

Serum zinc and copper levels in children with febrile convulsion**Mohammad Shokrzadeh¹, Ali Abbaskhaniyan², Mohammadreza Rafati^{3*}, Mahdi Mashhadiakabr⁴, Ali Arab²**¹Pharmaceutical Sciences Research Center, Department of Toxicology and Pharmacology, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran²Department of Pediatrics, Faculty of Medicine, Mazandaran University of Medical Science, Sari, Iran³Pharmaceutical Sciences Research Center, Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Science, Sari, Iran⁴Mazandaran University of Medical Science, Sari, Iran*Received: Jul 30, 2016, Revised: Aug 22, 2016, Accepted: Sep 10, 2016***Abstract**

Febrile convulsions (FC) are the most common neurologic disorder in children 6-60 months of age. Zinc (Zn) and copper (Cu) play role as cofactors in more than 300 enzymatic activities significantly. The aim of this study was to evaluate the relationship serum levels of Zn and Cu with seizure occurrence in febrile children. In this case-control study, 270 children with 6 month to 6 years were evaluated. The patients were enrolled in three groups: a) children with febrile convulsion, b) febrile children without convulsion and c) healthy ones. After recording of all patients' characteristics, 5 mL blood was taken from peripheral vessels at the first 12 hours of hospitalization. Absorption of all samples was read by BRAIC (Rayleigh instrument) company, WFX-130 model with calibration diagram, considering samples dilution levels. The mean of serum Zn levels in children with FC were significantly lower than other two groups. Mean serum Cu levels in children with FC and non-FC patients were significantly higher than healthy children. No meaningful differences were observed in serum levels of Zn and Cu among the girl or boy cases. This study showed significant lower serum zinc level in children with febrile seizure and meaningful higher serum copper level than control group cases. There was no significant difference in level of serum zinc and copper in term of sex.

Keywords: Children, seizure, fever, zinc, copper

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Introduction

Febrile seizures or febrile convulsions (FC) are the most common neurologic disorder of infants and children 6 through 60 months of age. They are age-dependent phenomenon, occurring in 2 to 5 percent of children younger than six years of age and are usually associated with fever (a temperature greater than 38 °C) but without evidence of intracranial infection or defined cause (1). If convulsion lasts more than 5 minutes, complications such as mental disability, hemiplegia and death will threaten children. Despite the fact that the exact mechanisms of fever and seizure genesis are not known yet, many etiologic factors contribute in creating it and the occurrence of fever alone does not result in convulsion in this group. In other hands, fever in these children is necessary but not enough. It has been proved that genetics plays a meaningful role in seizure type as a triggering factor (2).

Besides genetic factor, family background, immunologic disorders, iron deficiency, neural intermediaries' changes and trace elements effective on these intermediaries have been recognized to involve in this disease except of metal elements (3-5). Zinc (Zn) and copper (Cu) (human body basic cations) play role as cofactors in more than 300 enzymatic activities significantly (6). Zn ion is a necessary element with high importance for brain natural development (7) especially gamma-aminobutyric acid (GABA) pathway that reduction of its activity can create convulsion (8). Hypozincemia activates the NMDA receptor, one of the glutamate families of receptors, which may play an important role in the induction of epileptic electrical discharges (8).

Fever is a clinical signal that is characterized by rising body temperature more than normal level.

Hypothalamus controls the central body temperature in normal conditions, and set within the normal range (36.5-37.5 °C). An exogenous pyrogen (external fever-inducing substance such as gram-negative bacteria lipopolysaccharide) or endogenous ones (such as interleukin-1) caused fever by acting directly on the hypothalamic thermoregulatory center and then rise body temperature by releasing epinephrine, vessels contraction (particularly peripheral vessels), finally reach a new regulation point and fever occurs (9,10).

Considering of febrile seizures' incidence and probably their complications, high hospitalization costs, and ability to fear parents, identification of causes for their prevention are very essential. This study was evaluated the relationship serum levels of Zn and Cu with seizure occurrence and fever intensity in febrile children.

