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Correlation between Iron Status and Simple Febrile Seizures in Children

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ABSTRACT

- **Background:** Febrile seizures are non-epileptic types of seizure that occur frequently during early childhood. Multiple factors are implicated in the pathogenesis of these types of seizures. Iron deficiency might play as an etiological or, at least, augmenting factor in the development of febrile seizures.
- **Objective:** To study iron status among children with simple febrile seizures, and to estimate the prevalence of iron deficiency between them.
- Patients and methods: A case-control study included 100 febrile children aged 6 months to 60 months, and were ascribed to 2 groups; 50 children with simple febrile seizures [case group], and 50 children who had febrile disease without occurrence of seizures [control group]. Venous samples were obtained for the analysis of complete blood count, and iron indices [serum ferritin, serum iron and total iron binding capacity].
- **Results:** The peak temperature was significantly elevated among the case group [P=0.03]. Regarding iron profile, compared to controls, the case group had significantly lower iron [54.24±16.04 vs. 62.6±16.02; P=0.011], and lower ferritin [37.612±19.85 vs. 80.624±31.57; P <0.001]. Correlation analysis revealed a significant negative correlation between serum ferritin and frequency of febrile seizures [P=0.025]
- **Conclusions:** Iron deficiency and iron deficiency anemia were more common among children with simple febrile seizures, and they were associated with increase in the duration and frequency of seizures. Special attention should be paid for the assessment of iron status among children with febrile seizures.

Keywords: Fever; Seizures; Iron; Anemia; Febrile seizures.

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* Main subject and any subcategories have been classified according to the research topic.

INTRODUCTION

Febrile seizures are the most frequent types of seizures in children between 6 months to 60 months of age, which is associated with fever more than 38 °C without evidence of central nervous system affection, or electrolyte disorder, and lacking a history of past afebrile seizures ^[1]. Febrile seizures are either simple or complex. Simple febrile seizures are identified if seizures are generalized tonicclonic, persisting below 15 min, and do not reappear within 24 h^[2].

The etiology of febrile seizures seems to be multifactorial. Fever affects the immature central nervous system in a genetically susceptible individual, and may be aggravated by the presence of other specific disorders ^[3].

Iron is a vital element required for optimal development of children. Iron deficiency is associated with multiple undesirable consequences, including behavioral disturbances, abnormal growth, impaired cognition, and disruption of immune function ^[4, 5].

Iron deficiency might affect the threshold of neuronal excitability, because it is usually associated with a deficiency of certain neurotransmitters such as monoamine oxidase and aldehyde oxidase ^[6]. Furthermore, iron is essential for neuronal myelination, which constitutes the cornerstone of nerve conduction throughout the central nervous system ^[7].

In addition to the effect of iron deficiency on neuronal excitability, fever might aggravate the harmful consequences on the brain caused by iron deficiency and activate seizure ^[8].

AIM OF THE WORK

Because the correlation between iron deficiency anemia and simple febrile seizures during childhood is inconclusive, the current study was conducted in an attempt to investigate it, and to detect the effects of iron deficiency on the course and severity of simple febrile seizures.

PATIENTS AND METHODS

The present case control study included 100 children aged between 6 months to 60 months, presented with acute febrile illness. They were recruited from "Pediatric Department of Al–Azhar University Hospital [New Damietta]" during the period from February 2019 to March 2020. Included children were categorized into 2 groups; a case group which included 50 children with simple febrile seizures, and a control group which included 50 children who had febrile illness without seizures.

Simple febrile seizures are diagnosed in a child aged 6 months to 60 months with a generalized tonic-clonic seizure in the setting of febrile illness [temperature is at or more than 38 °C], not lasting more than 15 min, and does not recur within 24 h [1, 2].

Any child presented with manifestations of central nervous system affection, with a history of previous afebrile seizures and developmental delay, or received iron supplementation during the past three months was excluded from the study.

Full history was obtained, with special emphasis on seizure history, including age at first febrile seizure, the average duration of attacks, and family history. A general and systematic examination was completed to exclude any associated illnesses.

Sampling: Blood was collected from a peripheral vein under complete aseptic conditions, and distributed into several aliquot. One part was added to EDTA-containing tube for performing CBC. The other part was allowed to clot in a plain tube, and then centrifuged for separation of serum. The resulting serum was stored at -20° C until the assay. Complete blood count was analyzed using quantitative automated hematology analyzer [sysmex-21kx]. C-Reactive protein [CRP] levels were measured by ELISA with a sensitivity limit of 0.9 µg CRP/I. Serum ferritin was analyzed by [ELISA] using DRG® Ferritin [EIA-1872]. Serum iron was estimated by colorimetric methods using [SPECTRUM – CAT.NO.269 003], and total iron binding capacity [TIBC] was estimated by colorimetric methods using [SPECTRUM – CAT.NO.273 001].

