

SERUM ZINC AND MAGNESIUM LEVELS IN CHILDREN WITH FEBRILE CONVULSION

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ABSTRACT

Background: Febrile seizures are defined as seizures accompanied with fever that occur in neurologically healthy infants and children (6 through 60 months of age) with no intracranial infection, metabolic disturbance, or a history of afebrile seizures. Trace elements may have a role in febrile seizures by modulation of neurotransmission. We aimed to determine whether there was any change in serum zinc and magnesium level in children with febrile convulsion during the attack.

Method: This prospective case control study was performed on 100 children recruited from Pediatric Departments at Al-Hussein and Sayed Galal University hospitals during the period from June 2013 to June 2015. A total number of 50 children, age of 6 months to 5 years, who had febrile convulsion were served as the cases whereas another 50 children within the same age range with febrile illness who had fever without convulsion participated as the control group.

A thorough history was taken and complete examination was done for them together with estimation of serum zinc and magnesium levels.

Results: The male to female ratio was 1.27: 1 in the study group and the majority was in the age group between 13 – 24 months. The mean serum zinc level in children with febrile convulsion was found to be lower than that of febrile children without convulsion with statistically significant difference ($P < 0.001$). The serum Mg level didn't show significant difference between case and control groups ($P = 0.079$).

Conclusions: This study showed positive correlation between low serum zinc and febrile convulsions however, no significant difference in magnesium levels between case and control groups. It can emphasize the hypothesis that zinc deficiency could be a potential risk factor in febrile convulsions.

Keywords: Zink, Magnesium, Febrile, Convulsion.

INTRODUCTION

Febrile seizures are defined by the American Academy of Pediatrics as seizures accompanied with fever ($>38^{\circ}$) that occur in neurologically healthy infants and children (6 through 60 months of age) with no intracranial infection, metabolic disturbance, or a history of afebrile seizures. (Hodgson et al 2008). Febrile seizures are a common disorder in children with a prevalence of 3 to 4 %. (Michael, 2004) Febrile convulsions are generally benign; however, recurrence occurs in some patients and there a slight risk of developing epilepsy later in life. (Chungath & Shorvon, 2008) The definite cause of febrile convulsion is unknown; however, its occurrence is influenced by genetic and environmental factors. (Arzimanoglous et al, 2004).

Role of trace elements have been studied in association with febrile seizures as it may play a role in modulation of neurotransmission by acting on ion channels and their coenzyme activity. (Amiri et al, 2010) Recent evidences indicate that the deficiency of zinc and magnesium can play a significant role in febrile seizures. (Namakin et al, 2016) Zinc regulates the activity of glutamic acid decarboxylase which plays a role in production of

the inhibitory neurotransmitter γ -aminobutyric acid. In the other hand, magnesium plays a role in cell membrane stability and nerve conduction. (Hamed and Abdellah, 2004) Therefore, the deficiency of these elements may affect the incidence of febrile convulsion. (Papierkowski et al, 1999) (Ganesh, & Janakiraman 2008).

AIM OF THE STUDY

The study intended to compare the serum zinc and magnesium levels in children with febrile seizures and acute febrile illness without seizure to determine whether there was any change in serum zinc and magnesium level in children with febrile convulsion during the attack.

PATIENTS AND METHODS

Study procedure:

Sample size equation:

It was calculated using the G*power software (version 3.1.9.2) computer program. To reduce a type II error and increase the statistical power, and based on an independent samples t-test to compare the two studied groups, a minimum sample size of 50 children in each group was calculated considering a significance level of 0.05, an effect size of 0.45, a power $(1 - \beta)$

of 0.85, and α was set a priori at 0.05.

This prospective case control study was performed on 100 children recruited from Pediatric Departments at Al-Hussein and Sayed Galal University hospitals during the period from June 2013 to June 2015. A total number of 50 children, age of 6 months to 5 years, who had febrile convulsion were served as the cases whereas another 50 children within the same age range with febrile illness (such as upper or lower respiratory tract infections, gastroenteritis, or urinary tract infection) who had fever without convulsion participated as the control group.

Inclusion criteria:

All children fulfilling the criteria for febrile seizures. (Natsume et al, 2017) (Subcommittee on Febrile Seizures AAP 2011):

- A convulsion associated with an elevated temperature greater than 38°C.
- A child older than 6 months and younger than 5 years of age.
- Absence of central nervous system infection or inflammation.
- Absence of acute systemic metabolic abnormality that may produce convulsions.

- No history of previous afebrile seizures.

Exclusion criteria:

- Children with cerebral palsy or mental retardation.
- Atypical febrile convulsion.
- Chronic diseases and malnutrition (with weight for age less than 80% of the WHO classification).
- Children on zinc supplementation, or with diarrheal disease.
- Documented intracranial infection.
- Patients with developmental and growth disturbances.

Procedures:

The variable recorded for the study included age, gender, weight, height, the serum level of zinc and magnesium. All patients were subjected to:

1. A detailed history was obtained including age, gender, duration and type of seizures, developmental history and family history of epilepsy or febrile seizures. The temperature was recorded with mercury thermometer placed in axilla for 3 minutes.
2. Complete physical examination including the weight, height and head

circumference to emphasis that there is no evidence of malnutrition.

