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The Association Between Iron Deficiency and Febrile Seizures in Children Below 5 Years

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Abstract

Background Febrile seizures are prevalent in children aged between 6 months and 5 years with an incidence of 2-5%. Iron deficiency is the most common hematologic disease of infancy and childhood with a period of incidence that coincides with the time of febrile seizures. Although the most common manifestation of iron deficiency is anemia, it is frequently the source of a neurologic disorders in pediatrics, including developmental delay, seizure, stroke, breath-holding episodes, pseudo tumor cerebri, and cranial nerve palsies.

Objective To investigate the association between iron deficiency and febrile seizures.

Methods Two groups (80 for each) of 6 months to 5 years old febrile children were subjected to the study between 1st of Oct. 2017 to 1st of Oct. 2018. The first group, cases, included children with febrile seizures admitted to the Pediatric Ward in Al-Imamein Al-Kadhimein Medical City, whereas the control group, included febrile children, visited the hospital during the same period for febrile illness. History was taken, physical examination was done. Blood count indices, serum iron, total iron binding capacity and serum ferritin were estimated. Lumber puncture was done in some of the patients. Statistical Analysis was done using t-test and Chi-square test (x2), P-value was considered significant if less than 0.05. Percentages and Odds ratio were estimated. A prevalence of 20-25% among cases is considered clinically relevant.

Results Both groups were comparable for age and gender (17.5±8.81) and (17.6±8.54) months, male: female ratio was (1.75:1 and 1.2:1). Family history of febrile seizure were seen in 25% and 13.75% respectively. Simple febrile seizure was found in (72.5%). The blood indices were lower in patients than the control group and statistically have significant difference in hemoglobin, hematocrit, mean corpuscular volume, serum iron and serum ferritin level with a P-value less than 0.05. A total of 36 (45%) of the cases had iron deficiency, compared to 12 (15 %) of control respectively with P-value less than 0.05.

Conclusion Iron deficiency was more frequent among children with febrile seizure than those with febrile illness alone. The results suggest that iron deficiency may be a risk factor for febrile seizure.

Keywords Febrile seizure, infants, children, iron deficiency anemia

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List of abbreviations: CBP = Complete blood picture, CNS = Central nervous system, CSF = Cerebrospinal fluid, FS = Febrile seizure, Hb = hemoglobin, IDA = Iron deficiency anemia, LP = Lumber puncture, MCH = Mean Corpuscular Hemoglobin, MCHC = Mean corpuscular hemoglobin concentration, MCV = Mean corpuscular volume, RBC = Red blood cell, RDW = Red cell distribution width, TIBC = Total iron binding capacity

Introduction

Febrile seizures (FS) are the commonest cause of seizures in children, occurring in 2-5% of children [(1)]. Most febrile seizures are considered simple, those with focal onset, prolonged duration, or that occur more than

once within the same febrile illness are considered complex [2]. Iron deficiency is the most common nutritional deficiency. In the United States, 8-14% of children ages 12-36 months are iron deficient, and 30% of this group progresses to iron-deficiency anemia [3]. Iron deficiency anemia (IDA) in early life is related to altered behavioral and neural development [4]. Although the most common manifestation is that of anemia, iron deficiency is frequently the source of a host neurologic disorders presenting to general pediatric neurologic practices. These disorders include developmental delay, seizure, stroke, breath-holding episodes, pseudo tumor cerebri, and cranial nerve palsies [3,5]. There is support for iron deficiency with or without anemia causing these defects [3]. Evaluation of iron status is encouraged to be performed in children with febrile seizure [6].

This study aimed to investigate the association between iron deficiency and febrile seizure.