Materials and methods

In this case-control study, serum Zn and Cu levels of 270 children with febrile seizure, referring to a teaching hospital (Bu-Ali Sina, Sari, Iran), during 2 years evaluated. The study was approved by the Ethical and Research Committee of Mazandaran University of Medical Sciences (No: 88-142). Patients were 6 month to 6 years age bracket (samples number has been calculated based on previous studies sample volume & sample volume formula) (3-5). After explaining to parents and getting their consent, cases entered to study and examined by a pediatric neurology specialist to place in one of 3 groups: a) children with febrile convulsion, b) febrile children without convulsion and c) healthy ones (without fever and convulsion).

The exclusion criteria for patients in this study were including age younger than 6 months and older than 6 years, mental or cerebral retardation or signs of genetic syndrome, complex convulsion (atypical), chronic disease (heart, liver, kidney), malnutrition and situations that lead to decrease study metals levels in serum including hemolysis, dehydration, vomiting, dysentery and pneumonia.

After physical exams and measuring the body temperature to confirm the fever of case and controls, 5 mL blood was taken from peripheral vessels at the first 12 hours of hospitalization. All patients' characteristics were recorded and under sterile conditions, samples transferred

to hospital laboratory for centrifuge and isolation of serum from globule and then serum was kept at -20 °C. At the end of sampling, all samples were defreeze and diluted using 10% triton in 0.1 normal nitric acid solutions (Merck, Germany) to 1:10 level. Four standard concentrations were made for Zn and Cu.

Standard powders of Zn and Cu prepared from Merck (Germany) and atomic absorption level of standard solutions was measured by using atomic absorption method and then concentration-absorption calibration diagram was drawn. Absorption of all samples was read by the same instrument with calibration diagram, considering samples dilution levels with atomic absorption spectrophotometer made by Beijing Rayleigh Analytical Instrument Corporation (BRAIC) company, WFX-130 model (China).

Statistical analysis

Data were analyzed by SPSS16 software (Chicago, USA), independent samples t-test and ANOVA were used to compare serum levels between study groups and Pvalue ≤ 0.05 was considered statistically significant.

Results

Patients demographic characteristics presented in Table 1. It was insignificantly differences between three groups in age, weight and gender.

No meaningful differences were observed in serum levels of Zn and Cu among the girl or boy cases (Table 2 and 3). The mean of serum Zn levels in children with FC (0.43 ± 0.38 mg/l) were significantly lower than other two groups (Table 4). Also, serum Zn levels in convulsion free febrile children (0.66 ± 0.37 mg/l) had meaningful difference with healthy group patients (0.97 ± 0.15 mg/l).

Serum Cu concentrations in three study groups were reported in table 5. Mean serum Cu levels in children with FC and non-FC patients (1.16 ± 0.38 and 1.53 ± 0.76 mg/l, respectively) were significantly higher than healthy children 0.53 ± 0.24 mg/l (p value < 0.05).

Discussion

The results of the present study demonstrated children with fever convulsion had significantly lower serum Zn levels than two other groups (febrile children without

Table 1 Demographic characteristics of the study patients

| | | FC group | Non-FC group | Healthy group |
|--------------------|--------------|------------------|---------------------|----------------------|
| | | Mean ± SD | Mean ± SD | Mean ± SD |
| Gender | Girls | 61 | 43 | 52 |
| | Boys | 31 | 50 | 41 |
| Age (month) | | 26.15 ± 16.60 | 29.22 ± 20.25 | 26.57 ± 14.03 |
| Weight (kg) | | 11.98 ± 3.20 | 12.52 ± 3.78 | 13.64 ± 2.31 |

FC: febrile convulsion

Table 2 Relation of serum Zn concentration by gender

| Zn level (mg/L) | | | |
|------------------------|------------------|---------------------|----------------------|
| | FC group | Non-FC group | Healthy group |
| | Mean ± SD | Mean ± SD | Mean ± SD |
| Boys | 0.58 ± 0.27 | 0.614 ± 0.29 | 0.75 ± 0.32 |
| Girls | 0.51 ± 0.29 | 0.7 ± 0.33 | 0.76 ± 0.46 |
| p value | 0.78 | 0.37 | 0.94 |

