

Association between iron deficiency and provoked febrile seizure in a middle income country: A case control study in Tehran, Iran

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Research note

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Title: Association between iron deficiency and febrile seizure? A case control study in Tehran, Iran

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Abstract

Objective: Febrile convulsion (FC) is the most common form of seizures disorder (3-4%) in childhood with good prognosis. Some evidences indicate that iron deficiency (ID) might play a role in initiation of FC. The aim of this case-control study was to evaluate, the role for ID in pathogenesis of FC (febrile convulsion). We studied 35 FC children and 35 controls (febrile diseases without convulsion)

Results

The mean age of cases were 2.191 ± 0.946 vs 1.93 ± 1.433 years in controls. Mean Hemoglobin level (11.6 ± 0.79 vs 11.86 ± 0.71 ; p value= 0.2); MCV (75.8 ± 4.3 vs 77.62 ± 4.1 , p value= 0.08); serum ferritin levels (54.57 ± 24 vs 58.31 ± 23 , p value= 0.64) had not significant difference between 2 groups. The ferritin level 36ng/ml; had 74.3% sensitivity, 20% specificity, 56% PPV, 52% NPV, Positive likelihood Ratio: 1.3; Negative likelihood Ratio: 0.93 to

discriminate 2 groups. In our opinion, ID could not lead to FC in all children, but in some cases with genetic basis; ID raises the threshold for seizures. Due to high prevalence of ID (26%) especially in your Iranian population, adding the Iron to diet might be helpful in decreasing FC in susceptible cases.

Key words: febrile convulsion, children, Ferritin, Iron deficiency

Introduction

One of the most common childhood convulsive disorders are FC (Febrile convulsions); With wide incidence rate in world; 2–4% in United states; 9-10% in and Japan, the highest rate; 14% in Guam . (1-3) FC is a seizure associated with a febrile illness in the absence of central nervous system infections or acute electrolyte abnormalities in 6-60 months old children without previous afebrile seizures (2, 3). Multiple etiologic factors are considered for FC (4-9) ID reduces the metabolism of some neurotransmitters. On the other hand, fever may aggravate negative effects of ID on the brain (11) . Conflicting results are seen from previous studies about relationship between ID and FC (11-13)

Fc with incidence rate 2-5% is the most common seizures in Iranian children between 5 months - 6 years old (14-17) In spite of the efforts of ministry of health and medical education of Iran for supplemental iron for all Iranian infants at least for 1–2 years ;and also for girls, the prevalence of ID is considerable (14-15) In a recent systematic search study by Akbari et al (14))in population-based studies estimates the prevalence rate 26.9% for ID in Iran ,with 14 % prevalence rate in young population (<18 years) including 7.9% in males and 8.5% among females (< 18 yeas). Contradictory results between ID and FC have shown in Iran like the other parts of world . (16-21) First, Mahyar et al (16) reported the risk factors for FC in Iranian children. Recently, Heydarian et al explained the First FC and Clinical risk factors in our country . Veisani et al discussed the familial history and recurrence of FC in a Systematic Review and Meta-Analysis(17) Some studies by Iranian authors tried to evaluate role of ID in FC children (18-25) Some authors reported the ID were more frequent in children with FC in compare with non convulsive febrile and normal children(18,22,23,25) . On the contrary, Salehi Talebian , Amirsalari shown that ID plays no role in pediatric FC. (19-21) . We carried out this

prospective case-control study to report the ferritin cut off level which could discriminate the FC cases from non convulsive febrile children.

Main Text

Materials and Methods

This prospective case/control study was conducted during 2 years (2014-2016) in pediatric wards in Rasoul, 3th level referral hospital in Tehran,Iran

This study was approved by the by the scientific advisory and ethical committees of IranUniversity of Medical Sciences. A written informed consent forms were signed by the parents, and the procedures involved complied with Declaration of Helsinki study.before including the children in the study.

Seventhy febrile children were selected from cases were admitted in pediatric ward during 2 years .A check list was completed for the subjects who included complete history such as age, sex, seizure history, seizure type, systemic diseases . One milliter of blood in 2 groups in the first admission were tested for CBC, The serum ferritin for the cases and controls were studied by ELISA (enzyme-linked immunosorbent assay) in first day of admission.These values enrolled in the questionnaire.

Cases Definition:

Inclusion criteria: Thirty five patients with final diagnosis of febrile convulsion (without underlying disease and normal CSF analysis) selected as cases.

All febrile seizure group had the first bout of single generalized febrile seizure prolonged <15 minutes..