Methods

A hospital-based case control study consisting of infants and children aged between 6 months to 5 years. They were evaluated at the Department of Pediatrics, in Al-Imamein Al-Kadhimein Medical City, Baghdad during the period between October 1st 2017 to October 1st 2018. Family approval and approval by ethical review body was taken. Eighty children presented with FS were included in the study, while another 80 children who presented with febrile illnesses without seizures were recruited as control. They attended outpatient clinic for upper respiratory tract infection, gastroenteritis, urinary tract infection or nonspecific causes of fever and all were normal children without previous abnormal neurologic manifestations. Both groups are age and sex matched. Information regarding name, sex, age, residence, number of fits, type of fits, duration of fit, duration of fever, onset after fever, associated symptoms, family history (in the first- and second-degree relatives) of febrile convulsion, epilepsy and developmental delay. Physical examination was done.

A febrile seizure was defined as seizure that occur between the ages of 6 and 60 months (peak 12-18 months) with a temperature of 38 °C [1]. The cases of FS were divided into 2 types (simple and complex). A case was considered as a complex if one or more of the following criteria were present (duration is >15 min, repeated seizures occur within 24 hr, focal seizure activity or focal findings are present [7]. Investigations were done including complete blood picture (CBP), hemoglobin level (Hb), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), serum ferritin, serum iron and total iron binding capacity (TIBC) were estimated.

Iron deficiency was defined as the presence of Hb concentration <11 g/dl, hematocrit < 33%, MCV <70 fl, RDW >14% with blood film shows hypochromic, microcytic red blood cells (RBC) and serum iron concentration of <30 µg/dl, serum ferritin concentration <12 µg/dl and TIBC >480 µg/dl [3]. A serum ferritin level below 30 µg/dl is an indicator of iron deficiency status and level below 12 µg/dl indicates IDA [3]. Since serum ferritin is acute phase reactant and its level is increased in any inflammatory conditions, in presence of fever a higher cut-off value of serum ferritin (30 µg/dl) will be taken [3].

Cerebrospinal fluid (CSF) examination was done to rule out central nervous system (CNS) infections with indications such as age <12 months, complex febrile seizure or persistent lethargy. Lumbar puncture (LP) was done for 16 patients, all with negative findings regarding meningitis. LP not performed for 12 patients because their parents refused the procedure while other 72 were not meeting the LP indicative criteria for FS.

Statistical analysis was done using SPSS program version 22nd for Windows. Descriptive statistics presented as (mean±standard deviation) and frequencies with percentages. The Chi-square test was used for comparison of categorical variables, Fishers exact test was used when total of expected variables was less than (20%). Independent sample t-test was

used to compare between two means. In all statistical analysis. P-value considered significant if less than 0.05, highly significant if less than 0.01. We assumed that a prevalence of 20-25% among cases would be clinically relevant.

Results

A total of 80 cases, and 80 control were collected, the majority of both were between 13 to 24 months of age. The mean age of cases and control was (17.5±8.81) and (17.6±8.54) months, respectively as it is shown in table 1.

Table 1. Age distribution of the studied groups

Age in months	Cases		Control		P-value
	No.	%	No.	%	
6-12	17	21.2	17	21.2	
13-24	39	48.8	37	46.2	
25-36	13	16.2	16	20.0	0.9 *NS
37-48	9	11.3	7	8.8	
49-60	2	2.5	3	3.8	
Total	80	100	80	100	

* Fishers exact test, NS=Not significant

Of the cases, 51 (63.75%) were males and 29 (36.25%) were females with a male to female ratio of 1.75:1 while in the control, 44 (55%) were males and 36 (45%) were females with a male to female ratio of 1.2:1 as it is shown in table 2.

Table 2. Gender distribution of patients and control group

Groups	Males		Females		P-value
	No.	%	No.	%	
Cases	51	63.75	29	36.25	0.1 *NS
Control	44	55.0	36	45.0	

* Fishers exact test, NS=Not significant

Of the patients group 59 (73.75%) were from urban area and 21 (26.25%) were from rural area while 54 (67.5%) of the control were from urban area and 26 (32.5%) from rural area. Variables found to be significantly associated with FS included male gender, iron deficiency, family history of febrile seizures in first-degree relatives, family history of epilepsy in first-degree relatives and history of taking iron supplements as well as temperature on admission as shown in table 3.

