EVALUATION OF SERUM IRON AND ZINC LEVELS IN CHILDREN WITH FEBRILE SEIZURES

By

Khaled Hassaan Awad*, Ismael Abd El-Razek K. M. El-Lebedy*, Ahmed Mahmoud, Nawal B. Aly*****

Pediatric*, clinical pathology**, and physiology*** departments, Faculty of Medicine, Al-Azhar University, Egypt

Corresponding address: Correspondence to Khaled Hassaan Awad, MD, Assiut, Postal Code 17515. Landine.

Tel: 0882102068, **E-mail:** khaledelenaizy@yahoo.com

ABSTRACT

Background: *febrile seizures (FS) are the commonest cause of convulsions in children during the first five years of life, many factors can exacerbate the occurrence of febrile seizures.*

Objectives: *This study was done to evaluate the serum zinc and iron levels in children with febrile seizures.*

Patients and methods: *this was a prospective case-control study that was including 120 children aged 6-60 months attend to Al-Azhar university hospital Asyut in the period from August 2020 to August 2021, with fever, sixty patient of them has fever with convulsions (case group) and the other sixty patient has fever without convulsions (control group). Both groups fulfill the inclusion and exclusion criteria of the study and subjected to complete history, physical examination, routine investigations and serum iron and zinc levels evaluation.*

Results: *our study reveals that serum iron and zinc levels are significantly deficient in case group than control group (40.89±21.0), (59.96±17.51) vs (71.60±39.58), (94.22±12.50) respectively with P value (0.000) for both. Also the hematologic indices and serum ferritin were significantly lower in case group than control group.*

Conclusions: *Serum iron and zinc levels are significantly lower in patients with febrile seizures than febrile patients without seizures.*

Keywords: *iron, zinc, children, febrile seizures.*

INTRODUCTION

Febrile seizures are seizures that are caused by a sudden spike in body temperature with fevers greater than 38C or 100.4F, with no other underlying seizure-provoking causes or diseases such as the central nervous system

(CNS) infections, electrolyte abnormalities, drug withdrawal, trauma, genetic predisposition or known epilepsy. Febrile seizures categorize as either simple febrile seizures or complex febrile seizures **(Xixis K L et al., 2021)**.

Iron plays an important role in the metabolism of several neurotransmitters. In the case of IDA, the levels of aldehyde oxidase, monoamine oxidase, and the expression of cytochrome C oxidase, a marker of neuronal metabolic activity, are decreased. In developing countries, iron deficiency is the most prevalent nutritional problem, **(Vaghela R & Mandot S, 2020) (Srinivasa S and Reddy SP, 2014)**, especially, among infants aged 6–24 months **(Habibian N et al., 2014)**. Iron deficiency can affect a developing brain by altering the development of hippocampus neurons, impairment of energy metabolism, and alterations in synaptic neurotransmitter systems including norepinephrine, dopamine, glutamate, gamma-aminobutyric acid, and serotonin **(Lozoff B, 2011)**. IDA is common during the 2nd and 3rd years of life and is associated with developmental and behavioral impairments; hence, it can influence motor and cognitive skills **(Jáuregui-Lobera I, 2014)**. As iron plays an important role in the function of various enzymes and neurotransmitters in the CNS, low serum levels of ferritin may lower the seizure threshold **(Vaghela R & Mandot S., 2020)**.

Trace elements have several influences in the CNS. They are involved in Ion channels, synaptogenesis, membrane lipid peroxidation, etc. Over the past years, it was considered that trace elements may play a role in the pathogenesis of febrile seizure. It has been suggested that zinc as an essential trace element plays a role in the pathogenesis of seizures **(Heydarian F et al., 2020)**. There are many studies comparing the serum level of zinc in febrile seizure. In some studies levels of zinc in febrile seizure have been reported to be lower when compared with febrile cases without seizures **(Hubaira et al., 2018)** but in some studies no significant difference was reported **(Maheshwari N et al., 2018)**.

Aim of the work

The aim of our study was to evaluate the serum zinc and iron levels in children with febrile seizures.

SUBJECTS AND METHODS

This was a case-control study, conducted on one hundred twenty children attending to pediatric department at Al-Azhar university

hospital Asyut in the period from August 2020 to August 2021. Sixty children aged 6 to 60 months with febrile convulsions were taken as case group. Cases with seizures due to CNS infection, epilepsy, electrolyte disturbances and metabolic disorders were excluded from the study. Sixty children of matched age and sex with fever but without convulsions were included as a control group.