The diagnosis of iron deficiency anemia [IDA] was various according to the age of the child. For children between 6 months and two years of age, IDA was described as hemoglobin [Hb] < 10.5g/dl, mean cell volume [MCV] < 7 0 fL, and mean corpuscular hemoglobin [MCH] < 23 pg. For older children [>2 – 5 years], IDA was described as Hb < 11.5 g/dL, MCV< 75 fL, and MCH< 24 pg ^[9]. Iron deficiency is described as serum ferritin level < 12 ng/ml in case CRP was negative or serum ferritin level < 30 ng/ml if CRP is positive ^[10].

Ethical consideration: Approval of the "Research Ethics Committee of the Faculty of Medicine" was obtained before the study. The aim of the study was explained to parents. Informed consents from the caregivers were obtained for each patient enrolled in the study before taking blood samples.

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Statistical analysis: Data were supplied to the computer using "IBM Statistical Package for the Sociable Sciences [SPSS], version 20, SPSS Inc. Chicago, IL, USA]." For comparing categorical variables, Chi-square test was applied. For normally distributed data, comparisons between two independent samples were done using independent t-test or Mann-Whitney test. Pearson correlation co-efficient was used to correlate different variables. For all performed tests, P value < 0.05 is considered significant [11].

RESULTS

The age, sex and anthropometric measurements [weight and height] were comparable between both groups. Peak temperature has significantly elevated among the cases group [P=0.03]. Family history of both febrile seizures and epilepsy was more frequent among the cases group [Table 1]. All erythrocytes parameters [Hb, MCV, MCH, MCHC and RDW] were significantly affected among the case group. Regarding iron profile, compared to controls, cases group had significantly lower iron [54.24±16.04 vs. 62.6±16.02; P=0.011], and lower ferritin [37.612±19.85 vs. 80.624±31.57; P<0.001]. The frequency of iron deficiency anemia [48%] was significantly higher in cases group [P<0.001] as shown in [Table 2]. Finally, there was a significant correlation between hemoglobin and ferritin levels with frequency of seizures [r= -0.507; P=0.001 for Hb, and r= -0.355; P=0.025 for ferritin], and the average duration of seizures [r= -0.474; P=0.001 for Hb, and r= -0.381; P=0.009 for ferritin].

Table [1]: General characteristics of the studied cases					
	Case group [n=50]	Control group [n=50]			
	24.8±14.6	24.7±10.5			

Variables		Case	group [n=50]		Control group [n=50]	P value
Age [months]		24	1.8±14.6		24.7±10.5	0.497
Sex	Male	2	0 [40%]		22 [44%]	0.116
	Female	3	0 [60%]		28 [56%]	0.110
Peak temperatur	re [°C]	38	.90±0.46		38.20±0.47	0.030*
Weight [Kg]		11.	66 ± 3.21		12.61± 4.03	0.26
Height [cm]		80).9 ± 9.3		81.3 ± 9.1	0.85
Family history of	febrile seizures	1	3 [26%]		2 [4%]	0.001*
Family history of	ly history of epilepsy 6 [12%] 1 [2%]		1 [2%]	0.025*		
Underlying illnes	ss causing fever					
Upper respirator	y infection	2	4 [48%]		20 [40%]	
Gastroenteritis		1	0 [20%]	14 [28%]		0.776
Lower respirator	y infection		9 [18%]	10 [20%] 3 [6%] 3 [6%]		
Urinary tract infe	ection		5 [10%]			
Fever without for	cus		2 [4%]			
Table [2]: Comparison between study groups regarding hematological parameters and iron profile						
			Case group [n=	=50]	Control group [n=50]	P value
Hemoglobin leve	el [a/dl]		10.769±1.2		12.720±0.95	0.001*

	Case group [n=50]	Control group [n=50]	P value
Hemoglobin level [g/dl]	10.769±1.2	12.720±0.95	0.001*
Mean cell volume [fl]	72.06±3.87	75.336±8.56	0.015*
Mean corpuscular hemoglobin [pg/cell]	23.36±3.66	25.01±2.97	0.003*
Red cell distribution width [%]	16.33±1.10	13.216±2.46	0.004*
Mean corpuscular hemoglobin concentration [g/dl]	30.698±3.27	32.76±2.39	0.001*
Total iron binding capacity [µg/dL]	348.54±82.70	320.36±74.02	<0.001*
Serum ferritin [ng/ml]	37.612±19.85	80.624±31.57	<0.001*
Serum iron [µg/dl]	54.24±16.04	62.6±16.02	0.011*
C-Reactive protein [mg/l]	12.73±6.85	24.54±10.99	0.004*
Iron deficiency [without anemia]	6 [12%]	10 [20%]	
Iron deficiency anemia	24 [48%]	10 [20%]	<0.001*
Normal iron status	20 [40%]	30 [60%]	

*: significant

 Table [3]: Correlation between hemoglobin and serum ferritin with variable factors

Parametera	Hemoglobin		Serum ferritin	
Faiameters	r	p-value	r	p-value
Age [Months]	-0.216	0.132	-0.125	0.388
Age at onset	0.202	0.160	0.093	0.519
The average duration of seizures [min]	-0.474	0.001*	-0.381	0.009*
Peak temperature [°C]	-0.152	0.542	-0.235	0.100
Frequency of seizures	-0.507	0.001*	-0.355	0.025*

*: significant

DISCUSSION

Because iron deficiency anemia is a frequent health condition in pediatrics and primary results have failed to establish a conclusive relationship, this study was commenced to explore the association between iron status and simple febrile seizures in pediatrics.

