as:* Miri-Aliabad G, Khajeh A, Arefi M, Miri-Aliabad F. Iron status and iron deficiency anemia in patients with febrile seizure. *Zahedan J Res Med Sci (ZJRMS)* 2013; 15(9): 14-17.