Ethical considerations:

The present study was conducted in accordance with international ethical standards and applicable local registry rules. An approval of the study was gained from the academic and ethical committee of Al-Azhar Assiut Faculty of Medicine, Al-Azhar University. All participants' caregivers received a written consent form. The informed consent was clear and indicated the purpose of the study, and their freedom to participate or withdraw at any time without any obligation. Furthermore, participants' confidentiality and anonymity were assured by assigning each participant with a code number for the purpose of analysis only. The study was not based on any incentives or rewards for the participants. The study was conducted in accordance with Helsinki standards as revised in 2013.

The author declared that there is no funding and no conflict of interest regarding the study and publication.

Sample size calculation was carried out using G*Power 3 software **(Faul et al., 2007)**. A calculated minimum sample of 120 participants divided into equal groups (60 children with FS and sixty children with fever but without FS) was needed to detect an effect size of 0.3 in the rate of IDA among FS patients, with an error probability of 0.05 and 80% power.

Both groups underwent; full history taking, complete physical examination, and investigations (CBC by hematology cell counter Sysmex X N _ 330, serum ferritin by kinetic fluorescence using TOSOH AIA -360, and serum iron, total iron binding capacity and serum zinc by automated chemistry analyzer Beckman Coulter AU 480). Axillary temperature > 37.7 was recorded as fever **(Aziz K T et al., 2017)**. Iron deficiency anemia was diagnosed by decreased hemoglobin (<10.5g/dl), MCV (<71fl), RBC count (<3.8), hematocrit (<33), MCH (<23 pg), and MCHC (<31 g/d) and increased RDW (>15) **(Miniero R et al., 2019)**.

Statistical analysis:

Data was revised, coded, processed and analyzed using IBM-SPSS program (Statistical Package for Social Science) for windows version 20 (SPSS Inc., Chicago, IL, USA). Data were presented as number, percentage, mean, median, and SD using $\chi 2$ test for comparing qualitative variables. Independent samples t test was used to compare quantitative variables. P value was considered significant if P value less than or equal to 0.05 after consulting a statistician.

RESULTS

Table (1): Age, sex, and temperature of the study groups

		Case group (n: 60)	Control group (n: 60)	P value
Age (month)		26.18 ±11.9	26.9 ± 12.2	0.881
sex	Male	39 (65%)	42 (70%)	0.724
	Female	21 (35%)	18 (30%)	
Temperature (°C)		39.1 ± 0.4	38.8 ± 0.5	0.781

This table shows no statistical significant difference (p-value <0.05) between patients and control as regard demographic data.

Table (2): Hematologic values of the study groups

	Case group (n: 60)	Control group (n: 60)	P value
Hb level (gm/dl)	10.4 ± 1.1	11.8 ± 1.6	0.001
Hematocrit percent	32.17 ± 3.91	35.01 ± 3.83	0.001
RBCs count	3.89 ± 0.51	4.32 ± 0.72	0.04
MCV (fl)	71.2 ± 1.3	75.9 ± 2.4	0.03
MCH	23.94 ± 2.6	26.21 ± 3.51	0.01
MCHC	32.0 ± 0.93	33.1 ± 1.3	0.03
RDW	13.7 ± 0.6	13.93 ± 0.53	0.07

This table shows highly significant statistical difference (p-value <0.001) as regard to hemoglobin level and hematocrit value, and statistically significant difference (p-value <0.05) as regard to RBCs count, MCV, MCH and MCHC, with no statistically significant difference as regard to RDW, between patients and control.

Table (3): Serum iron status and zinc level in the study group

	Case group (n: 60)	Control group (n: 60)	P value
Serum iron (µg/dl)	40.89 ± 21.11	71.60 ± 39.58	0.0001
Serum ferritin (ng/ml)	39.18 ± 18.99	69.82 ± 32.13	0.001
TIBC	378.27 ± 46.17	325.21 ± 41.33	0.05
Serum zinc (µg/dl)	59.96 ± 17.51	94.22 ± 12.50	0.0001

This table shows highly significant statistical difference (p-value <0.001) as regard to Serum iron, Serum ferritin, and Serum zinc, and statistically significant difference (p-value <0.05) as regard to TIBC, between patients and control.

DISCUSSION

FS is a common neurological problem in children. Etiopathogenesis of FS is not known. Most factors that lead to FS include iron deficiency, family background, genetic factors, immunological disorder, and zinc deficiency **(Abdelrahman R A et al., 2020)**.

Iron has several biological impacts, and it is involved in important neurological processes, such as neurotransmitter metabolism, myelin formation, and brain energy metabolism. According to some experimental studies, in the case of iron deficiency, along with that of gamma aminobutyric acid, iron concentration decreases in some brain regions (hypothalamus, mesencephalon, thalamus, hippocampus, and corpus striatum) **(Kartal A T & Mutlu Z C, 2021)**.

