

The role of anemia in first simple febrile seizure in children aged 6 months to 5 years old

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ABSTRACT

الأهداف: تقييم العلاقة بين فقر الدم والاختلاج الحموي البسيط الأولي لدى الأطفال الذين تتراوح أعمارهم ما بين 6 أشهر إلى 5 سنوات.

الطريقة: أُجريت هذه الدراسة الاستطلاعية في مستشفى غهيم، ومستشفى إمام ريزا، ومستشفى الدكتور شيخ، إيران وذلك خلال الفترة من أكتوبر 2010م إلى ديسمبر 2011م. شملت الدراسة 240 مريضاً تتراوح أعمارهم ما بين 6 أشهر إلى 5 سنوات. لقد قمنا بتقسيم الأطفال المرضى إلى مجموعتين وهما: مجموعة الشاهد التي كانت مصابة بالحمى من غير تشنجات، ومجموعة الدراسة التي كانت مصابة بالاختلاج الحموي البسيط الأولي. وبعد ذلك قمنا بتحليل مستويات فقر الدم لدى المجموعتين وعمل مقارنة فيما بينهما.

النتائج: لقد كان متوسط عمر المرضى 20.7 ± 14.8 شهراً، حيث كان متوسط عمر المرضى في مجموعة الدراسة 20.53 ± 15.07 شهراً، فيما كان متوسط عمر المرضى في مجموعة الشاهد 20.9 ± 14.6 شهراً ($p=0.74$). وكان متوسط مستوى هيموغلوبين الدم لدى مجموعة الدراسة 11.05 ± 1.37 ، فيما كان متوسط الهيموغلوبين لدى مجموعة الشاهد 11.14 ± 1.19 ($p=0.58$). وقد قمنا بإثبات وجود فقر الدم لدى 37.5% من مجموعة الدراسة، و 36.7% من مجموعة الدراسة ($p=0.89$).

خاتمة: أثبتت هذه الدراسة عدم وجود علاقة بين فقر الدم والاختلاج الحموي البسيط الأولي.

Objective: To assess the relationship between anemia and first simple febrile convulsion in patients 6 months to 5 years old.

Methods: This cross-sectional study was performed on 240 patients aged 6 months to 5 years old from 10 October 2010 to 15 December 2011 at Ghaem Hospital, Imam Reza Hospital, and Dr. Sheikh Hospital, Mashhad, Iran. Patients were divided into

2 groups: the control group who had fever without seizure, and the case group who had first simple febrile seizure. The anemia levels in both groups were evaluated and compared.

Results: The mean age of patients was 20.7 ± 14.8 months. It was 20.53 ± 15.07 for the case group, and 20.9 ± 14.6 for the control group ($p=0.74$). The mean hemoglobin in the case group was 11.05 ± 1.37 , and 11.14 ± 1.19 in the control group ($p=0.58$). Anemia was detected in 37.5% of the case group, and 36.7% of controls ($p=0.89$).

Conclusion: There was no relationship between anemia and first simple febrile seizure.

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The most common seizure in children is febrile seizure, occurring in 2-4% of patients aged 6 months to 5 years old. In the simple form, single, short, and generalized seizures occur.¹⁻⁴ Some previous studies have evaluated the probable risk factors in febrile convulsions.⁵⁻⁸ Genetic factors, history of febrile

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seizures in first- or second-degree relatives, smoking during pregnancy, day-care attendance, and high fever were among the risk factors for febrile convulsions identified. It is estimated that 46-66% of children below 4 years old suffer from anemia in developing countries. In Iran, it is estimated that 20% of children suffer from anemia.¹ Studies suggest that iron contributes to the production of serotonin, dopamine, and gamma amino-butyric acid (GABA) as well as myelin synthesis in brain cells, and some specific neurotransmitters such as monoamine, and aldehyde oxidase are decreased in iron deficiency.^{1,4,9,10} Iron deficiency anemia has been shown to be a risk factor for febrile seizure.^{11,12} One study¹ reported patients with first febrile seizure had less iron deficiency anemia than the control group who had fever without seizures. Another study¹³ reported no significant difference in plasma ferritin and hemoglobin levels in patients with febrile seizures and febrile children without seizure.

Considering the importance of febrile seizures in children, the high prevalence of anemia as a probable risk factor in developing countries such as Iran, and the conflicting results of previous studies, we conducted this study to evaluate the role of anemia in first febrile convulsion. If a relationship between anemia and febrile seizure is revealed, complete blood count and screening for anemia can be recommended in the work up of patients with febrile seizures and also in those children who have risk factors for febrile seizure.