Among 80 cases, 64 (80%) cases presented with history of first episode of simple febrile seizures and the rest 16 cases (20%) presented with history of multiple episodes of febrile seizures in the past. From the 80 cases, 22 cases (27.5%) had complex seizures and 58 (72.5%) cases had simple FS. Table 4 shows lower indices of hematology results found in cases in comparison with control with statistically significant in Hb, PCV, MCV, SF, SI, RDW, and higher TIBC (P-value < 0.05).

Table 3. Differences in demographic characteristics

Variable	Cases = 80		Control = 80		P-value
	No.	%	No.	%	
Gender male	51	63.75	44	55.0	0.023[a] S
Gender female	29	36.25	36	45.0	0.254[a]
Family history of febrile seizure	20	25.0	11	13.75	0.004[a] S
Family history of epilepsy	4	5.0	2	2.5	0.041[a] S
Upper respiratory tract infection	47	58.75	48	60.0	
Gastroenteritis	25	31.25	26	32.5	0.910[a]
Other illnesses	8	10.0	6	7.5	
Iron deficiency	36	45.0	12	15.0	0.050[a] S
History of taking iron supplements	58	72.5	54	67.5	0.003[a] S
Age in months (mean±SD)	17.5±8.81		17.6±8.54		0.909[b]
Temperature on admission (°C)	38.9±0.77		38.5±0.63		0.003[b] S

a: Chi Square, b: t-test, S=Significant

Table 4. Hematological indices in cases and control

Variable	Cases Mean± Standard deviation	Control Mean± Standard deviation	P-value
Hemoglobin (g/dl)	10.99±1.46	12.06±0.97	0.042 *S
Hematocrit (%)	32.41±5.36	34.39±2.38	0.029 *S
MCHC(g/dl)	33.06±1.76	35.08±2.66	0.582
MCH (pg/cell)	24.54±2.79	26.55±8.58	0.206
MCV (fl)	70.94±5.44	74.92±7.11	0.047 *S
S. Ferritin (ng/ml)	16.57±13.84	19.78±10.45	0.012 *S
S. Iron (µg/dl)	33.9±18.07	43.36±12.94	0.01 *S
TIBC (µg/dl)	390.56±5.67	325.6±8.62	0.01 *S
RDW (%)	43.65±4.5	24.38±4.0	0.05 *S
RBC/mm^3	3.39±0.2	4.64±0.6	0.14

* t-test, S=Significant

In the present study, 46 of 80 cases (57.5%) had normal peripheral smear and the rest 42.5% (34 cases) had abnormal smear i.e., microcytic and hypochromic RBCs, compared to 86.25% of the controls (69 subjects) having normal peripheral smears and 13.75% (11 subjects) had abnormal peripheral smears. Chi square test value was (9.72, with P-value of 0.001). According to parameters mentioned, 36 (45%) cases and 12 (15%) control had iron deficiency, which is statistically significant (X2=4.32, P-value less than 0.05, Odd ratio= 3.16, 95% C.I. 2.07 to 4.24) as it is shown in figure 1.

In children with iron deficiency, simple FS is more frequent and seizure is longer as it is shown in table 5.