Serum zinc has an important role in good functioning of the central nervous system. Zinc is mainly present in the hippocampus area. Zinc deficiency leads to FS. In patients with FS, the cause of low serum levels of zinc is unknown, although acute infection and fever play an important role. During fever or tissue injury, the release of interleukin and tumor necrosis factor may result in low level of serum zinc **(Abdelrahman, R A et al., 2020)**.

In the present study both the control and case groups were matched regarding to age, sex, and temperature that were important for decreasing the bias in results.

Our study revealed that the hemoglobin (Hb) level, hematocrit (HCT) percent, red blood cells (RBCs) count, mean cell volume (MCV), mean cell hemoglobin (MCH), and mean cell

hemoglobin concentration (MCHC), are significantly lower in case group than control group, that was in agreement with the study done by **Hameed et al., (2019)**, **Aziz et al., (2017)**, **Kartal, A T & Mutlu Z C (2021)**, **Mahmoud et al., (2021)**, **Khan Z et al., (2021)**, **Khan S A et al., (2021)**, and **Fallah et al., (2013)**.

In contrast to results of our study, **Shamallakh et al., (2021)**, showed no significant difference between patient and control groups regarding to Hb and MCV, also **Yarigarravesh et al., (2021)** found no significant difference between patient and control groups regarding to Hb and HCT. **Bidabadi E & Mashouf M (2009)**, revealed that there was no significant difference between patient and control groups regarding to Hb, HCT, MCV, MCH, and MCHC, but found that the hemoglobin level was significantly higher in case group than control group. Also **karimi et al., (2019)** found no significant difference between patients with febrile seizures and febrile patients without seizures regarding to Hb, HCT, RBCs, MCV, MCH and MCHC levels.

In the present study we found that serum iron and serum ferritin levels were significantly lower in case group than control group and the TIBC was significantly higher in case group than control group, that's mean that iron deficiency is one of the factors that exaggerate the occurrence of febrile seizures in a genetically susceptible children. These results were correlated with the results of with the results of **Hameed et al., (2019)**, **Kartal A T & Mutlu Z C (2021)**, **Khan Z et al., (2021)**, **Khan S A et al., (2021)**, **Jang et al., (2019)**, **Mahmoud et al., (2021)**, **Aziz et al., (2017)**, **Sharif et al., (2016)**, **Habibian et al., (2014)** and **Fallah et al., (2013)**, all of them conclude that iron deficiency is more prevalent in patients with febrile seizures than febrile patients without seizures. In contrast to our results **Bidabadi E & Mashouf M (2009)**, **Yarigarravesh et al., (2021)** and **Shamallakh et al., (2021)** whom conclude that there is no effect of iron deficiency anemia on the development of febrile convulsions.

The results of our study regarding serum zinc level showed that there is significantly low serum zinc level in patients with febrile seizures as compared to febrile patients without seizures. Zinc plays a vital role in the neuronal terminals of the hippocampus and amygdala by producing pyridoxal phosphate

and affecting glutamatergic, gamma-aminobutyric acidergic (GABAergic), and glycinergic synapses. Glutamic acid decarboxylase (GAD) acts as a ma¬jor inhibitory neurotransmitter in the synthesis of gamma-aminobutyric acid (GABA). A study by **Ganesh R and Janakiraman L (2008)** on 38 children with febrile convulsion and 38 children as a control group, aged between 3 months and 5 years, indicated that a serum zinc deficiency was significantly more prevalent in their case group than in the control group. Another study has reported that there is a correlation between disruption in Zn2+ homeostasis and fever seizure **(Nabavi F et al., 2021)**. The results of our study are congruent with the studies done by **Nabavi F et al., (2021)**, **Mahmoud et al., (2021)**, **Abdelrahman R A et al., (2020)**, **Debroy P & Baruah A (2021)**, **Heydarian et al., (2020)**, **Arul et al., (2020)**, **Hameed et al., (2020)** and **Sowjan et al., (2019)**, as all of them conclude that there was significant decrease in serum zinc level in children with febrile seizures than those without febrile seizures. On contrary to our results **Shamallakh et al., (2021)** and **Singh V & Yadav D (2018)** revealed that serum zinc level has no effect on the frequency of febrile seizures as compared to febrile patients without seizures.

CONCLUSION AND RECOMMENDATION

From the finding that was proved in our study we conclude that iron and zinc deficiencies have a role in the development of febrile seizures in genetically susceptible children, hence iron and zinc supplementation can decrease the frequency of febrile seizures. We also recommend further evaluation of the frequency of febrile seizures in iron and zinc deficient children as compared to children with febrile seizures but without iron and zinc deficiency.

