The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 2288-2292

Association between Serum Zinc level and Febrile Seizures

Abdullatif Mohammed Amneenah [1] and Hamad Ali Hamad Alqatani*

[1] Associate Professor of Pediatrics, Derna University, Consultant Pediatrician,

*Head of Pediatrics Department- Al Wahda Hospital (Derna), Libya

Corresponding author: Abdullatif Mohammed Amneenah, E mail: aemnaina@gmail.com, Mobile phone: 0021891385153

ABSTRACT

Background: The febrile seizure is the commonest form of seizure in children. Several hypotheses propose that neurotransmitters and trace elements have a role in the beginning of a febrile seizure. Inhibitory pathways in the central nervous system (CNS) can be affected by zinc, an essential component of many enzymes.

Aim and objectives: This study aimed to determine the relation between serum zinc level and febrile seizures.

Subjects and methods: This prospective case control study was carried in Al -Wahda hospital- pediatrics department in Derna city in the north-eastern part of Libya in the period between March 2019 to March 2020. This study comprised 120 children aged between 2 months and 6 years. They were divided to 3 groups: 40 children with febrile seizures, 40 children with fever and no seizures, and 40 healthy children.

Results: Zinc levels varied significantly amongst the three groups investigated. The differences between the groups with and without febrile seizures, as well as between febrile seizure groups and the controls, are also notable. The seizure-free group and the controls, on the other hand, showed no considerable differences.

Conclusion: According to the current findings, serum levels of zinc were lower in children with febrile seizures. Seizures in febrile children may be facilitated by zinc deficiency.

Keywords: Seizures, Febrile, Zinc, Central nervous system, Children.

INTRODUCTION

Febrile convulsions afflict 2-5% of children aged 6 months to 60 months [(1)], as well as 2 months to 6 years old, according to the International League against Epilepsy (ILAE). There must be no central nervous system infection or metabolic condition in order for febrile seizures to occur, according to the American Academy of Pediatrics (AAP) [(1)].

A fair prognosis exists for febrile seizures [(2)]. Fever-induced seizures have yet to be explained. Some elements are hypothesized to have a considerable role in febrile seizures because of their coenzyme activity and influence on ion channels and receptors.

Deficiencies of iron, zinc and magnesium may lead to fetal convulsions [(1)]. Zinc involvement in the nervous system has been studied. The studies indicated that zinc deficiency may have a function in pathophysiology of febrile seizures.

This work aimed to determine the relationship between serum level of zinc and febrile seizures.

SUBJECTS AND METHODS

This study was performed in Al -Wahda hospital-pediatrics department in Derna city in the north-eastern part of Libya in the period between March 2019 to March 2020

It's a prospective case-control study that was performed on 120 children aged between 2 months and 6 years. They were divided into 3 groups 40 children for each: Children with febrile seizures (40), children with fever and no seizures (40) , and (40) healthy children.

Inclusion criteria: Age from 2 months up to 6 years, simple febrile seizure and normal development.

Exclusion criteria: Age less than 2 months and more than 6 years, complex febrile seizure, CNS infection, history of recent zinc intake, developmental delay, history of chronic diseases or malnutrition, electrolytes imbalance and acute and chronic diarrhea.

Ethical approval:

The study was approved by the Ethics Board of University of Derna and an informed written consent was taken from every participant in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical Analysis

SPSS 22.0 for Windows was used to assemble and analyse the data (SPSS Inc., Chicago, IL, USA). Data were subjected to the Shapiro Walk test in order to see if they were distributed normally. Qualitative data was represented using frequencies and percentages. The qualitative variables were compared using Fisher exact and chi square tests, as described. The variation between quantitative variables in two groups was calculated using the t-test. In order to compare more than two dependent groups of normally distributed variables, the one-way ANOVA test available with the LSD test was employed. If p-value was 0.05, there is considerable variation for all of our comparisons. To be regarded nonsignificant, p-Values over 0.05 were used to show that the variation was not statistically significant, whereas values below 0.001 indicated a highly considerable difference.

RESULTS

In terms of age or gender, there was no discernible variation among the three groups investigated **(Table 1)**.