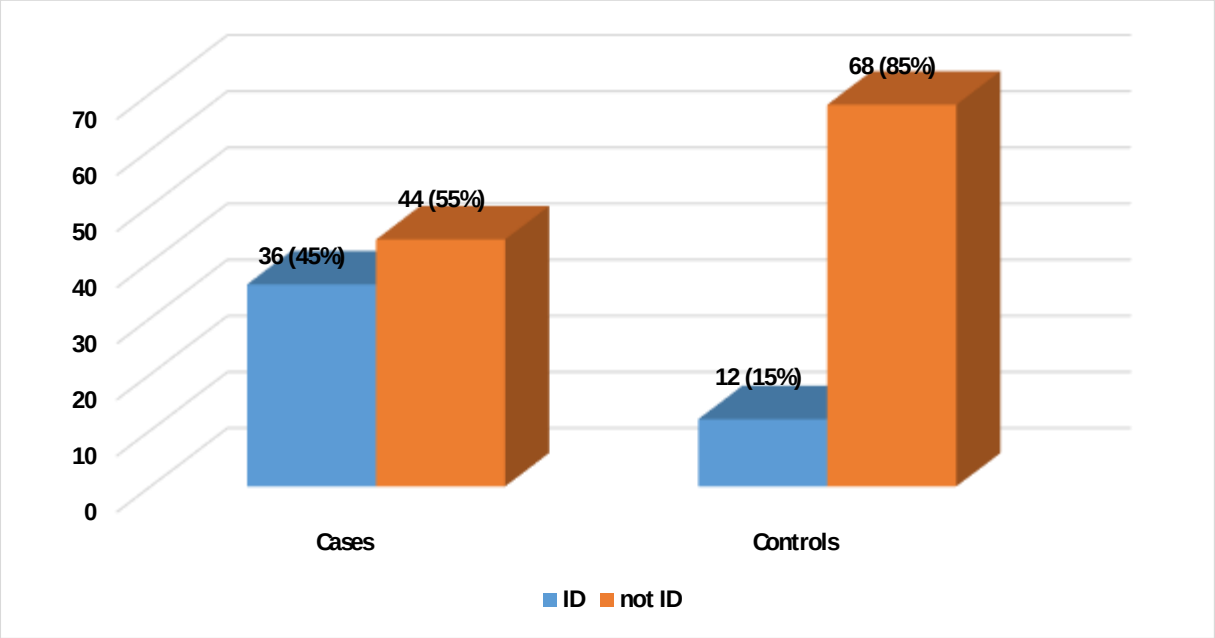

Figure 1. Cases and control with iron deficiency anemia

Table 5. Comparison of type of febrile seizure and seizure duration in children with and without iron deficiency

Type of Seizure	Cases with ID		Cases without ID		Total No. of cases	P-value
	No.	%	No.	%		
Simple FS	23	41	35	59	58	0.04[a] S
Complex FS	13	59	9	41	22	
Total	36	100	44	100	80	
Duration of seizure in minute (mean ±SD)	7.52±3.77		5.17±2.95			0.01[b] S

a: Chi Square, b: t-test, S=Significant

Discussion

The selection of this age group 6 months to 5 years for the study purpose came because FS usually occur in this period and this may be related to the higher incidence of viral upper respiratory tract infections at this age group [8]. Also, the highest incidence of IDA is between the ages of 6 months and 24 months but it is not uncommon up to the age of 5 years [3].

In this study, the majority of FS occur between 6 months and 3 years of age, with the mean age of (17.5±8.81) months, with higher incidence of seizures in boys than girls, which is in agreement with previous studies [9,10]. There is also higher proportion of children from the FS group with a family history of epilepsy, which is in agreement with previous study [11]. The higher prevalence in the urban area can be attributed to sample collection.

There is a controversy regarding the role of ‘‘iron status’’ in the occurrence of FS. This study reported a significantly higher rate of IDA among children with FS (36/80 cases vs. 12/80 controls). These findings are in agreement with other studies, which showed that anemia was significantly more common in cases (30%) than hospital (14%) and population (12%) [12,13]. Hartfield et al. from Canada (2009) reported

that children with febrile seizures were twice as likely to have iron deficiency as those with febrile illness alone [14]. While Bidabadi et al. in Iran (2009) suggested that IDA was less frequent among the cases with FS, as compared to the control [15]. These differences in observations among these studies may be due to the differences in age groups, ethnicities, sample sizes of groups and nutritional status of subjects.

Serum ferritin is lower in cases than the control group, which is in agreement with Daoud et al. in Jordan (2002), the mean serum ferritin level in the cases was 29.5 µg/l, much lower than the values in the control (53.5 µg/l) [16]. Similar observations were seen in a study done by Vaswani et al. in India (2010) [17].

