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Relation of Iron Profile Parameters, Zinc and Magnesium with Febrile Seizures in Children from Gaza City

Ohood M. Shamallakh[1], Kholoud M. Shamallakh[1], Heba M. Arafat[2] & Mazen M. Alzaharna[1]*

[1]*Department of a Medical Laboratory Sciences, Faculty of Health Sciences, Islamic University of Gaza, Gaza City, Palestine*
[2]*Department of Laboratory Medicine, Al Azhar University-Gaza, Gaza Strip, Palestine*
**Corresponding Author: Dr. Mazen M. Alzaharna*
Postal addresses: Room C321, Scientific Building, Islamic University of Gaza, Gaza, Gaza Strip, Palestine.

Abstract
Objective: *To investigate the association between iron profile parameters, Zn, and Mg levels with febrile seizure (FS) among children in Gaza City.*
Materials and Methods: *A case-control study, performed on 80 children (6–60 months), 40 with FS and 40 without seizures. Serum ferritin, iron, total iron-binding capacity (TIBC), soluble transferrin receptor, Zn and Mg were measured, transferrin saturation was calculated, CBC indices and anthropometric measurements were performed. An approval was obtained from Helsinki committee. SPSS program version 22 was used for all data analysis.*
Results: *The mean levels of serum iron, and transferrin saturation among cases were higher significantly compared to controls (P<0.001). The mean level of TIBC among cases was lower significantly compared to controls (P<0.001). In addition, the percentage of cases with anemia was 85% compared to 80% for controls (P = 0.556). In contrast, 12.5% of cases had iron deficiency (ID) compared to 30% in controls respectively (P>0.05). The mean levels of Mg and hs-CRP were lower among cases compared to controls (P<0.05).*
Conclusion: *There was no association between ID or decreased serum level of Zn and the presence of FS. While results showed that Mg may play a role in FS pathogenesis.*
Keywords: *Febrile Seizures, Serum Iron, iron deficiency anemia, Zinc, Magnesium, Gaza City.*

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Abbreviations: FS: Febrile seizure; **Hb:** Hemoglobin; **hs-CRP:** High-sensitivity C-reactive Protein; **ID:** Iron deficiency; **IDA:** Iron deficiency anemia; **MCV:** Mean Corpuscular Volume; **Mg:** Magnesium; **NMDA:** N-methyl-d-aspartate; **RDW:** Red Blood Cell Distribution Width; **SF:** Serum Ferritin; **SI:** Serum Iron; **sTfR:** Soluble Transferrin Receptors; **Tfsat:** Transferrin Saturation; **TIBC:** Total Iron Binding Capacity; **URTI:** Upper respiratory tract infection; **Zn:** Zinc.

I. Introduction

Febrile seizure is the most common form of seizures in children aged between 6-60 months with body temperature ≥38^{o}C, which is not the result of central nervous system (CNS) infection or any metabolic imbalance, and which occur in the absence of a history of prior afebrile seizures. Most FS cases are benign and self-limiting, and generally, treatment is not recommended (1).

Currently identified risk factors for FS include, close blood relative with history of FS, cigarette smoking during gestation, low birth weight, a neonatal nursery stays greater than month, attending to daycare center, fever higher than 39.4^{o}C, specific infectious diseases, disturbance in the levels of serum minerals, and iron deficiency anemia (IDA) (2, 3).

Iron deficiency is considered the commonest micronutrient deficiency globally which can be prevented and treated. ID can cause several neurological manifestations including, delayed motor development, learning deficits, poor attention span, weak memory, and behavioral disturbances. In addition, high body temperature can exacerbate negative effects of ID on the brain. Therefore, it is likely that ID may predispose to other neurological disturbances like FS (4, 5). ID can alter brain synaptic neurotransmitters. Increase of glutamate excitatory neurotransmitters, decrease of GABA inhibitory neurotransmitters, decrease of monoamines and hypoxemia from IDA may be responsible for induction of seizure due to ID (5).

Minerals and trace elements have been demonstrated to affect several biochemical and physiological processes (4). Zinc (Zn) and Magnesium (Mg) play a crucial role in the function of the brain and neurological

disorders development and prevention. It was assumed that certain elements might be involved in the etiology of FS (2).