Received: 8/11/2022
Accepted: 6/1/2022

Table (1): Demographic data of the three studied groups

		Febrile seizures (N=40)	**No seizures** (N=40)	**Controls** (N=40)	**F/χ^2**	**P**
Age (months) Mean ± SD		28.05 ± 14.68	29.4 ± 17.38	36.38 ± 22.01	2.39	.096
Sex	Male	26 (65%)	16 (40%)	18 (45%)	5.6	.061
	Female	14 (35%)	24 (60%)	22 (55%)		

There was a highly considerable variation between the three studied groups as regards Zinc. Moreover, there was a considerable variation between febrile seizures group and no seizures group and between febrile seizures group and controls. However, there was no considerable variation between no seizures group and controls **(Table 2).**

Table (2): Zinc levels between the three studied groups

	Febrile seizures (N=40)	**No seizures** (N=40)	**Controls** (N=40)	**F**	**P**	**LSD**
Zinc (mcg/dl) Mean ± SD	64.73 ± 15.02	80.8 ± 16.74	85.18 ± 21.57	**14.3**	**.001**	**1*2 p=.000** **1*3 p=.000** 2*3 p=.279

The most prevalent diagnosis was Non-localized fever (viral) in both groups followed by acute respiratory infection **(Table 3)**.

Table (3): Diagnosis distribution among cases groups

	Febrile seizures (N=40)		**No seizures** (N=40)	
	N	%	N	%
Non localized fever (viral)	22	55	18	46
Acute respiratory infection	8	20	17	42
Acute suppurative otitis media	5	12.5	3	7.5
UTI	3	7.5	2	5
Bronchiolitis	2	5	1	2.5

There was a considerable positive correlation between zinc and platelets, while there is a considerable negative relation between zinc with WBCs and CRP **(Table 4)**.

Table (4): Correlation between zinc with other parameters in patients with febrile seizures

Febrile seizures	**Zinc**	
	R	P
Age	.173	.284
Number of seizures attack	-.129	.427
Hb	.104	.474
Platelet	**.316***	**.020**
WBCs	**-.591****	**.001**
CRP	**-.482**	**.005**

Table (5): Correlation between zinc with other parameters in patients with fever without seizures

No seizures	**Zinc**	
	R	P
Age	.034	.833
Hb	-.088	.956
Platelet	.081	.575
WBCs	**-.389***	**.028**
CRP	**-.402***	**.009**

DISCUSSION

Febrile seizures (FS) are convulsions or seizures occurring in children of six months to six years [3]. The most prevalent cause of a child's seizures to be reported to a health practitioner is febrile convulsions (FC) [4].

In terms of age or gender, there was no discernible variation among the three groups investigated. Similarly, among 60 included children in **Bakhtiari *et al.*** [5] where Males comprised 53.3% of the patients in the FS group, with an average age of 25.21±15.91 months. Sixty-three percent of children aged six to twenty-four months were in the FS group. Thirty-three% of the febrile patients were male, with an average age of 26.47±17.61 months. Fifty% of children aged six to twenty-four months are in the febrile category. A p-value of 0.77 and 0.19 respectively indicated no considerable variation in age or gender between the groups. Furthermore, **Bakri *et al.*** [6] study where there were 50 newborns with febrile seizures (27 males, 23 females) involved in the research, which was compared to 50 feverish infants matched in age and gender without seizures (35 males and 15 females). There were no variations in age or gender between the two groups. Similar results were in **Jang *et al.*** [7] study, **Mahmoud *et al.*** [8] study and **Sharif *et al.*** [9] study. In **Kannachamkandy *et al.*** [10] study, children with febrile seizures included 35 of the study's subjects, whereas controls included 35 youngsters free of febrile seizures. There were a greater number of individuals in the age range of 1–2 years (42.9 percent). Males were 65.7 percent of cases and 54.3 percent of controls. In **Khajeh *et al.*** [11] study, 43 males (47.2%) and 47 females (52.8%) were investigated, with an average age of 2.43 ± 1.23 years. Age and gender differences among the three groups were insignificant.

In a case-control study, 60 instances of FS and 60 cases of fever without seizures were documented and compared. Only 36.7% of patients with febrile seizures had a positive family history of the disorder, which was statistically considerable (p=0.003). In contrast, there was no statistically considerable variation found when epilepsy was included in the family (p=0.43) [12]. **Fallah *et al.*** [13] reported that lower levels of haemoglobin, iron, and ferritin were reported in children with FCs in a case–control research that included 50 cases and 50 controls aged 6–60 months. This is in accordance with our results that iron-deficiency anaemia is more prevalent in children with FCs. These results are matched with **Tahir Aziz *et al.*** [14] and **Goyal *et al.*** [15] study results.