Methods. We conducted a prospective cross-sectional study including 240 patients aged 6 months to 5 years old over 14 months from October 2010 to December 2011 at Ghaem Hospital, Imam Reza Hospital, and Dr. Sheikh Hospital, Mashhad, Iran. Patients were divided into 2 groups: controls that had febrile illness requiring hospital admission without seizure and without any signs of malnutrition, and the case group admitted with

first simple febrile seizure. Both case and control groups were normal in growth. To provide 95% confidence and 80% power in statistical analysis, a sample size of 120 for each group was calculated. Data including age, gender, body temperature, seizure characteristics, family history of febrile seizure, and laboratory findings consisting of hemoglobin, hematocrit, and mean corpuscular volume (MCV) were recorded. Anemia was considered when hemoglobin was below 10.5 g/dl. Simple febrile seizures were single, generalized convulsions lasting less than 15 minutes. The inclusion criteria were patients aged 6 months to 5 years old with first simple febrile seizure and with normal growth and development. Exclusion criteria were neurodevelopment delay, previous history of febrile convulsion or epilepsy, complex febrile seizures, meningoencephalitis, metabolic disorders, moderate to severe dehydration, congenital heart disease, chronic renal failure, malnutrition, and incomplete data in the records. The ethics committee of Mashhad University of Medical Sciences approved the study, and the work was conducted according to the principles of the Helsinki Declaration.

Data were analyzed with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 11.5. Quantitative data was analyzed by Mann-Whitney test, and Chi-square test was used for qualitative data. For all tests, the level of statistical significance was considered as $p < 0.05$.

Results. The mean patient age was 20.7 ± 14.8 months. The demographic data and laboratory results are shown in Table 1. In the case group, 24 out of 63 patients (38.1%) with anemia were male, and 21 out of 57 patients (36.8%) were female ($p = 0.88$). In the control group, 24 out of 72 patients (33.3%) with anemia were male, and 20 out of 48 patients (41.7%) with anemia were female ($p = 0.35$). In patients aged 6-24 months, 41 out of 96 patients (42.7%) in the case group had anemia, and 38 out of 89 patients (42.7%) in the control group suffered from anemia ($p = 0.999$) (odds ratio [OR] : 1, 95% confidence interval [CI]: 0.56-1.7).

Table 1 - Demographic data and laboratory results of febrile patients aged 6 months to 5 years with seizure (study group) and without seizure (control group).

Characteristics	Case group	Study group	P-value	95% CI
Age	20.53±15.07	20.9±14.6	0.74	
Male (%)	52.5	60	0.24	
Body temperature	38.5±0.74	38.5±0.68	0.94	-0.59-0.21
Hemoglobin	11.05±1.37	11.14±1.19	0.58	-0.42-0.24
Hematocrit	33.06±3.82	33.65±2.88	0.17	-1.46 0.26
MCV	76.39±4.79	77.24±7.4	0.29	-2.44-0.73
Anemia (%)	37.5	36.7	0.89	0.57-1.63

MCV - mean corpuscular volume, CI - confidence interval, all results are shown as mean±SD unless otherwise indicated

Table 2 - Underlying diseases in febrile patients aged 6 months to 5 years with seizure.

Underlying disease	Negative	Positive
	n (%)	
Upper respiratory tract infection	78 (65.0)	42 (35.0)
Lower respiratory tract infection	114 (95.0)	6 (5.0)
Urinary tract infection	118 (98.3)	2 (1.7)
Unknown	66 (55.0)	54 (45.0)
Others	104 (86.7)	16 (13.3)

Forty out of 120 patients (33.3%) in the case group, and 44 out of 120 (36.7%) in the control group had a temperature above 39°C ($p=0.59$). Table 2 summarizes the underlying illnesses in the case group.

Discussion. Previous studies evaluated the relationship of different risk factors with febrile seizures.⁵⁻⁸ In this work, we studied the relationship between anemia and first simple febrile seizure, and found no relationship between anemia and simple febrile seizure in children aged between 6 months and 5 years old.

Kumari et al¹⁴ performed a study on 308 children aged 6 months to 3 years old, they found 63.6% of the case group suffered from iron deficiency in comparison with 24.7% of the control group. They concluded that iron deficiency was an important risk factor in simple febrile convulsion. In another study by Hartfield et al,⁴ 361 patients with febrile seizure and 390 patients with febrile illness without seizure were compared. They found that 6% of the case group, and 4% of the control group showed iron deficiency anemia, and concluded that iron deficiency should be evaluated in patients with febrile seizure. Naveed-ur-Rehman & Billoo¹² conducted a study on 60 patients, the case group with febrile seizure had a mean age of 22.94±9.52 months, and the control group with febrile illness without any seizures had a mean age of 22.77±11.33 months. They reported that serum ferritin, hematocrit, MCV, and hemoglobin were significantly lower in the case group than the control group, and suggested iron deficiency anemia as a predisposing factor for febrile convulsion.