REFERENCES

1. **Abdelrahman RA, Shokeir MA, Abd Elmagid DS. (2020):** Serum zinc level in children presenting with febrile seizures. Alexandria Journal of Pediatrics. 2020 Sep 1; 33(3):144.
2. **Arul J, Kommu PP, Kasinathan A, Ray L, Krishnan L. (2020):** Zinc Status and Febrile Seizures: Results from a Cross-sectional Study. Journal of Neurosciences in Rural Practice. 2020 Oct; 11(04):597-600.
3. **Aziz KT, Ahmed N, Nagi AG. (2017):** Iron deficiency anaemia as risk factor for simple febrile seizures: a case control study. Journal of Ayub Medical College Abbottabad. 2017 Apr 8; 29(2):316-9.
4. **Bidabadi E, Mashouf M. (2009):** Association between iron deficiency

anemia and first febrile convulsion: a case–control study. Seizure. 2009 Jun 1; 18(5):347-51.

5. **Debroy P, Baruah A.:** Serum Zinc and Magnesium Levels in Children with Febrile Seizure: A Hospital Based Cross-Sectional Study.
6. **Fallah R, Tirandazi B, Karbasi SA, Golestan M. (2013):** Iron deficiency and iron deficiency anemia in children with febrile seizure. Iranian journal of pediatric hematology and oncology. 2013; 3(1):200.
7. **Faul F, Erdfelder E, Lang AG, Buchner A. G* Power 3 (2007):** A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behavior research methods. 2007 May; 39(2):175-91.
8. **Ganesh R, Janakiraman L. (2008):** Serum zinc levels in children with simple febrile seizure. Clinical pediatrics. 2008 Mar; 47(2):164-6.
9. **Habibian N, Alipour A, Rezaianzadeh A. (2014):** Association between iron deficiency anemia and febrile convulsion in 3- to 60-month-old children: a systematic review and meta-analysis. Iranian journal of medical sciences. 2014 Nov; 39(6):496.
10. **Hameed ZA, El-Tellawy MM, Embaby M, Kamel YS. (2019):** Relation of iron and zinc deficiencies to the occurrence of febrile convulsions. Journal of pediatric neurosciences. 2019 Apr; 14(2):61.
11. **Heydarian F, Nakhaei AA, Majd HM, Bakhtiari E. (2020):** Zinc deficiency and febrile seizure: a systematic review and meta-analysis. Turkish Journal of Pediatrics. 2020 May 1; 62(3).
12. **Hubaira WZ, Qadri SM. (2018):** Relationship between serum zinc levels and simple febrile seizures: hospital based case control study. Int J Contemp Pediatr. 2018; 5:42.
13. **Jang HN, Yoon HS, Lee EH. (2019):** Prospective case control study of iron deficiency and the risk of febrile seizures in children in South Korea. BMC pediatrics. 2019 Dec; 19(1):1-8.
14. **Jáuregui-Lobera I. (2014):** Iron deficiency and cognitive functions. Neuropsychiatr Dis Treat, 2014, 10:2087-95.
15. **Karimi P, Sayehmiri K, Azami M, Tardeh Z. (2019):** The association between iron deficiency anemia and febrile seizure. International journal of adolescent medicine and health. 2019 Jul 13.
16. **Kartal AT, Mutlu ZC. (2021):** Relationship between serum iron level and febrile convulsion in children. INVESTIGACION CLINICA. 2021 Jan 1; 62(2):112-8.
17. **Khan SA, Khan J, Gul MS, Akbar K, Farid A, Adnan M. (2021):** Iron deficiency associated with febrile seizures. Rawal Medical Journal. 2021 Jul; 46(3):530-2.
18. **Khan Z, Naibzai ZK, Sethi MA, Ghaffar S, Makhdoom S, Khan A. (2021):** Iron Deficiency Association as A Possible Cause of First Febrile Seizure. Pakistan Journal of Medical and Health Sciences. 2021; 15(5):1728-30.
19. **Lozoff B. (2011):** Early iron deficiency has brain and behavior

effects consistent with dopaminergic dysfunction. The Journal of nutrition. 2011 Apr 1; 141(4):740S-6S.