In **Kim *et al.*** [16] study, the CRP was considerably elevated in the control group than in the FS group (0.55 ± 0.7 vs. 3.6 ± 2.6) (p < 0.001). Similarly, **Liu *et al.*** [17] study showed that the CRP was considerably elevated in the control group than in the FS group (14.0 ± 23 vs. 9.4 ± 12) (p = 0.007). In other study, binary logistic regression analysis based on the determined risk factors identified negative qualitative CRP and low WBC count as considerable predictors for non-classical FS (OR=1.388, 95% CI 1.051-1.834 and OR=9.021, 95% CI 1.298-62.702, respectively) [18]. On the contrary, **Kamalammal,** [19] observed that only serum iron levels differed significantly between cases and controls and no changes were identified in the levels of haemoglobin (HB), MCH, MCHC, or ferritin. However, **Jang *et al.*** [7] study revealed that the variation was not considerable between the febrile seizure group and the control group regarding hemoglobin levels and white blood cells however, the variation was considerable between the two groups regarding platelets. In **Tahir Aziz *et al.*** [14] study, there was no considerable variation between the febrile fits group and case group regarding the TLC. **Chen *et al.*** [20] investigated 3 groups: febrile seizures (FS), without febrile seizures (FC group), and those in good health (HC group). Age, sex ratios, WBC count, neutrophil ratio, CRP, and serum glucose levels were all determined to be equivalent across the FS, FC, and HC groups (p > 0.05). A substantial variation between the FS and FC/HC groups was detected in hemoglobin, platelet count, and serum sodium levels. (p < 0.05).

In the current study, there was a highly considerable variation between the three studied groups as regards zinc. Moreover, there was a considerable variation between febrile seizures group and no seizures group also, between febrile seizures group and controls. However, there was no considerable variation between no seizures group and controls. Our study is in agreement with **Mahmoud *et al.*** [8] where there was statistically considerable differences in zinc and iron levels between group I (FS children, n = 20), group II (children with afebrile seizures, n = 20), group III (children with febrile illness, n = 20), and group IV (healthy children, n = 20). Study participants in group I were found to have lower mean serum zinc levels than those in the other three groups (68.25 ± 11.2, 96.1 ± 6.05., 99.3 ± 6.38, and 97.2 ± 6.58, respectively). For the sake of comparison, the mean serum iron levels of group I were found to be substantially lower than those of the other three groups (0.43 ± 0.20; 0.88 ± 0.12, 0.86 ± 0.13, 0.83 ± 0.15). Similarly, there were considerably lower levels of serum zinc among febrile seizures cases (6.85–8.7) compared to febrile illness without seizures (14.93–19.6) (p < 0.001) in **Bakri *et al.*** [6] study. Additionally, a meta-analysis by **Heydarian *et al.*** [21] showed that zinc deficiency was found to be a substantial risk factor for seizures in febrile children. Zinc levels were lower in 68% of children with febrile convulsions, compared to a control group comprising 36%, which was significant. Furthermore, the mean zinc concentration in patients was substantially lower than in the control group [22]. In **Hosseini *et al.*** [23], blood zinc levels averaged 70.41 ± 20.46 mcg/dL in the case group and 92.73 ± 17.62

mcg/dL in the control group. Febrile children without FS by ANOVA test showed a considerable variation in zinc levels between the three groups of participants (P = 0.01) [11]. Similar results are in **Gattoo *et al.*** [24] study. In addition, **Kafadar *et al.*** [25] concluded that those with febrile convulsions had a mean serum zinc content of 110.49 ± 35.03 µg/dL, compared to 107.12 ± 21.66 µg/dL and 116.12 ± 32.07 µg/dL for children with fever and healthy children, respectively. According to zinc levels, there was no statistically considerable variation among the three groups. Similar results are in **Amouian *et al.*** [26] study.