Table 3 Relation of serum Cu concentration by gender

| Cu level (mg/L) | | | |
|------------------------|------------------|---------------------|----------------------|
| | FC group | Non-FC group | Healthy group |
| | Mean ± SD | Mean ± SD | Mean ± SD |
| Boys | 1.18 ± 0.37 | 1.24 ± 0.62 | 0.76 ± 0.36 |
| Girls | 1.11 ± 0.26 | 1.56 ± 0.4 | 0.48 ± 0.16 |
| p value | 0.58 | 0.06 | 0.16 |

Table 4 Comparing of serum Zn concentration in 3 study groups

| | FC group | Non-FC group | Healthy group |
|------------------------|------------------------|---------------------|----------------------|
| | Mean ± SD | Mean ± SD | Mean ± SD |
| Zn level (mg/l) | 0.43 ± 0.38 | 0.66 ± 0.37 | 0.97 ± 0.15 |
| p value | 0.008 (1 and 2 groups) | | |
| | 0.002 (2 and 3 groups) | | |
| | 0.001 (1 and 3 groups) | | |

Table 5 Comparing of serum Cu concentration in 3 study groups

| | FC group | Non-FC group | Healthy group |
|------------------------|------------------------|---------------------|----------------------|
| | Mean ± SD | Mean ± SD | Mean ± SD |
| Cu level (mg/l) | 1.16 ± 0.38 | 1.53 ± 0.76 | 0.53 ± 0.24 |
| p value | 0.005 (1 and 2 groups) | | |
| | 0.001 (2 and 3 groups) | | |
| | 0.001 (1 and 3 groups) | | |

convulsion and healthy children, without fever and convulsion). There was a statistically significant difference in mean serum zinc level in between febrile children without convulsion and healthy group patients. Mean serum Cu levels in children with FC and non-FC patients were significantly higher than healthy children. There were no statistically meaningful differences in the mean serum Zn and Cu levels in boys and girls.

Yılmaz and Balcı (11); Talebian *et al.* (12) Ganesh *et al.* (13), Amiri *et al.* (14) reported no significant difference in serum Z level in relation to sex, this is in agreement with result of our study.

Gheini *et al.* (15) Vidyasagar *et al.* (16) and Burhangnoglou *et al.*; (17) found the lower mean serum Zn level in children with febrile seizure than the other children without fever. Also, Mahyar *et al.* (18), Saghazadeh (19) and Amiri *et al.* (14) reported the lower

serum Zn level in children with febrile seizure compared to control group. There was a correlation between serum Zn level and febrile seizure in Margaretha *et al.*; study (20). They reported that lower serum Zn level related to longer the duration of seizure. Results of our study was similar to Modarresi *et al.* (21) and Ehsanipour *et al.* (22) studies who found that serum Zn level was lower in children with febrile seizure than the other two control groups (febrile with non-convulsion and healthy children).

Children with febrile seizure in our study had meaningful higher serum Cu level than control group cases. This is in agreement with Prasad *et al.* (23) that found serum Cu levels in children with seizures were significantly increased and opposed to Amiri *et al.* (14) Yılmaz and Balcı; (11) who reported no significant change in serum Cu level in cases of febrile convulsion or Gheini *et al.*

(15) who found mean serum Cu level in the control group was significantly lower than that of the case group.

Conclusion

We observed significant lower serum Zn level in children with febrile seizure and meaningful higher serum Cu level than control group cases. There was no significant difference in level of serum Zn and Cu in term of sex.

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Conflict of interest

The authors declare that they have no competing interests.