It is known that ferritin is an acute-phase reactant that increases nonspecifically in response to any febrile illness [12,18]. Fever, however, was present in all patients in the two groups, therefore differences in ferritin concentration between the two groups cannot be explained by fever alone although fever can worsen the negative effects of anemia or of iron deficiency on the brain and a seizure can occur as a consequence. Alternatively, anemia can be associated with the severity of a febrile illness, and more severe cases of anemia could be more likely to get seizures [12].

Iron deficiency is affecting cases with simple FS 23/58 more than complex FS 13/58 with significant variable result, which is in agreement with a study done by Sharif et al. in Iran (2016) [19].

The association of iron deficiency with an increased risk of FS can be explained by the following, iron deficiency might lower the seizure threshold [20]. IDA in early life is related to altered behavioral and neural development. Studies in human infants suggest that this is an irreversible effect that may be related to changes in chemistry of neurotransmitters, organization and morphology of neuronal networks, and neurobiology of myelination [4]. Animal studies have shown that iron deficiency affects myelination, as well as enzymes (tyrosine and tryptophan hydroxylase), which are involved in the synthesis of neurotransmitters. Degradation of neurotransmitters is altered, and extracellular levels of noradrenaline and dopamine are elevated [21]. In addition, the function of Thy-1, a cell adhesion molecule that plays a regulatory role in the release of neurotransmitters from vesicles, is altered [22]. Thy-1 deficiency may affect the release of neurotransmitters and synaptic efficacy, and could contribute to a variety of abnormal neuron-neuron communications. Iron deficiency cause reduction of neurotransmitters release (glutamate dehydrogenase, glutamic acid decarboxylase, and GABA-transaminase (GABA-T) in brain [23], (selectively GABA) is postulated to predispose to a situation of hyper-excitability, and thus, may account for the pathophysiologic association of iron deficiency to the occurrence of seizures [24].

This study concluded that FS are more common in males. Mean hemoglobin and PCV, MCV, serum iron and serum ferritin were lower among the children with FS. There is significant association between IDA and FS, as low body iron status may decrease the threshold of seizure and be a risk factor for the development of FS.

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Author contribution

All authors contributed to this manuscript. They coordinated study recruitment, implementation and progress of this study and helped with data interpretation and manuscript organization and editing.

Conflict of interest

There are no conflicts of interest.

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References

1. Mikati MA, Tchapyjnikov D. Seizures in childhood. In: Kliegman RM, Geme ST, Blum NJ, et al (eds). Nelson Textbook of Pediatrics, 21st ed. Philadelphia: Elsevier; WB Saunders company; 2019. p. 12071-9.
2. Shinnar S, Glauser TA. Febrile seizures. J Child Neurol. 2002; 17 Suppl 1: S44-52. doi: 10.1177/08830738020170010601.