Several studies showed a statistical association between IDA and FS (4, 6), while other studies haven't found a significant association (7, 8). Numerous case-control studies found lower levels of serum Zn in FSs children than those who had only fever (2, 9). Furthermore, several studies show a significant relationship between low Mg levels with FS (10). Therefore, the aim of the present study was to investigate the association between iron profile parameters and selected minerals (Zn and Mg) with FS among children from Gaza City.

II. Materials and Methods

The study was a case-control one. The target population of this study comprised of children with FS (Case Group) and children with febrile illness without any seizures (Control Group).

The study was conducted at Al Nassir Pediatric Hospital in Gaza. The samples were 40 infant/children with FS taken from the emergency room and 40 infant/children with febrile illness but without any seizures selected from the outpatient clinic. The cases and controls were matched for age and gender.

The infant/children aged 6-60 months, both genders, with temperature of 38°C or higher, and normally developed neurologically with an FS diagnosis were included in the study. While, the following individuals were excluded from the study to eliminate potential confounding factors: seizures caused by infection of CNS or by metabolic imbalance; developmentally delayed children and children on iron therapy or had received Zn or/and Mg supplements or both.

The necessary approval was obtained from the Helsinki committee to carry out the study in the Gaza City. Parents of each of the participants were provided with enough knowledge about the purpose of the study. The acceptance was taken from parents of all participants. A formal letter of request was sent from the Palestinian ministry of health to Al Nassir Pediatric Hospital in Gaza City to facilitate the task of the researcher. All participants' parents were interviewed face to face by the researcher. The questionnaire included questions about child personal data (address, age, and gender); occupation of children parents; socioeconomic status (family income, source of income, number of household and type of home); child anthropometric measurements (body weight, length/height); child neonatal history (birth weight and admission to ICU) and child medical history.

Blood samples were collected from all participants, children with FS (case group) as well as from children with febrile illness without any seizures (control group), after getting informed consent from the parents.

The blood sample collection process began with blood collection at Al Nassir Pediatric Hospital and then samples were transferred under proper conditions to avoid high or low-temperature exposure, to Palestinian Medical Relief Society (PMRS) laboratory, where blood tests for cases and controls were performed.

Five ml of venous blood samples were obtained from each child by a qualified nurse and divided into two tubes. About one-ml was placed into Ethylene diamine tetra acetic acid (EDTA) vacutainer tube to perform CBC test. The remaining quantity of the blood was placed into the vacutainer plain tube that was left to clot for a short time, and then clear serum samples were centrifuged for 10 minutes at 3000 revolutions per minute. The separated serum was placed in plain tubes and sealed for biochemical analysis (Serum ferritin, iron, total iron-binding capacity, soluble transferrin receptor, Zn and Mg). To prevent loss of bioactivity and contamination, samples were stored at -20°C.

Statistical Package for the Social Science (SPSS, version 22) was used for data processing and analysis. For all variables of the study, cross tabulation and simple distribution system were used. To identify the significance of the associations, relationships, and interactions between the different variables, Chi-square ($\chi 2$) was used and means of quantitative variables were compared by independent sample t-test. Pearson correlation test and range as minimum and maximum values were also used. The results of the aforementioned techniques were statistically significant when the p-value was <5% ($P<0.05$).

III. Results

General characteristics of the study population

Table (1) shows that the age of the participants ranged from (6–60 months). The mean age of the cases (24.7±13.8 months) and controls (23.2±15.7 months) were not significantly different (P=0.634). There was no statistically significant difference between the cases and controls regarding the height, and weight. On the other hand, the percentage of male and female participants was 52.5% & 47.5% for cases while 60.0% & 40.0% for controls respectively with no significant difference (P=0.499). There was also no significant difference between cases and controls in the parental consanguinity.

Table 1: General characteristics of the study population.