In the present study, the most prevalent diagnosis was non localized fever (viral) in both groups followed by acute respiratory infection. These findings are analogous to those obtained by **Gattoo *et al.*** [24] study, which reported that non localized fever (viral) predominated as the cause of fever in both groups (simple febrile seizure group and children with acute febrile illness without seizure group), followed by acute respiratory infections and acute suppurative otitis media. In contrary to this result, **Bakhtiari *et al.*** [5] study results showed that respiratory tract infection (RTI) and gastroenteritis were the most prevalent causes of fever in the FS group. Moreover, in **Kannachamkandy *et al.*** [10], Fifty-one% of the patients with febrile seizures were found to have an upper respiratory tract infection as an accompanying disease. In **Yahyaoui *et al.*** [12] study, viral infection (50.8%), followed by ear, nose, and throat (32.5%), urinary tract (9.2%), and respiratory infection (7.5%) were the most prevalent causes of fever in both groups. Neither group had a considerable variation in fever aetiology (p = 0.40).

Regarding correlation between zinc with other parameters in patients with febrile seizures in this study, there was a considerable positive correlation between zinc and platelets, while there was a considerable negative correlation between zinc with WBCs and CRP. However, there was no considerable correlation between zinc and age, Hb and number of seizures attack. In **Sakr *et al.*** [27] study, there was a positive (proportional) strong relation between zinc and each of hemoglobin and K. No considerable correlation was found between serum zinc and heart rate, respiratory rate, body temperature, seizure duration, random blood glucose, serum Na, ionized Ca, or other hematological values. There was no strong correlation between zinc value and each of consanguinity, preliminary diagnosis, and family history. Serum zinc levels were lower in children who had a febrile seizure, according to the current findings. In children with fever, zinc deficiency may increase the risk of seizures.

In future investigations, blood zinc levels should be evaluated during acute phase and then again during recovery phase in order to investigate variations in serum zinc levels. The effectiveness of zinc supplementation in FS prevention requires more fundamental study as well.

CONCLUSION

In children who had a febrile seizure, serum zinc level was shown to be decreased. Zinc deficiency has been incorporated to an elevated risk of seizures in children with fever. Children's febrile seizures may be linked to high zinc content in their blood, according to one study.

Declarations:

Consent for Publication: I confirm that all authors accept the manuscript for submission.

Availability of data and material: Available

Competing interests: none.

Funding: No fund

Conflicts of Interest: The authors declare no conflicts of interest regarding the publication of this paper.

REFERENCES

1. **American Academy of Pediatrics (2008):** American Academy of' Pediatrics: Steering Committee on Quality Improvement and Management, Subcommittee on Febrile Seizures. Febrile Seizures: clinical practice guideline for the long-term management of the child with simple febrile seizures. Pediatrics, 121:1281-6.
2. **Khair A, Elmagrabi D (2015**): Febrile seizures and febrile seizure syndromes: an updated overview of old and current knowledge. *Turkish Journal of Pediatrics*, *62*(3):.358-347
3. **Laino D, Mencaroni E, Esposito S (2018):** Management of pediatric febrile seizures. https://doi.org/10.3390/ijerph15102232
4. **Kavanagh F, Heaton P, Cannon A *et al.* (2018):** Recognition and management of febrile convulsions in children. British Journal of Nursing, 27 (20): 1156–1162.
5. **Bakhtiari E, Heydarian F, Khalesi M *et al.* (2021):** A Comparison Between Serum Selenium Level in Febrile Children with or Without Seizure. Biological Trace Element Research. https://doi.org/10.1007/s12011-021-02936-3
6. **Bakri A, Hassan M, Ahmed A *et al*. (2021):** Biochemical Assessments of Neurotrophin-3 and Zinc Involvement in the Pathophysiology of Pediatric Febrile Seizures: Biochemical Markers in Febrile Seizures. https://doi.org/10.1007/s12011-021-02886-w
7. **Jang H, Yoon H, Lee E (2019):** Prospective case control study of iron deficiency and the risk of febrile seizures in children in South Korea. https://doi.org/10.1186/s12887-019-1675-4
8. **Mahmoud A, Albassuoni M, Abd El Nabi S *et al.* (2021):** Serum zinc and iron levels in children with febrile seizures. Menoufia Medical Journal, 34 (2): 611.
9. **Sharif M, Kheirkhah D, Madani M *et al*. (2015):** The Relationship Between Iron Deficiency and Febrile Convulsion: A Case-Control Study. Global Journal of Health Science, 8(2): 185–189.
10. **Kannachamkandy L, Kamath S, Mithra P *et al.* (2020):** Association between serum micronutrient levels and febrile seizures among febrile children in Southern India: A case control study. Clinical Epidemiology and Global Health, 8 (4): 1366–1370.