20. **Maheshwari N, Shaikh M, Hingorjo B, Kazi Y, Rehman A. FEBRILE SEIZURES. (2018):** The Professional Medical Journal. 2018 Mar 10; 25(03):461-5.
21. **Mahmoud AT, Albassuoni MA, Abd El Nabi SA, El-Behairy MA. (2021):** Serum zinc and iron levels in children with febrile seizures. Menoufia Medical Journal. 2021 Apr 1; 34(2):611.
22. **Nabavi F, Akhondian J, Karkon Shayan S, Babaniamansour S. (2021):** The Prevalence of Zinc Deficiency in Children with Febrile Seizure. Reviews in Clinical Medicine. 2021; 8(1):1-5.
23. **Shamallakh O, Shamallakh K, Arafat H, Alzaharna M. (2021):** Relation of Iron Profile Parameters, Zinc and Magnesium with Febrile Seizures in Children from Gaza City. IOSR Journal of Pharmacy and Biological Sciences. 2021; 6(6 (2)).
24. **Sharif MR, Kheirkhah D, Madani M, Kashani HH. (2016):** The relationship between iron deficiency and febrile convulsion: a case-control study. Global journal of health science. 2016 Feb; 8(2):185.
25. **Singh V, Yadav D. (2018):** Serum zinc levels in children with simple febrile seizure. Indian Journal of Child Health. 2018 Sep 25; 5(9):584-7.
26. **Sowjan, M. A. (2019):** prospective study of serum zinc levels in children presenting with simple febrile seizures. Print ISSN: 2349-5499, Online ISSN: 2349-3267, 2019, March / Vol 6/ Issue 03.
27. **Srinivasa S, Reddy SP. (2014):** Iron defeiciency anemia in children with simple febrile seizures-A cohort study. Current Pediatric Research. 2014. 18:95-8.
28. **Vaghela R, Mandot S. (2020):** A case–control study to find the association between iron deficiency anemia and simple febrile seizures in children between 6 months and 5 years of age group. Indian Journal of Child Health. 2020; 7(2):57-9.
29. **Xixis KL, Samanta D, Keenaghan M. (2021):** Febrile Seizure. StatPearls [Internet]. 2021 Jul 6.
30. **Yarigarravesh MH, Izadbakhsh S, Amiri P, Goudarzian M, Akbariyan MJ, Hassanpour K. (2021):** The relationship between iron deficiency anemia and simple febrile convulsion in children aged 6 months to 5 years. European Journal of Molecular & Clinical Medicine. 2021 Mar 16; 8(3):1049-57.

تقييم مستوى الحديد والزنك في بلازما الأطفال الذين يعانون من التشنجات الحرارية

خلفية البحث:

تعد التشنجات الحرارية اشهر أسباب حدوث التشنجات في الأطفال تحت عمر خمس سنوات، وهناك العديد من العوامل التي ممكن ان تؤثر على حدوثها.

اهداف البحث:

يهدف هذا البحث الى تقييم مستوى الحديد والزنك في الأطفال اللذين يعانون من تشنجات حرارية.

المرضى والطرق:

دراسة مستقبلية تشتمل على 120 طفل تتراوح أعمارهم من 6-60 شهر حضروا الى مستشفى كلية الطب جامعة الازهر بأسيوط في الفترة من أغسطس 2020 حتى أغسطس 2021م، جميعهم يعاون من ارتفاع في درجة حرارة الجسم. ستون طفل منهم يعانون من تشنجات حرارية وقد تم تصنيفهم على انهم المجموعة المريضة وستون اخرون يعانون فقط من ارتفاع درجة حرارة الجسم بدون تشنجات حرارية وقد تم تصنيفهم على انهم المجموعة المتحكمة. كلا من المجموعتين يتوفر بهم جميع خصائص الشمول والاستبعاد.

وقد تعرض كلا من المجموعتين لاخذ تاريخ مرضي كامل وفحص جسدي وعمل الفحوصات الروتينية وقياس مستوى الحديد والزنك في الدم.

النتائج:

أوضحت النتائج ان مستوى الحديد والزنك في الدم اقل في المجموعة المريضة عن المجموعة المتحكمة مع وجود دلالة إحصائية واضحة، كما أوضحت النتائج أيضا ان مؤشرات الدم ومستوى مخزون الحديد اقل في المجموعة المريضة عن المجموعة المتحكمة مع وجود دلالة إحصائية واضحة.

الاستنتاج:

يستنتج من الدراسة ان الأطفال المصابون بالتشنجات الحرارية يعانون أيضا من نقص الحديد والزنك في الدم.

التوصيات:

نوصي باعطاء الأطفال اللذين يعانون من حدوث تشنجات حرارية جرعات محددة من الحديد والزنك للتقليل من معدل حدوث التشنجات الحرارية. كما توصي الدراسة أيضا بعمل المزيد من الأبحاث في هذا الشأن.