Characteristics		Cases (n = 40)	Controls (n = 40)	P-value
Age (Months)	Mean ± SD (min-max)	24.7 ± 13.8 (6.0-60.0)	23.2 ± 15.7 (8.0-58.0)	0.634
Height (cm)		85.4 ± 13.9 (64.0-122.0)	83.5 ± 13.5 (60.0-115.0)	0.538
Current Weight (kg)		11.3 ± 3.0 (7.0-20.5)	10.7 ± 3.4 (5.5-20.0)	0.360
Gender	n (%)			
Male		21 (52.5)	24 (60.0)	0.499
Female		19 (47.5)	16 (40.0)	
Parental consanguinity				
Positive		10 (25.0)	14 (35.0)	0.329
Negative		30 (75.0)	26 (65.0)	

n: Number of the subjects; **SD:** Standard deviation.

Clinical characteristics and medical history of the study population

Although the mean admission temperature of the cases (39.1±0.7) was higher compared to that of the controls (38.9±0.7), the difference was not statistically significant (P=0.215). In contrast, the heart rate of the cases (129.6±25.3) was significantly higher than that of the controls (100.9±35.6) (P<0.001).

The participants of the cases and controls had fever upon admission to hospital. The cause of the fever was due to URTI in (85.0%) of the cases and (57.5%) of the controls compared to (15.0%) of cases and (42.5%) of controls due to Gastroenteritis (P=0.007) (Table 2). Moreover, most of the cases and controls did not have past history of FS (92.5 & 100.0%) nor family history of epilepsy (95.0 & 100.0%) (P=0.077 & 0.152) respectively. In contrast, there was a statistically significant difference between the cases (30.0%) and controls (0.0%) regarding the family history of FS (P<0.001).

Table 2: Clinical characteristics and medical history of the study population.

Variables	Research Category		P-value
	Cases (40) n (%)	Controls (40) n (%)	
Admission to ICU			
Yes	6 (15.0)	7 (17.5)	0.762
No	34 (85.0)	33 (82.5)	
Fever			
Yes	40 (100.0)	40 (100.0)	1.000
No	0 (0.0)	0 (0.0)	
Cause of fever			
URTI	34 (85.0)	23 (57.5)	**0.007**
Gastroenteritis	6 (15.0)	17 (42.5)	
Past history of febrile seizure			
Yes	3 (7.5)	0 (0.0)	0.077
No	37 (92.5)	40 (100.0)	
Family history of febrile seizure			
Yes	12 (30.0)	0 (0.0)	< **0.001**
No	28 (70.0)	40 (100.0)	
Family history of epilepsy			
Yes	2 (5.0)	0 (0.0)	0.152
No	38 (95.0)	40 (100.0)	

n: Number of the subjects; **ICU:** Intensive care unit**; URTI:** Upper respiratory tract infections.

Biochemical parameters among the study population

Table 3 shows that the mean level of serum iron (SI) was higher in cases (50.9±23.0 µg/dL) compared to controls (24.3±16.3 µg/dL) (P<0.001). There was also a statistically significant difference in the mean levels of TIBC (296.6 vs 372.1 µg/dL) and Transferrin Saturation (Tfsat) (19.8 vs 7.5%) between cases and controls respectively (P<0.001).

On the other hand, the mean Serum Ferritin (SF) levels (37.5 & 47.9 ng/ml) and serum transferrin (sTfR) mean levels (23.1 & 26.9 nmol/L) were lower in cases compared to controls respectively, the difference was not statistically significant (P=0.362 & 0.173) respectively.

In addition, the mean levels of Zn were not significantly different between cases (77.3±11.4 µg/dL) and controls (78.8±9.5 µg/dL) (P=0.518). In contrast, the mean levels of Mg were lower in cases (2.0±0.2 mg/L) compared to controls (2.1±0.2 mg/L) and the difference was statistically significant (P=0.028). Moreover, the mean levels of hs-CRP were significantly lower in cases (3.0±2.7 mg/L) compared to controls (8.5±5.8 mg/L) (P<0.001).

Table 3: The mean of different biochemical parameters among the study population.

