Evaluation of serum iron level among epileptic children

Mohamed I. Omar[1]; Sherief M. AL-shazly[1]; Mohie El-Din T. Mohamed[1]; Ahmed E. El Gayar[2] and Ahmed M. Taha[1]

[1]Neurology Department, Faculty of Medicine, Al-Azhar University, Egypt
[2]Clinical Pathology Department, Faculty of Medicine, Al-Azhar University, Egypt
Ahmedtaha112016@yahoo.com

Abstract: Background: Iron in epileptic patients can show some abnormalities. Studies showed controversial results as regards serum iron. **Objective:** Evaluation of the serum iron level among epileptic children. **Patients and Methods:** Eighty children included in the study were classified into 2 equal groups, i.e. patient group and control group matched for age, sex and level of education. Each child was subjected to careful history taking, clinical examination, and investigations (routine laboratory investigations, serum iron levels, electroencephalogram and brain magnetic resonance imaging). **Results:** There was a statistically significant increase of positive family history in epileptic group. There were statistically significant decreases of RBCs, hemoglobin, and significant increase of WBCs in epileptic group. There was a statistically significant decrease of iron in epileptic children. There was a proportional correlation between serum iron from one side and each of hemoglobin, RBCs, HCT% and MCV. **Conclusion:** there was an association between decreased serum iron levels and epilepsy in children.
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1. Introduction

Epilepsy is a chronic condition characterized by recurrent clinical events of epileptic seizures which occur in the absence of a metabolic or toxic disease or fever **(Fisher et al., 2005).** Epilepsy is one of the most common serious neurological disorders prevalent in childhood and more than 50% of seizures have their onset in childhood **(Pandey et al., 2014).** Its prevalence worldwide ranges between 2 and 10 per 1000 with considerable variation between different countries **(Simms et al., 2008)**. In one of Upper Egypt governments, the prevalence was estimated to be 6.98/1000 **(El-Tallawy et al., 2010)**.

It has been suggested that serum trace elements concentrations in epileptic patients can show some abnormalities **(Hirate et al., 2004).** Balance in certain minerals is crucial for healthy nervous system and neuronal susceptibility to excitability. Several reports have suggested that disturbance of the level of some trace elements such as iron and chromium play an important role in the development of seizure condition **(Hamed et al., 2004).**

Iron deficiency and iron deficiency anemia may play an important role in inducing seizures from the following mechanisms: 1. Decrease of GABA inhibitory neurotransmitter due to change in its metabolism; 2. Change in neuron metabolism; 3. Reduction of enzymes such as monoamine and aldehyde oxidases; 4. Impairment in oxygenation and energy metabolism of the brain **(Fallah et al., 2014).**

Iron is involved in the metabolism of several neurotransmitters, and monoamine and aldehyde oxidases are reduced iron-deficiency anemia **(Daoud et al., 2002**). There are many studies that had described the role of iron deficiency in the induction of convulsion in epileptic patients **(Idro et al., 2010).**

The aim of this work was to evaluate the serum iron level among epileptic children to correct any disturbances in its level to avoid worsening of epilepsy.

2. Subjects and Methods

A case control study was conducted on children attending Al-Azhar university hospital (New Damietta) during the period from start of December 2015 to the end of June 2016.

Inclusion criteria:

Epileptic children below 18 year of both sexes were included in the study.

Exclusion criteria:

Subjects with one or more of the following were excluded from the study: 1) Patients with chronic medical illness of other systems or with history of surgery, 2) Patients on chronic medications besides anti-epileptic drugs which can affect the level of iron, e.g. penicillamine, deferasirox, desferoxamine, dimercaprol, 3) Patients taking supplementations containing iron in last 3 months e.g. multivitamin supplements, and 4) Patients who were critically ill.

Eighty children included in the study were classified into 2 equal groups: Patients group; epileptic children on antiepileptic drug therapy, and Control group; apparently healthy children, matched with study group for age, sex and level of education. After

full explanation of the study procedure, an informed consent from relatives of every child was taken before enrolling in the study. Each child enrolled in this study was subjected to the following: 1) Careful history taking with special entity on history of epilepsy and its drug treatment, 2) Thorough clinical examination (general and neurological examination), and 3) Investigations (routine laboratory investigations in the form of complete blood count, erythrocyte sedimentation rate, fasting blood sugar, postprandial blood sugar, serum aspartate aminotransferases, serum alanine aminotransferase, international normalized ratio, serum albumin, serum bilirubin, serum creatinine, serum iron levels, electroencephalogram and brain magnetic resonance imaging).