References

1. American Academy of Pediatrics. Clinical Practice Guideline Febrile Seizures: Guideline for the Neurodiagnostic Evaluation of the Child with a Simple Febrile Seizure. *Pediatrics* 2011; 127: 389-94.
2. Menkes J, Sarnat H. Paroxysmal disorders. In: Menkes J, Sankar R. *Child Neurology*. 6th edition. Philadelphia, USA: Lippincott Williams & Wilkins, A wolters Kluwer Company 2000; 987-90.
3. Tütüncüoğlu S, Kütükçüler N, Kepe L, Coker C, Berdeli A, Tekgül H. Proinflammatory cytokines, prostaglandins and zinc in febrile convulsions. *Pediatr Int* 2001; 43:235-39.
4. Pisacane A, Sansone R, Impagliazzo N, Coppola A, Rolando P, D'Apuzzo A, Tregrossi, C. Iron deficiency anaemia and febrile convulsions: case-control study in children under 2 years. *BMJ* 1996; 313, 343.
5. Prakash O, Deepak M, Ram SU. Cerebrospinal fluid zinc, magnesium, copper and gamma-amino butyric acid levels in febrile seizures. *J Pediatr Neurol* 2007; 5: 39-44.
6. Anonymus, Minerals and trace elements. Available at: <http://mefanet-motol.cuni.cz/articles.php?aid=motol.cuni.cz/articles.php?aid=610>. 14 Sep, 2009.
7. Tuula E. The adverse effects of Zinc deficiency. *J Orthomolecular Med* 1995; 10:146-64.
8. Izumi Y, Ishii K, Akiba K, Hayashi T. Hypozincemia during fever may trigger febrile convulsion. *Med Hypotheses* 1990; 32:77-80.
9. Dinarello CA. Infection, fever, and exogenous and endogenous pyrogens: some concepts have changed. *J Endotoxin Res* 2004; 10:201-22.
10. Gatti S, Vezzani A, Bartfai T. Mechanisms of fever and febrile seizures: putative role of the interleukin-1 system. Academic Press 2002; 169-88.
11. Yilmaz D, Balci O. Serum selenium and copper levels in children with simple febrile seizure and viral infections. *Pediatr Practice Res* 2014; 2:41-5.
12. Talebian A, Vakili Z, Talar SA, Kazerni M, Mousavi GA. Assessment of the relation between serum zinc and magnesium levels in children with febrile convulsion. *Iran J Pathol* 2009; 4:157-60.
13. Ganesh R, Janakiraman L. Serum Zinc levels in children with simple febrile seizure. *Clin Pediatr (Phila)* 2008; 47:164-6.
14. Amiri M, Farzin L, Moassesi ME, Sajadi F. Serum Trace Element Levels in Febrile Convulsion. *Biol Tr Elems* 2010; 135: 38-44.
15. Gheini S, Kiani A, Sedighei M, Hojabri K. Assessment of serum zinc, selenium and copper in simple febrile convulsions in children aged 6 to 60 months in Mohammad Kermanshahi Hospital in 2012. *J Kermanshah Univ Med Sci* 2015;19:16-23 (Persian).
16. Vidyasagar V, Venugopal BL, Darshan MS. Comparison of serum zinc level in patients with simple febrile seizure versus acute febrile illness. *Sch J App Med Sci* 2015; 3:2210-19.

17. Burhanoglu M, Tutuncuglu S, Coker C, Tekgül H, Ozgür T. Hypozincaemia in febrile convulsion. *Eur J Pediatr* 1996; 155:498-501.
18. Mahyar A, Pahlavan A, Varasteh-Nijad A. Serum zinc level in children with febrile seizure. *Acta Medica Iranica* 2008; 46:477-80.
19. Saghazadeh A, Mahmoudi M, Meysamie A, Gharedaghi M, Zamponi GW, Rezaei N. Possible role of trace elements in epilepsy and febrile seizures: a meta-analysis. *Nutr Rev* 2015;73:760-79.
20. Gattoo I, Harish R, Quyoom Hussain S. correlation of serum zinc level with simple febrile seizures: A Hospital based Prospective Case Control Study. *Int J Pediatr* 2015;3:509-15.
21. Rabbani MW, Ali I, Latif HZ, Basit A, Rabbani MA. Serum zinc level in children presenting with febrile seizures. *Pak J Med Sci* 2013; 29:1008-11.
22. Ehsanipour F, Talebi-Taher M, Harandi NV, Kani K. Serum zinc level with febrile convulsion and its comparison with that of control group. *Iran J Pediatr* 2009; 19: 65-8.
23. Prasad R, Singh A, Das B, Upadhyay R, Singh T, Mishra O. Cerebrospinal fluid and serum zinc, copper, magnesium and calcium levels in children with Idiopathic seizure. *J Clin Diagn Res* 2009; 3:1841-6.