Biochemical parameters	Cases (40)	Controls (40)	P-value
	Mean ± SD (min-max)		
SI (µg/dL)	50.9 ± 23.0 (10-98)	24.3 ± 16.3 (7.2-98)	**< 0.001**
TIBC (µg/dL)	296.6 ± 64.6 (192-462)	372.1 ± 56.5 (197-470)	**< 0.001**
Tfsat (%)	19.8 ± 13.3 (2.2-51)	7.5 ± 8.0 (1.6-49.8)	**< 0.001**
SF (ng/ml)	37.5 ± 31.1 (7.3-158.5)	47.9 ± 64.3 (4.5-390)	0.362
sTfR (nmol/L)	23.1 ± 9.3 (11.6-51.6)	26.9 ± 14.7 (12.4-72.3)	0.173
Zn (µg/dL)	77.3 ± 11.4 (52.8-98.2)	78.8 ± 9.5 (58-96.3)	0.518
Mg (mg/dL)	2.0 ± 0.2 (1.6-2.4)	2.1 ± 0.2 (1.7-2.4)	**0.028**
hs-CRP (mg/L)	3.0 ± 2.7 (0.4-12.7)	8.5 ± 5.8 (0.7-20.8)	**< 0.001**

SD: Standard deviation; **SI:** Serum Iron; **TIBC:** Total Iron Binding Capacity; **Tfsat:** Transferrin Saturation; **SF:** Serum Ferritin; **sTfR:** Soluble Transferrin Receptors; **Zn:** Zinc; **Mg:** Magnesium; **hs-CRP:** High-sensitivity C-reactive Protein.

Complete blood count indices (Hemoglobin, MCV, and RDW) among the study population

The mean value of Hb (g/dl) and RDW (%) were lower in cases compared to controls (10.2±1.0 & 10.4±1.3) and (15.9±3.2 & 16.7±2.0) respectively (Table 4), and the differences were not statistically significant (P>0.05). While, the mean value of MCV was significantly higher in cases (72.8±6.5 fL) compared to controls (69.8±6.8 fL) (P=0.045).

Table 4: The mean of CBC indices among the study population.

Variables	Cases (40)	Controls (40)	P-value
	Mean ± SD (Min-Max)		
Hb (g/dl)	10.2 ± 1.0 (7.9-12.6)	10.4 ± 1.3 (8.4-13.5)	0.382
MCV (fL)	72.8 ± 6.5 (53.8-82.9)	69.8 ± 6.8 (57-82.1)	**0.045**
RDW (%)	15.9 ± 3.2 (1.9-23.2)	16.7 ± 2.0 (13.5-20.1)	0.164

SD: standard deviation; **Hb:** Hemoglobin; **MCV:** Mean Corpuscular Volume; **RDW:** Red Blood Cell Distribution Width.

Anemia, iron deficiency and iron deficiency anemia among the study population

According to WHO guidelines, Anemia was defined as Hb<11.0 g/dl, ID was defined as SF<12 and <30 µg/l in the presence of infection and inflammation (hs-CRP >5 mg/L) (11) and Tfsat <16% and IDA was defined as having both anemia and ID (12).

Table 5 shows that the percentage of cases with anemia was 85.0% compared to 80.0% for controls (P=0.556). In contrast, 32.5% of cases had an **ID** and 32.5% had **IDA** compared to 40.0% and 30.0% in controls respectively, and the difference was not statistically significant (P>0.05).

Table 5: Anemia, iron deficiency and iron deficiency anemia among the study population.

Category		Research Category		OR	95% CI	P-value
		Cases (40) n (%)	Controls (40) n (%)			
Anemia	Yes	34 (85.0)	32 (80.0)	1.42	0.4-4.5	0.556
	No	6 (15.0)	8 (20.0)			
ID	Yes	13 (32.5)	16 (40.0)	0.72	0.3-1.8	0.485
	No	27 (67.5)	24 (60.0)			
IDA	Yes	13 (32.5)	12 (30.0)	1.12	0.4-2.9	0.809
	No	27 (67.5)	28 (70.0)			

n: number of the subjects; **OR:** Odds Ratio; **CI:** Confidence Interval; **ID:** Iron Deficiency; **IDA:** Iron Deficiency Anemia.

Correlation between SI, sTfR, Zn, Mg and different characteristics and parameters among the study population

Table 6 presents the correlation between SI, sTfR, Zn, and Mg with the studied parameters. SI has a moderate negative correlation with hs-CRP ($r = -0.462$, $P<0.001$). On the other hand, sTfR has a moderate negative correlation which is statistically significant with age ($r = -0.403$, $P<0.001$), height ($r = -0.494$, $P<0.001$), and weight ($r = -0.413$, $P<0.001$), while a weak negative correlation with birth weight ($r = -0.226$, $P=0.044$). There is also a significant weak correlation between the Mg and Age ($r = -0.274$, $P=0.014$), height ($r = -0.267$, $P=0.017$), and weight ($r = -0.239$, $P=0.033$).