Exclusion criteria: All children with known causes for convulsion after complete clinical studies (e.g. electrolyte imbalance, , leukemia , metabolic disorders, , chronic diseases, malnutrition,);CNS infection (meningitis, encephalitis,brain abscess)) excluded from study. Also we excluded all Children who had mental retardation, brain anomalies, brain tumor ,atypical convulsion, focal seizure, chronic diseases, moderate to severe malnutrition,

Controls

Thirty five febrile children without convulsion and normal CNS examination (unconsciousness r/ no meiningeal signs and symptoms / no other abnormal neurologic deficits),negative bacterial culture (CSF/Blood) .Viral infection was the final diagnosis febrile control group.

Lab test:

Two milliter of peripheral blood collected within the first day of admission in hospital. The blood were tested for CBC, HB ,MCV,MCH ,MCHC in 2 groups. The remaining blood in an acid-propylene tube were centrifuged and serum was preserved in -80°C. Serum ferritin was estimated by EIAS test for the cases and controls

Statistical Analysis

All analyses were conducted using SPSS, version 13.5. Quantitative variables were summarized as mean \pm standard deviation (SD) and qualitative variables were counted and expressed as percentages. The Student's t test was used to determine significant differences in means of all continuous variables. . Chi-square test was performed to compare proportion between 2 or more discrete variables. $P < 0.05$ was considered statistically significant .

ROC (receiver-operating-characteristic curve) illustrated and the cut-off level for serum Ferritin, Sensitivity, specificity, PPV, NPV, of test was calculated.

Results

Of 70 admitted children, the cases included 35 children (mean age: 2.191 ± 0.946 years); 62.9% male, 37.1% female who were referred due to FC . Also, 35 children who were hospitalized due to febrile diseases without convulsion enrolled in this trial as controls (mean age: 1.93 ± 1.433 years) 65.7% male, 34.3% female.

No significant difference observed in age and gender between FC cases and controls (p value=0.3; 08). No significant difference were determined between 2 groups for mean the Hemoglobin level (11.6 ± 0.79 vs 11.86 ± 0.71 ; p value= 0.2); MCV (75.8 ± 4.3 vs 77.62 ± 4.1 , p value= 0.08); and MCH (26.2 ± 1.5 vs 27.3 ± 2.8 , p value= 0.07)

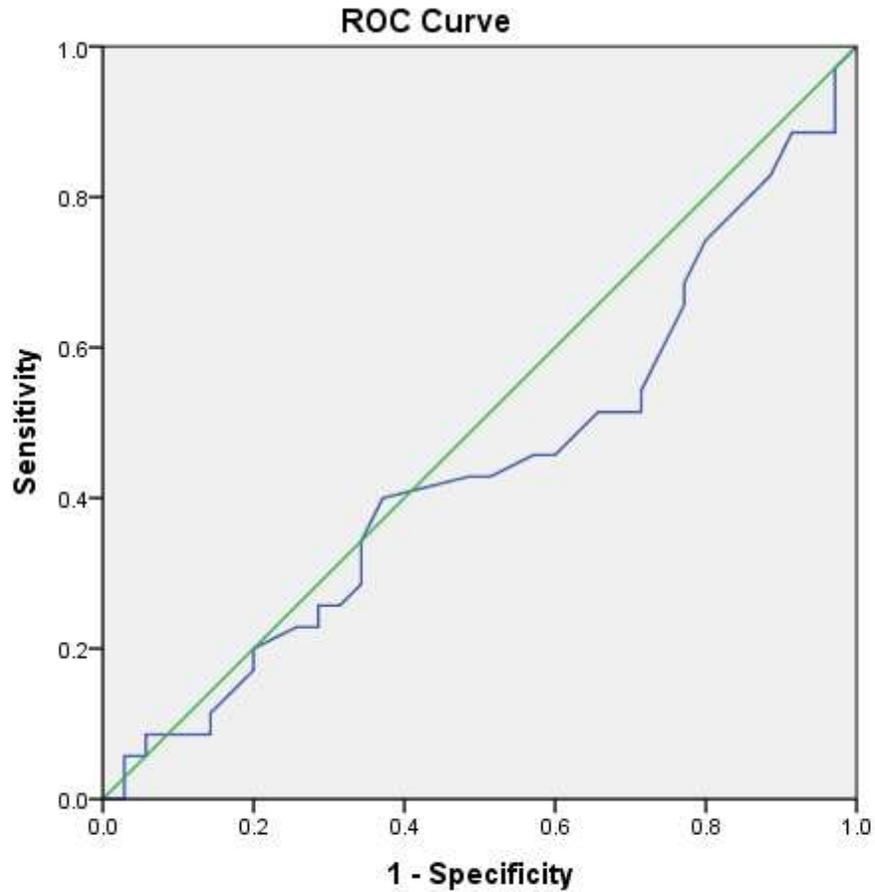
The mean level for serum ferritin in 2 groups was 56.4 ng/ml. All data Compared between cases and controls in Table- 1.