In this study, all red blood cell indices [Hb, MCV, MCH, and MCHC] were significantly lower in the case group compared to the control group. These findings were consistent with the results observed by Ganie et al. [12] and Malla et al. [13] who reported that the mean Hb, MCV, MCH, MCHC were significantly lower in cases with febrile seizures compared to the control group. In contrast, Gontko-Romanowska et al. [14] and Yousefichaijan et al. [15] found that the levels of hemoglobin were significantly higher in the case group. In addition, they reported significantly higher RBC indices [MCV, MCH, MCHC] in cases as compared to controls. Ghosal [16] revealed that the mean hemoglobin concentration for cases and controls was low and the difference was non-significant while, the mean MCH, MCHC and MCV was significantly less in cases than in controls. Ghasemi et al. [9] reported that the means of hemoglobin, hematocrit, and RBC, were significantly lower in the febrile convulsion group but no significant differences were found among their study groups in terms of RBC indices.

On comparing the iron indices between cases and controls, we found that the mean serum ferritin and serum iron levels were significantly lower in the case group than in the control group, while the total iron binding capacity was significantly higher in the case group than in controls. The results of this study were consistent with Ganie *et al.* ^[12]. Also, these results were in agreement with Ghosal ^[16] who found that a significant number of cases had a low serum ferritin level compared to controls. Furthermore, Malla *et al.* ^[13] found that the mean for serum iron and ferritin was significantly lower, while the mean for TIBC was significantly higher in cases than in controls.

In this study, the incidence of iron deficiency anemia was more frequent in the case group than in controls, and this was in agreement with Sharif et al. ^[8] who reported that iron deficiency anemia was higher in the febrile seizure group than in the control group. Sadeghzadeh *et al.* ^[17] reported that iron deficiency was more common with febrile seizures, but iron deficiency anemia was not significantly frequent. Based on the results of a study by Fallah *et al.* ^[10], iron deficiency was found to be a significant risk factor for developing febrile seizures.

On the other hand, Shah and Parmar ^[18] suggested that there was no significant association of iron deficiency anemia with febrile seizures. Even Yousefichaijan et al. ^[15] observed that iron deficiency anemia is significantly less frequent in cases than in controls. The difference reported between these studies might be due to a number of factors as a larger sample size and nutritional habits.

The inconsistency among different studies in the association of febrile seizures with ID/IDA may be attributed, among others, to differences in ethnic background, socioeconomic status & accompanying nutritional status, definitions and diagnostic criteria of ID and IDA, duration of fever at the time of sampling, and duration between onset of seizures and time of sampling. Fever can exacerbate the outcomes of iron deficiency anemia on the immature brain, and therefore leads to higher opportunity for developing seizures ^[8]. Furthermore, children with iron deficiency anemia are more vulnerable to acquire recurrent infections, especially upper respiratory tract infections and gastro-enteritis, which might increase the frequency of febrile illnesses among those children ^[19].

It is noteworthy that cases group had significantly lower CRP levels compared to controls, which was in agreement with Gontko-Romanowska *et al.* ^[14] who reported the same significant difference. This can be explained by the fact that CRP rises to the maximum values in 24–48 h after the onset of inflammatory reaction. Thus, children with febrile seizures may develop rapid inflammatory processes and rising temperature quickly enough that CRP levels do not attain their maximum values, while in children with fever but without seizures, the inflammatory process was progressing slow enough to obtain higher CRP levels ^[14].

Correlation analysis of different variables revealed that low Hb and serum ferritin levels were associated with increased severity of seizures [as verified by an increase in the frequency]. Ozaydin *et al.* ^[20] assessed the duration of seizures in 100 febrile seizures patients and found that the duration of seizures is longer in patients with iron deficiency anemia [7.52±3.7] min than in patients without iron deficiency anemia [5.12±2.9] min.

Regarding the frequency of febrile seizures, Atwa *et al.* ^[21] found that children with a recurrence of febrile seizures had significantly lower hemoglobin, serum iron and serum transferring receptor [s-TFR]. Thus, there was a significant positive correlation between the recurrence of febrile seizures and the presence of iron deficiency.

Alternatively, Lee *et al.* ^[22] reported that MCV was significantly lower in cases with a recurrence of febrile seizures but there were no significant differences in cases with recurrence and those with no recurrence regarding RBC, hematocrit, MCHC, and RDW.

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The limitations of the study include the case control study design with no follow-up, possibly small sample size, and possible confounding factors [e.g., duration of fever at the time of sampling, duration between seizures and sampling].

Conclusion: Iron deficiency and iron deficiency anemia were more common among children with febrile seizures. Low serum ferritin was associated with an increase in the severity of febrile seizures, in terms of increasing the duration and frequency of seizures. Special attention should be given to the assessment of iron status among children with febrile seizures.

Financial and Conflict of interest disclosure

"Authors declare no conflict of interest"

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