11. **Khajeh A, MIRI G, Fayyazi A *et al.* (2016):** Serum zinc level in children with febrile convulsion. https://www.sid.ir/en/journal/ViewPaper.aspx?id=505410
12. **Yahyaoui S, Lammouchi M, Yahyaoui O *et al.* (2019):** Risk Factors for Febrile Seizures in Tunisian Children: A Case-Control Study. https://doi.org/10.35248/2472-4971.19.4.176
13. **Fallah R, Sabbaghzadegan S, Karbasi S *et al*. (2015):** Efficacy of zinc sulfate supplement on febrile seizure recurrence prevention in children with normal serum zinc level: A randomised clinical trial. Nutrition, 31 (11–12): 1358–1361.
14. **Tahir Aziz K, Ahmed N, Nagi A *et al*. (2017):** iron deficiency anaemia as risk factor for simple febrile seizures: a case control study. http://www.jamc.ayubmed.edu.pk316
15. **Goyal R, Gupta A, Pandita N *et al*. (2020):** Study the iron status in children with febrile seizures: a hospital based cross sectional study. International Journal of Contemporary Pediatrics, 7 (9): 1844.
16. **Kim K, Kwak B, Kwon A *et al*. (2017):** Analysis of plasma multiplex cytokines and increased level of IL-10 and IL-1Ra cytokines in febrile seizures. https://doi.org/10.1186/s12974-017-0974-7
17. **Liu Z, Li X, Zhang M *et al*. (2018):** The role of Mean Platelet Volume/ platelet count Ratio and Neutrophil to Lymphocyte Ratio on the risk of Febrile Seizure OPEN. https://doi.org/10.1038/s41598-018-33373-3
18. **Cokyaman T (2019):** Febril nöbetler: Ateş sonrası nöbet zamansal sıralamasının bir önemi var mıdır? https://doi.org/10.22391/fppc.491220
19. **Kamalammal R (2016):** Association between iron deficiency anemia and various red cell parameters with febrile convulsions in children of age group 3 to 60 months. https://doi.org/10.18203/2349-3291.ijcp20161038
20. **Chen J, Jin M, Tang L *et al*. (2020):** Acute Phase Serum Leptin, Adiponectin, Interleukin-6, and Visfatin Are Altered in Chinese Children With Febrile Seizures: A Cross-Sectional Study. https://doi.org/10.3389/fendo.2020.00531
21. **Heydarian F, Nakhaei A, Majd M *et al.* (2020**): Zinc deficiency and febrile seizure: a systematic review and meta-analysis. *https://doi.org/10.24953/turkjped.*
22. **Abdel Hameed Z, El-Tellawy M, Embaby M *et al*. (2019):** Relation of iron and zinc deficiencies to the occurrence of febrile convulsions. Journal of Pediatric Neurosciences, 14 (2): 61–64.
23. **Hosseini F, Nikkhah A, Goli M (2020):** Serum zinc level in children with febrile seizure. Iranian journal of child neurology, 14 (1): 43.
24. **Gattoo I, Harish R, Hussain Q (2015):** Correlation of Serum Zinc Level with Simple Febrile Seizures: A Hospital based Prospective Case Control Study. http://ijp.mums.ac.ir
25. **Kafadar I, Akinci A, Pekün F *et al*. (2012):** Febril konvulsiyon etyolojisinde serum çinko düzeyinin rolü. Cocuk Enfeksiyon Dergisi, 6 (3): 90–93.
26. **Amouian S, Mohammadian S, Behnampour N *et al*. (2013):** Trace elements in febrile seizure compared to febrile children admitted to an academic hospital in Iran, 2011. Journal of Clinical and Diagnostic Research, 7 (10): 2231–2233.
27. **Sakr M, Abdel-Aal M, Emran T *et al*. (2019):** Serum zinc status in febrile seizures. https://doi.org/10.4103/AZMJ.AZMJ_82_18