Statistical analysis of data:

The collected data were statistically analyzed using statistical package for social sciences (SPSS) version 16 (SPSS Inc, Chicago, USA). For qualitative data, frequency and percent distributions were calculated. For comparison between categorical groups, the Chi square (X^2) test was used. For quantitative data, mean and standard deviation (SD) were calculated and for comparison between two groups. The independent samples student's *t*- test was used for parametric values or Mann Whitney (u) test for non-parametric values. Pearson correlation co-efficient (r) was used for correlating different variables. For all statistical tests, p value ≤ 0.05 was considered significant**.**

3. Results

In the present study, we included 40 healthy children 26 (65.0%) of them were males and 14 (35%) of them were females, and 40 epileptic children, 23 (57.5%) of them were males and 17 (42.5%) were females. Age ranged from 5 to 13 years (the mean age was 8.77±1.40 and 8.60±1.75 years in control and epileptic groups respectively). The age of first seizure in epileptic group ranged from 4 to 8 years and the mean age was 5.77±1.09 years. In epileptic group 9(22.5%) out of 40 patients reported positive history of previous status epilepticus. 12(30.0%) out of 40 patients reported frequency of one or more per week; and 28 (70.0%) patients reported frequency of one or more per month. There was statistically significant decrease of positive family history in control when compared to epileptic group (7.5% vs 25.0% respectively) (table 1).

The most common precipitating factor of last seizure before inclusion in the study was fever (reported in 12 (30.0%) patients; then dehydration in 11 (27.5%) patients, followed by trauma in 9 (22.5%) patients and sleep deprivation in 5 (12.5%) patients. Finally, the least reported precipitating factor was stress in 3 (7.5%) patients.

Table (1): Characteristic of studied children

Variables \ Groups		Control	Epileptic	P value
Sex (n,%)	Male	26(65.0%)	23(57.5%)	0.49
	Female	14(35.0%)	17(42.5%)	
Age(mean±SD)		8.77±1.40	8.60±1.75	0.63
Age at diagnosis		-	5.77±1.09	-
PH of status epilepticus		-	9(22.5%)	-
Frequency of seizures	One or more/week		12(30.0%)	
	One or more/month		28(70.0%)	
Positive family history		3(7.5%)	10(25.0%)	0.034*
WBCs (x10^3/ml)		6.37±1.45	11.09±1.12	<0.001*
Hemoglobin (g/dl)		12.29±0.38	10.76±0.73	<0.001*
RBCs (x10^6/ml)		4.55±0.14	3.98±0.27	<0.001*
HCT%		45.49±1.42	39.81±2.73	<0.001*
MCV(fl)		80.22±3.68	78.80±3.56	0.0834
Serum iron (µg/ml)		79.75±14.52	51.87±14.07	<0.001*
Iron deficiency (< 60µg/ml (n,%)		8(20.0%)	33(82.5%)	<0.001*

WBCs ranged from (4.30 to 13.50) x10^3cells/dl, and there was a statistically significant decrease in control when compared to epileptic group (6.37±1.45 vs 11.09±1.12 respectively). On the other hand, hemoglobin ranged from 9.90 to 13.20g/dl; RBCs ranged from 3.67 to 4.89 million/ml; HCT ranged from 36.63 to 48.84% and MCV ranged from 73 to 87fl. There were statistically significant increases of hemoglobin, RBCs and HCT in control when compared to epileptic group. Serum iron ranged from 34 to 102 microgram/dl with statistically significant increase of iron in control when compared to epileptic group (79.75±14.52 vs 51.87±14.07 respectively). Iron deficiency was reported in 41(51.3%) out of 80

patients, with statistically significant decrease of iron-deficient subjects in control when compared to epileptic group (20.0% vs 82.5% respectively- Table 1).

EEG findings in epileptic group were normal in 12(30.0%) out of 40 patients, focal epilepsy in 12 (30.0%) patients, focal with generalization in 4 (10.0%) patients, multifocal in 2 (5.0%) patients and generalized in 10 (25.0%) patients.

There was a positive proportional correlation between serum iron from one side and each of hemoglobin, RBCs, HCT% and MCV. The correlation with hemoglobin, RBCs and HCT were powerful, and with MCV was moderate (Table 2).

Table (2): Correlation between serum iron and other variables in epileptic group

Serum iron / Parameters	r	p
Age (year)	0.210	0.193
Age at first seizures (year)	-0.028	0.862
WBCs ($x10^3$/ml)	0.154	0.343
Hemoglobin (g/dl)	0.74	0.001*
RBCs ($x10^6$/ml)	0.71	0.001*
HCT%	0.73	0.001*
MCV (fl)	0.427	0.006*

4. Discussion

Imbalance in trace elements may be involved in epileptogenesis **(Hamed et al., 2004).** The present study was designed to evaluate the serum iron level among epileptic children.

In the present study, we included 80 patients; 49 (61.3%) of them were males and 31(38.8%) were females. Males presented 57.5% and 65.0% of epileptic and control groups respectively. **Elshorbagy et al. (2016)** reported a comparable sex distribution where their study included 80 children with epilepsy. They consisted of 46 males (57.5%) and 34 females (42.5%).

In the present work, there was a statistically non-significant difference between epileptic and control groups as regards their ages. These results agreed with **Ohtsuka et al. (2002)** who found that there was no significant difference between epileptic and controls as regard to age.

As regards family history; it was positive in 16.3% of subjects with statistically significant increase of positive family history in epileptic when compared to control group. **Kheradmand et al. (2014)** reported that family history of epilepsy were seen in 31.4% of cases, and of febrile seizures were seen in 27.1% of the patients. These percentages were higher than that reported in the present study, and this may be attributed to the different sample size (they included 70 while we included only 40 epileptic children).