3. Rothman JA. Iron-deficiency anemia. In: Kliegman RM, Geme ST, Blum NJ, et al (eds). Nelson Textbook of Pediatrics, 21st ed. Philadelphia: Elsevier; WB Saunders company; 2019. p. 9920-9.
4. Beard J. Iron deficiency alters brain development and functioning. J Nutr. 2003; 133(5 Suppl 1): 1468S-72S. doi: 10.1093/jn/133.5.1468S.
5. Yager JY, Hartfield DS. Neurologic manifestations of iron deficiency in childhood. Pediatr Neurol. 2002; 27(2): 85-92. doi: 10.1016/s0887-8994(02)00417-4.
6. Fallah R, Tirandazi B, Akhavan Karbasi S, et al. Iron deficiency and iron deficiency anemia in children with febrile seizure. Iran J Ped Hematol Oncol. 2013; 3(1): 200-3.
7. Waruiru C, Appleton R. Febrile seizures: an update. Arch Dis Child. 2004; 89(8): 751-6. doi: 10.1136/adc.2003.028449.
8. Chung B, Wong V. Relationship between five common viruses and febrile seizure in children. Arch Dis Child. 2007; 92(7): 589-93. doi: 10.1136/adc.2006.110221.
9. Esmaili Gourabi H, Bidabadi E, Cheraghalipour F, et al. Febrile seizure: demographic features and causative factors. Iran J Child Neurol. 2012; 6(4): 33-7.
10. Stafstrom CE. The incidence and prevalence of febrile seizures. In: Baram TZ, Shinnar S (eds). Febrile seizures. San Diego, CA: Academic Press; 2002. p. 1-25.
11. Abou-Khalil B, Krei L, Lazenby B, et al. Familial genetic predisposition, epilepsy localization and antecedent febrile seizures. Epilepsy Res. 2007; 73(1): 104-10. doi: 10.1016/j.eplepsyres.2006.08.005.
12. Pisacane A, Sansone R, Impagliazzo N, et al. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. BMJ. 1996; 313(7053): 343. doi: 10.1136/bmj.313.7053.343.
13. Kwak BO, Kim K, Kim SN, et al. Relationship between iron deficiency anemia and febrile seizures in children: A systematic review and meta-analysis. Seizure. 2017; 52: 27-34. doi: 10.1016/j.seizure.2017.09.009.
14. Hartfield DS, Tan J, Yager JY, et al. The association between iron deficiency and febrile seizures in childhood. Clin Pediatr (Phila). 2009; 48(4): 420-6. doi: 10.1177/0009922809331800.
15. Bidabadi E, Mashouf M. Association between iron deficiency anemia and first febrile convulsion: A case-control study. Seizure. 2009; 18(5): 347-51. doi: 10.1016/j.seizure.2009.01.008.
16. Daoud AS, Batieha A, Abu-Ekteish F, et al. Iron status: a possible risk factor for the first febrile seizure. Epilepsia. 2002; 43(7): 740-3. doi: 10.1046/j.1528-1157.2002.32501.x.
17. Vaswani RK, Dharaskar PG, Kulkarni S, et al. Iron deficiency as a risk factor for first febrile seizure. Indian Pediatr. 2010; 47(5): 437-9. doi: 10.1007/s13312-010-0080-8.
18. Kobrinsky NL, Yager JY, Cheang MS, et al. Does iron deficiency raise the seizure threshold? J Child Neurol. 1995; 10(2): 105-9. doi: 10.1177/088307389501000207.
19. Sharif MR, Kheirkhah D, Madani M, et al. The Relationship between iron deficiency and febrile convulsion: a case-control study. Glob J Health Sci. 2015; 8(2): 185-9. doi: 10.5539/gjhs.v8n2p185.
20. Papageorgiou V, Vargiami E, Kontopoulos E, et al. Association between iron deficiency and febrile seizures. Eur J Paediatr Neurol. 2015; 19(5): 591-6. doi: 10.1016/j.ejpn.2015.05.009.
21. Lozoff B, Beard J, Connor J, et al. Long-lasting neural and behavioral effects of iron deficiency in infancy. Nutr Rev. 2006; 64(5 Pt 2): S34-43; discussion S72-91. doi: 10.1301/nr.2006.may.s34-s43.
22. Wang X, Wiesinger J, Beard J, et al. Thy1 expression in the brain is affected by iron and is decreased in Restless Legs Syndrome. J Neurol Sci. 2004; 220(1-2): 59-66. doi: 10.1016/j.jns.2004.02.004.
23. Mittal RD, Pandey A, Mittal B, et al. Effect of latent iron deficiency on GABA and glutamate neuroreceptors in rat brain. Indian J Clin Biochem. 2003; 18(1): 111-6. doi: 10.1007/BF02867677.
24. Taneja V, Mishra K, Agarwal KN. Effect of early iron deficiency in rat on the gamma-aminobutyric acid shunt in brain. J Neurochem. 1986; 46(6): 1670-4. doi: 10.1111/j.1471-4159.1986.tb08483.x.

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