Data	Hb		MCV /MCH		Ferritin level (ng/ml)	
	Case I	Control	Case	Control	Casel	Control

						ferritin
Mean	11.6	11.86±	75.8 /26.2	77.62/27.3	54.57	58.31
Standard deviation	079	071	4.3 /1.5	4.1/2.1	24	23
P value	0.2		0.08		0.64	

Table -1: Comparison the data between cases and controls

Figure-1:show the area under curve (AUC) .AUC was 0.442(0.306-0.578, P value=0.4). According to this curve, the calculated cut-off level for ferritin was 36ng/ml.; it had 74.3% sensitivity ,20% specificity , 56% PPV, 52% NPV.The Positive likelihood Ratio: 1.3 ; Negative likelihood Ratio: 0.93 was calculated .



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s): FERRITIN

Area	Std. Error ^a	Asymptotic Sig. ^b	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.442	.069	.404	.306	.578

The test result variable(s): FERRITIN has at least one tie between the positive actual state group and the negative actual state group.

Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Coordinates of the Curve

Test Result Variable(s): FERRITIN

Positive if Greater Than or Equal To ^a	Sensitivity	1 – Specificity
9.00	1.000	1.000
15.00	.971	.971
20.50	.943	.971
21.50	.914	.971
23.00	.886	.971
26.00	.886	.943
29.00	.886	.914
32.50	.829	.886
36.00	.743	.800
37.50	.686	.771
39.00	.657	.771
41.50	.543	.714
43.50	.514	.714
44.50	.514	.657
46.00	.457	.600
47.50	.457	.571
48.50	.429	.514
49.50	.429	.486
52.00	.400	.371
54.50	.343	.343
56.50	.314	.343
59.00	.286	.343
62.00	.257	.314
64.50	.257	.286
66.50	.229	.286
69.00	.229	.257
71.50	.200	.200
74.00	.171	.200

77.50	.114	.143
82.50	.086	.143
89.00	.086	.114
109.50	.086	.086
128.00	.086	.057
135.00	.057	.057
145.00	.057	.029
160.00	.029	.029
173.50	.000	.029
178.00	.000	.000

The test result variable(s): FERRITIN has at least one tie between the positive actual state group and the negative actual state group.

- a. The smallest cutoff value is the minimum observed test value minus 1, and the largest cutoff value is the maximum observed test value plus 1. All the other cutoff values are the averages of two consecutive ordered observed test values.

Figure-1: Area under curve for Ferritin in ROC curve

The Cut off for ferritin (<36ng/ml) observed in 30% (9/35) of convulsive cases in compare with 21% (7/35) in controls, without significant difference (54.57 ± 24 vs 58.31± 23, p value= 0.64) :

Table-2

	Ferritin level (<36ng/ml)
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Febrile convulsion	Positive	Negative
	Positive	9
Negative	7	28

Table-2: The ferritin Cut off (<36ng/ml) compared between cases and controls

Discussion

The present study is the first to report the ferritin cut off level which discriminates the FC cases from non-convulsive febrile children. Ferritin cut off (36ng/ml) observed in 30% of FC cases without significant difference observed (21%) of in non convulsive febrile controls (p value= 0.64). The ferritin as an acute phase reactant in all febrile patients might explain this no significant difference. This level has an acceptable sensitivity (74.3%) but poor specificity (20%) and just 56% PPV, 52% NPV to differentiate the FC cases from non-convulsive febrile children.

The mean ferritin level (58) in all children in present study is very close to normal children (58.75), reported by Soheilipour et al (15) ,none of the children had ferritin level < 12mic/.a significant difference between children with 3 usual acute infections(GI, RTI, UTI) in compare with normal children (60.05, 62.00 , 60.60, vs 58.75).[15] .

Association between ID and FC have shown contradictory results in Iran like the other countries. The higher rate for ID in Children with FC in some Iranian studies (14-18,22,24,25) . In contrast, Bidabadi et al (19) reported that ID in FC was less than afebrile controls (44% vs 48%) Salehi et al (21) observed that ID plays no role in pediatric FC. According to Fallah et all (22) ID was more frequent in FC cases (48% vs. 28%, p= 0.04).