Table 6: Correlation between SI, sTfR, Zn, Mg and different characteristics and parameters among the study population.

Variables	SI (µg/dL)		sTfR (nmol/L)		Zn (µg/dL)		Mg (mg/dL)	
	r	P-value	r	P-value	r	P-value	r	P-value
Age (Months)	0.035	0.755	-0.403	< **0.001**	-0.153	0.176	-0.274	**0.014**
Number of households	0.015	0.895	0.025	0.829	-0.053	0.643	-0.096	0.396
Birth weight (kg)	-0.049	0.663	-0.226	**0.044**	0.105	0.353	-0.081	0.475
Heart Rate (bpm)	0.146	0.198	0.041	0.721	0.002	0.984	-0.017	0.884
Height (cm)	0.117	0.300	-0.494	< **0.001**	-0.15	0.186	-0.267	**0.017**
Weight (kg)	0.067	0.555	-0.413	< **0.001**	-0.096	0.398	-0.239	**0.033**
Temperature at admission (°C)	-0.099	0.384	0.03	0.794	0.069	0.543	-0.165	0.143
hs-CRP	-0.462	< **0.001**	-0.002	0.986	0.048	0.671	0.114	0.313

SI: Serum Iron; **sTfR:** Soluble Transferrin Receptors; **Zn:** Zinc; **Mg:** Magnesium; **hs-CRP:** High-sensitivity C-reactive Protein.

IV. Discussion

In febrile children, some may develop FSs and others may not. Various mechanisms like genetic factors, family history of FS, disturbance in the levels of serum minerals, and IDA were proposed (1).

The age of the children who participated in the present study was between (6-60 months) with a male to female ratio of 1.3:1. The mean age of occurrence of FS was 24.7±13.8 months which was comparable to the other studies who reported similar observation with mean age of 24 months (9, 13). The male predominance agrees with other studies which showed that males have consistently emerged with a higher frequency of FS (14-16).

Our findings showed that, SI was significantly higher ($P<0.001$) and TIBC was significantly lower ($P<0.001$) in cases compared to controls which disagree with the studies that related FSs with IDA. The results agree with those of Bidabadi & Mashouf (17). and disagree to the results of Nawar et al. and Modaresi et al. who indicated that the mean SI levels were lower significantly in the FS group than those in the control group (18, 19). However, the mean level of TIBC in Nawar et al., study was higher significantly in cases compared to controls (18).

The mean Tfsat percent in our study was higher in the seizure group compared to controls with statistically significant difference ($P<0.001$). The results coincide with Shaikh et al. study which showed that the mean value of Tfsat in children with FS was higher compared to the control group, but the difference was not statistically significant ($P>0.05$) (20). Our findings are inconsistent with the results of different studies who showed that the mean value of Tfsat in children with FS was lower compared to the control group, but the difference was statistically non-significant (21, 22).

According to our results, 85.0% of children in the case group and 80.0% in the control group were anemic, revealing no significant relationship ($P=0.556$). The results also show that 32.5% of cases had an ID and 32.5% had IDA while 40.0% had ID & 30.0% had IDA in controls with no statistically significant

difference between the results. The findings of the previous studies are controversial; some of them concluded that ID &/or IDA caused intensification of FS (23, 24)., others mentioned protective effects of ID &/or IDA against FS and the remaining confirmed our results (17, 25).

Possible factors that may cause contradictory of the results of various studies include different diagnostic criteria for the diagnosis ID &/or IDA, sample size, age of patients in each study, nutritional status, geographical area, retrospective nature of many studies and the background prevalence of ID &/or IDA. However, even with greater frequency of anemia in patients, a causal relationship cannot be assumed between ID and FS. More prospective studies with a larger sample size should be conducted. Furthermore, another possible explanation is that the rate of anemia is high (59.7%) in our population (26), the difference between the ratio of anemia in FS patients and controls is not high enough to show a significant difference.