The above findings may be explained by the role of iron in the CNS, and neurologic dysfunction may occur as a result of iron deficiency. Dopamine, GABA, and serotonin production may be affected by iron as a cofactor in brain cells. The activity of GABA is altered and some neurotransmitters including monoamine, and aldehyde oxidase are decreased. Also, DNA replication and myelinogenesis in oligodendrocytes may be disturbed in these patients.^{4,12} It is thought that fever may augment the adverse effect of low iron levels in developing brain cells to decrease the threshold level of the convulsion and as a result, convulsion attack may develop.¹⁵

Salehi Omran et al¹³ conducted a study on 180 children aged 9 months to 5 years old. They divided patients into a control group with a febrile disease without convulsion, and a case group with febrile seizure, and detected no statistically significant differences between hemoglobin and mean plasma ferritin in both cases and controls. In another study¹ performed on

200 children aged 6 months to 5 years, patients were also divided into 2 groups: case group with first febrile seizure, and controls with febrile illness without any seizures. This study revealed that the case group had less iron deficiency anemia than the controls, but it did not reach a statistically significant level. Another study by Amirsalari et al¹⁶ performed on 220 patients aged 9 months to 5 years old, included 132 patients with first febrile seizure as a case group, and 88 febrile patients without seizure as controls. They reported that iron deficiency anemia was not related to febrile convulsion.

We also found no relationship between anemia and first febrile seizure in our study. This may be due to reasons such as: differences in sample size and age of cases. We suggest that different ethnicity or nutritional conditions may also be considered as other probable causes of such different findings. Our study was limited by the fact that we did not include patients with complex febrile seizures, and further studies assessing the relationship between anemia and complex febrile seizures are recommended. However, our study was performed in 3 separate hospitals, and this can be considered a strength.

In conclusion, we did not find any relationship between anemia and first simple febrile convulsion.

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References

1. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. *Seizure* 2009; 18: 347-351.
2. Shinnar S. Febrile seizure. In: Swaiman KF, Ashwal S, Ferriero DM, editors. *Pediatric Neurology Principles and Practice*. 4th ed. Philadelphia (PA): Mosby Elsevier; 2006. p. 1079-1089.
3. Hampers LC, Thompson DA, Bajaj L, Tseng BS, Rudolph JR. Febrile seizure: measuring adherence to AAP guidelines among community ED physicians. *Pediatr Emerg Care* 2006; 22: 465-469.
4. Hartfield DS, Tan J, Yager JY, Rosychuk RJ, Spady D, Haines C, et al. The association between iron deficiency and febrile seizures in childhood. *Clin Pediatr (Phila)* 2009; 48: 420-426.
5. Okumura A, Ishiguro Y, Sofue A, Suzuki Y, Maruyama K, Kubota T, et al. Treatment and outcome in patients with febrile convulsion associated with epileptiform discharges on electroencephalography. *Brain Dev* 2004; 26: 241-244.
6. Heydarian F, Ashrafzadeh F, Kam S. Simple febrile seizure: The role of serum sodium levels in prediction of seizure recurrence during the first 24 hours. *Iranian Journal of Child Neurology* 2009; 3: 31-34.
7. Heydarian F, Ashrafzadeh F, Ghasemian A, Serum zinc level in patients with simple febrile seizure. *Iranian Journal of Child Neurology* 2010; 4: 41-44.

8. Camfield P, Camfield C, Gordon K. Antecedence and risk factors for febrile seizure. In: Baram TZ, Shinnar S, editors. *Febrile Seizures*. 1st ed. San Diego (CA): Academic Press; 2002.
9. Ozaydin E, Arhan E, Cetinkaya B, Ozdel S, Degerliyurt A, Guven A, et al. Differences in iron deficiency anemia and mean platelet volume between children with simple and complex febrile seizures. *Seizure* 2012; 21: 211-214.
10. Auvichayapat P, Auvichayapat N, Jedsrisuparp A, Thinkhamrop B, Sriroj S, Piyakulmala T, et al. Incidence of febrile seizures in thalassemic patients. *J Med Assoc Thai* 2004; 87: 970-973.
11. Sherjil A, us Saeed S, Shehzad S, Amjad R. Iron deficiency anemia--a risk factor for febrile seizures in children. *J Ayub Med Coll Abbottabad* 2010; 22: 71-73.
12. Naveed-ur-Rehman, Biloo AG. Association between iron deficiency anemia and febrile seizures. *J Coll Physicians Surg Pak* 2005; 15: 338-340.
13. Salehi Omran MR, Tamaddoni A, Nasehi MM, Babazadeh H, Alizadeh navaei R. Iron status in febrile seizure: A case control study. *Iranian J Child Neurology* 2009; 3: 39-42.
14. Kumari P, Nair MK, Nair SM, Kailas L, Geeta S. Iron deficiency as a risk factor for simple febrile seizure--a case control study. *Indian Pediatrics* 2012; 49: 17-19.
15. Daoud AS, Batieha A, Abu-Ekteish F, Gharaibeh N, Ajlouni S, Hijazi S. Iron status: a possible risk factor or the first febrile seizure. *Epilepsia* 2002; 43: 740-743.
16. Amirsalari S, Keihani Doust Z, Ahmadi M, Sabouri A, Kavemanesh Z, Afsharpeyman S, et al. Relationship between iron deficiency anemia and febrile seizures. *Iran J Child Neurology* 2010; 4: 27-30.

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Dad MI, Ismael GA, Al-Oufi AA, Al-Mohammadi AH. Clinical pattern of seizures in hospitalized children. *Neurosciences* 2003; 8: 107-109.