The power of present study is comparing the febrile children as controls not afebrile children. Like us, Ghasemi et al reported ferritin level (36ng/ml) in 40% of FC, 26% of children with non-convulsive febrile cases, 12% of healthy children (non-febrile, non-convulsive) (24). Sharif et al (25) reported ID in 45% of FC and 12% of non-convulsive febrile children (25) The 21% ID in non-convulsive febrile children (control group) in present study was just similar to 26% study by Hashemi et al (26%). They realized that Children with FC were more likely to suffer from iron

deficiency compared to those with solitary febrile illness or healthy children. Thus, ID could be considered as a risk factor for Fc, but in both mentioned studies, no cut-off point was determined for discrimination in three groups. ID could be an important risk factor for development of FC. Evaluation of iron status was encouraged to be performed in children with FC. Indeed, Sadeghzadeh et al (23) reported ID in 6% of FC cases in Zanjan; like as healthy groups. According to this study, it was suggested that although ID was not frequent in febrile seizure group of children, but iron deficiency was more reported in patients with Fever (23).

The peak incidence for FC is near 18 months age. (2-3) Height of temperature, positive family history of FC , maternal smoking and alcohol consumption during pregnancy, and perinatal exposure to antiretrovirals are probable risk factors for FC.(3) Although ,multiple etiologic factors are considered for FC such as molecular genetic basis(4) ,reduction of neurotransmitters (zinc and magnesium,,GABA) in pathogenesis of several seizure disorders(5,6,7) ,low level of trace element in sera or CSF of children with FC (8-9) Changes in the levels of pro inflammatory cytokines,;prostaglandins and zinc in FC is reported (9)

In developing countries 46–66% of children under 4 years are anemic, with half attributed To ID (10) Pisacane et al.(11) showed the higher rate of ID in younger (<2yold) FC cases .Also, Kumar and Al Rahman showed lower level of ferritin in FC cases in compare with non-convulsive febrile children (12,13).These previous results were totally contrary to results of both Iranian studies; (22, 24) and other studies carried out in other countries (11-13).

The cut off level for was not reached in none of previous studies in Iran, except for the present study. In our study, all patients that were chosen as patient group were admitted with their first FC, but in most previous mentioned studies, some Fc cases had a recent history of febrile convulsion. Various diagnostic criteria of ID in different references and ferritin level as an age dependent factor in diagnosis of ID might be another reason for unmatched results (22, 24,11).

We are in favor of the results mentioned in Bidabadi et al (19) study_that no identified relationship has been detected yet between ID and FC, maybe it could be considered as an accidental correlation or interference of other unknown factors such as genetic, viral and other transmitters (19) . Talebian (20) reported the Pooled recurrent rate of febrile seizure in Iran was 20.9% (95% CI: 12.3-29.5). In 28.8% (95% CI: 19.3-38.4) of children there was positive family history. They concluded that the risk of FC occurrence in children with ID seems to be more frequent than children with convulsive febrile seizure, ID could be considered as a protective factor against the risk of convulsion occurrence by raising the threshold of convulsion (20)

Conclusion: Inconsistency and conflict were detected in results of previous studies regarding the relationship between ID and FC. In spite of this fact that fever could be considered as an aggravating factor in negative effects of iron deficiency on nervous system. In our opinion, ID could not lead to FC in all children, but in some cases with genetic basis; ID raises the threshold for seizures. Due to high prevalence of ID (26%) especially in your Iranian population, adding the Iron to diet, might be helpful in decreasing FC in susceptible cases.

Limitation of study: The increasing of ferritin levels (above the bases line) as an acute phase reactant is acceptable in every febrile cases. We did not know the ferritin base level in each children(case /control) before infection.

List of abbreviations:

Febrile convulsion (FC),Iron efficiency (ID), ELISA (enzyme-linked immunosorbent assay),ROC (receiver-operating-characteristic curve) ,PPV (positive predictive value) ;NPV(negative predictive value) , Gamma Aminobutyric acid(GABA)

Declarations:

Ethics approval and consent to participate:

This study was accredited by Ethical Committee of Iran University of Medical Sciences. Helsinki Declaration was respected across the study and the informed consent form was signed by the parents.

Consent for publication: All authors confirm Consent for publication

Availability of data and material: we confirm availability of data and materials in Records of hospital.

Competing interests:

The authors declare no conflict of interest in preparing this study.

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Leila Tahernia : MD, Fellowship of Pediatric ICU, Pediatrics Depart, Tehran University of Medical Sciences, Tehran, Iran.