In epileptic group 22.5% of patients reported positive history of previous status epilepticus; and 77.5% of patients reported negative history of previous status epilepticus. **Raspall-Chaure et al. (2007)** reported that the percentage of patients with epilepsy who develop status epilepticus varied from 1.3-16%. The first seizure lasted longer than 30 minutes in 12.6% of cases.

The most common precipitating factor of last seizure before inclusion in the study was fever, then dehydration, followed by trauma and sleep deprivation. The least reported precipitating factor was stress. These results were comparable to previous work reported that fever can induce seizures either directly by high body temperatures (typically above 38^{o}C), by changes in body temperature or by the inflammatory mediators associated with infection **(Knudsen, 2000).**

Hyperthermia leads to an excitatory effect by decreasing the mechanisms involved in stopping action potential firing, mainly due to a reduction in Ca^{2+} influx and transient increase in excitatory synaptic transmission. It may also decrease inhibition in the immature hippocampus through a reduction of GABA release **(Liebregts et al., 2002).** Furthermore, infectious diseases may also act indirectly by releasing pyrogenic inflammatory mediators such as interleukin 1β, which has proconvulsant properties **(Vezzani et al., 2000 and Virta et al., 2002).**

In the present study, WBCs showed a statistically significant increase in epileptic group when compared to control group. On the other hand there were statistically significant decreases of hemoglobin, RBCs, HCT and MCV in epileptic when compared to control group. These results agreed with **Zareifar et al. (2012)** who reported that hemoglobin levels were significantly lower in epileptic children than in healthy children. On the other hand, and in contradiction to results of the resent work, **Tombini et al. (2013)** reported that there was a statistically non-significant difference between epileptic and control groups as regard to RBCs, hemoglobin and hematocrit percentage. This can be attributed to the fact that their

study included adult subjects, but we included children. Interestingly, **Derakhshanfar et al. (2012)** reported a higher hemoglobin levels in epileptic children than in healthy children. This contradiction can be attributed to different inclusion criteria and different ages in the study.

Serum iron showed statistically significant decrease of iron in epileptics when compared to control group. In addition, iron deficiency was reported in 51.3%. There was a statistically significant increase of iron-deficient subjects in epileptics when compared to control group. These results agreed with **Daoud et al. (2002)** who reported that iron deficiency can be associated with seizures. **Zhang et al. (2014)** observed decrease in iron levels in the basal ganglia subcortical nuclei, including the bilateral putamen, globus pallidus, substantia nigra and red nucleous in the patients. This revealed that these subcortical nuclei, which containing the highest levels of non-heme- iron in the brain, are sensitive to the disturbance of iron metabolism in epilepsy. Basal ganglia subcortical nuclei may contribute to the patho-physiological process of epilepsy through their role in unilateral dystonic posturing seizure and inhibition of seizure activity **(Thornton et al., 2011).**

Furthermore, in disorders associated with subcortical iron deficiency, such as restless legs syndrome and Attention-Deficit/Hyperactivity Disorder, decreased iron in the subcortical nuclei have been shown to relate to alterations in dopamine production **(Konofal et al., 2008).** Finally, **Torres-Vega et al. (2012)** stated that, because neuronal development is especially important during gestation and infanthood, the impact of iron deficiency on developmental processes is potentially severe, leading to functional, morpho-logical, neurochemical, and bioenergetics alterations. Taken as a whole, the negative impacts of iron deficiency on developmental processes can persist for the duration of an afflicted person's life, depending on the timing of onset and the duration and severity of the deficiency.

On the other hand, **Wojciak et al. (2013)** have not found significant differences between epileptic patients and control. However, the serum iron concentration in epileptic girls was significantly lower than in control girls.

The pattern of results suggests a clear pattern of association between iron deficiency and febrile seizures but not necessarily so with all acute seizures **(Idro et al., 2010).**

Many human studies have demonstrated the negative effects of ID on behaviors that include learning and memory, and affective and social behavior **(Lozoff and Georgieff, 2006).** In humans, early life ID (i.e. late gestation through 2–3 y of age) results in learning and memory deficits that persist beyond the period of ID despite prompt iron treatment (**Burden et al., 2007; Riggins et al., 2009 and Lukowski et al., 2010).** In addition, the developing hippocampus has been shown to be particularly vulnerable to the effects of early ID, a finding that is consistent with the acute and persistent effects of early ID on declarative learning and memory in humans and animal models **(Rao et al., 2003).** This increased vulnerability is due in large part to its rapid maturation rate in the late fetal-neonatal period with the dependence of these maturational processes on iron **(Fretham et al., 2011).**

In conclusion, results of the present study found an association between decreased serum iron levels and epilepsy in children. In addition, results revealed decreased values of IQ in epileptic children. So, iron deficiency can affect developing brain to some extent and effects will depend on the age at which iron deficiency was occurred and which part of the brain developed at this age.

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