In children with FS, the levels of CRP were lower significantly compared to children in the control ($P < 0.001$). This may depend on the infection which leads to a significant increase in children's body temperature, usually viruses. The half-life of CRP is about 19 hours, begins to rise after 12-24 hours of an inflammatory response, and peaks within 2-3 days. The presence of infection causes an increase in CRP values. Children with FS may be suspected of developing inflammatory processes and increasing body temperature to very high values fast enough that CRP levels do not reach their highest values. In febrile children without seizures, the inflammatory process grew slowly enough to achieve higher levels of CRP (27, 28).

Several studies evaluated CBC in febrile and FS children but they did not analyze the inflammatory mediators. However, a study reported that the mean CRP levels in FS children were lower significantly in comparison to children without seizures (15.73 versus 58.50 mg/L; $P < 0.001$) which is similar to our observation (28).

In our study, the mean level of serum Zn in the case group was lower compared to the control group but the differences were not statistically significant. Similar to our observations, different studies found that the difference in the concentration of serum Zn in children with FS and control groups were not statistically significant (14, 29, 30). On the other hand, different studies disagree with our results. They found that Zn levels are significantly lower in the case group compared to those in the control group (31, 32).

The relationship between low levels of Zn and convulsion is not understood whether it is a cause or a result. The lower levels of serum Zn in the FS group were elucidated by the fact that Zn levels decrease in cases of acute infection and stress, and that Zn is found in concentrated levels in recovering tissue (29).

On the other hand, we observed that mean serum levels of Mg were lower significantly in the FS group when compared with controls. Chhaparwal et al., (1971) found out that levels of serum Mg were low significantly among children with FS than that of normal children in the same region, boosting the hypothesis that Hypomagnesemia may be related to the occurrence of FS (33). In contrast to our results, it was reported that the level of serum Mg in children with FS is in the normal range. The results indicate that there was no role for serum Mg in the case of FS (34, 35).

Overall, two major reasons for diversity in the results: the difference in the target population of studies and sample sizes. Given present discrepancies among findings, it seems that there is a need for further researches with larger sample sizes or different methodologies to show the role of Mg in inducing convulsion in febrile children.

The mean levels of SI had a negative correlation which is statistically significant with hs-CRP. A Similar finding was observed in Richardson et al. study (36). Our results also showed that the mean levels of sTfR have a moderate negative correlation which is statistically significant with age, our results are in line with a physiological perspective of Kratovil et al., (2007) study who found that sTfR levels appear to be high during the toddler period, a period in which ID is common, is potentially novel finding because it suggests that there may be increased physiological need for iron during this time. Increased sTfR levels reflect increased RBC surface expression of transferrin receptor on RBCs which in turn reflects increased iron need (37).

Febrile seizures are one of the most common causes of pediatric emergencies in the world. It leads to hospital admission that actually costs families and the health sector. It tends to cause emotional, physical, and mental damage that is stressful to parents and has an impact on the quality of life of families. After a simple FS, a child's risk of developing epilepsy is 1.5 %. However, if the child was under 12 months of age when he had his first seizure, the risk rises to 2.5 %. Understanding the risk factors associated with FS could help parents take the necessary precautions during the seizure episode and help doctors to take appropriate treatment by formulating guidelines for the supplementation of minerals as part of the FS management for the prevention of recurrence and/or its associated complications. In this context, early detection with proper correction of IDA, hypomagnesemia, and hypozincemia will be effective in reducing rates of FSs among those children.

V. Conclusion

The predominant cause of febrile illness in the FS group was the upper respiratory tract infection which accounted for a significantly higher percentage when compared to the control group. The incidence of ID

& IDA was higher among the control group compared with the case group. There was no association between IDA and the presence of FS. The mean level of serum Zn and the percentage of Zn deficiency in the case group was lower than in the control group, but the differences were not statistically significant. On the other hand, the mean levels of serum Mg were low significantly in FS group when compared with control group. Despite, hypomagnesemia between cases and controls was statistically insignificant. Early detection and proper treatment can play a prominent role in limitation the prevalence of FS among children below 5 years. Attention, as well as rapid management for children, admitted with respiratory tract infection very necessary to prevent worse deterioration as it may happen when such cases confront delayed medical procedures.

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