Authors' contributions:

Fahimeh Ehsanipour designed and supervised the study

Samileh Noorbakhsh:.,corrosponder : writing the initial report and full article .

Azita Tavassoli: visited and interpreted the data.

Leila Tahernia: major contributors in rewriting and English editing the manuscript.

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Figures

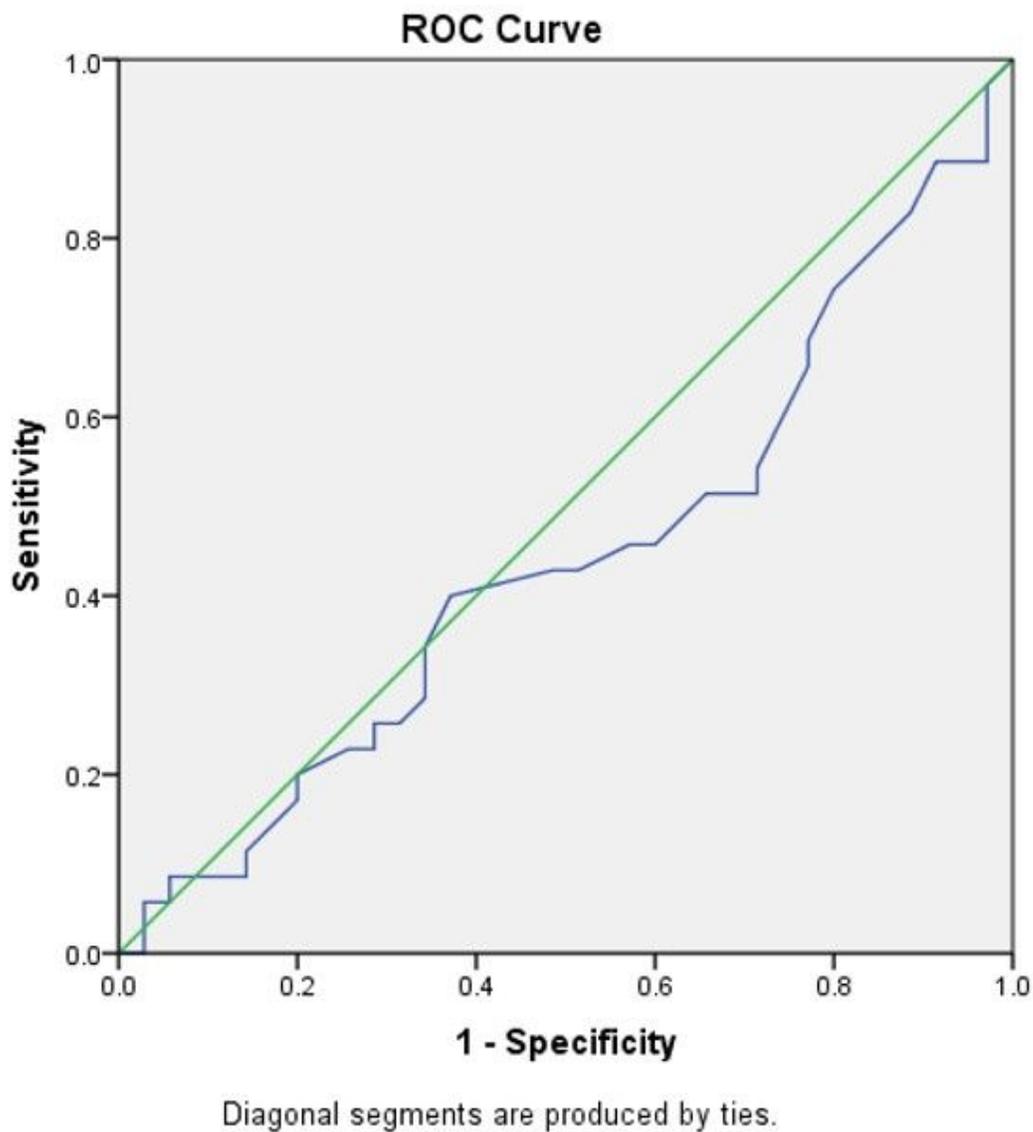


Figure 1

show the area under curve (AUC) .AUC was 0.442(0.306-0.578, P value=0.4). According to this curve, the calculated cut-off level for ferritin was 36ng/ml.; it had 74.3% sensitivity ,20% specificity , 56% PPV, 52% NPV.The Positive likelihood Ratio: 1.3 ; Negative likelihood Ratio: 0.93 was calculated .