3. Laboratory investigation to measure zinc and magnesium level in the blood. Under complete aseptic precautions, a venous blood sample of 2 ml was collected from every child within 24 hours of convulsion and centrifuged. The sera were separated and stored at -18°C for measuring zinc and magnesium. The level of zinc and magnesium was measured by using Biosystem BTS 310 analyzer. The cut off value for hypozincemia was taken as 50 $\mu\text{g}/\text{dl}$ and the cut off value for hypomagnesemia was taken as 1.8 mg/dl . (Wilmshurst et al, 2015).

Ethical consideration:

1. Ethical clearance was obtained from the local ethical committee at Al-Azhar University Hospitals (Al-Hussein and Sayed Galal hospitals).
2. Sampling was performed after obtaining a signed written informed consent from parents.
3. Privacy and confidentiality were maintained throughout the study process using a unique code number.

4. The patient has the right to withdraw from the study at any time.
5. The author declared there is no conflict of interest regarding the study or publication.
6. No financial support regarding the study or publication.

Statistical Analysis:

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges when their distribution found parametric. The comparison between two groups with qualitative data were done by using Fisher's Exact test. The comparison between two independent groups with quantitative data and parametric distribution was done by using independent samples t-test while Kruskal-Wallis test was used for non-parametric distribution within the case group. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant at the p-value < 0.05 .

RESULTS

Our study will be demonstrated in the following tables and figures:

Table (1): Age and gender distribution of the studied groups

Variables		Case (n=50)		Control (n=50)		P-value
		N	%	N	%	
Age group (months)	Mean±SD	19.68 ± 10.11		21.06 ± 11.56		0.527 ¹
	Min – Max	6 – 56		6 – 58		
	6-12	10	20%	11	22%	
	13-24	29	58%	25	50%	
	25-36	8	16%	8	16%	
	37-48	2	4%	4	8%	
	49-60	1	2%	2	4%	
Gender	Male	28	56%	25	50%	0.689 ²
	Female	22	44%	25	50%	
	Male:female ratio	1.27:1		1:1		

¹: Independent Samples t-test.

²: Fisher's Exact test.

This table shows the distribution of age and sex in both studied groups. No statistically significant

differences were found in the age, gender distribution and nutritional status between the case and control groups.

Table (2): Anthropometric measures of studied groups

Anthropometric measures	Case (n=50)	Control (n=50)	P- value ¹
	Mean±SD	Mean±SD	
Weight for age percentile	46.16 ± 19.51	44.00 ± 16.80	0.554
Length for age percentile	27.17 ± 19.79	32.40 ± 9.95	0.098

¹: Independent Samples t-test.

This table shows the anthropometric measures in both studied groups. No statistically significant differences were

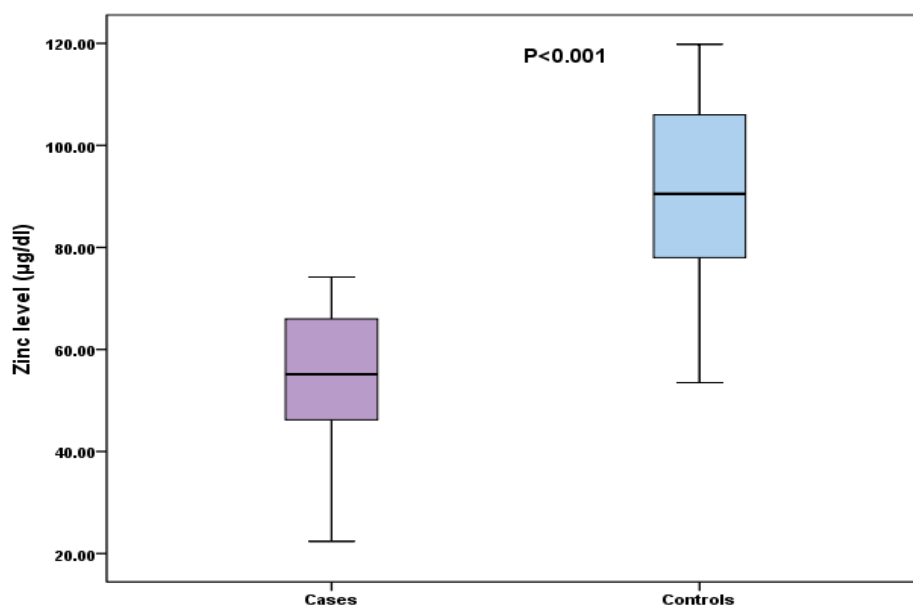
found in the weight and height distribution and nutritional status between the case and control groups.

Table (3): Comparison between both groups regarding zinc and magnesium levels

Variables	Case (n=50)	Control (n=50)	P- value ¹
	Mean±SD	Mean±SD	
Zinc level (µg/dl)	54.40 ± 23.95	90.40 ± 14.84	< 0.001*
Min – Max	22.4 – 74.2	53.5 – 119.8	
Magnesium level (mg/dl)	2.08 ± 0.21	2.16 ± 0.24	0.079
Min – Max	1.6 – 2.2	1.8 – 2.4	

¹: Independent Samples t-test.

*: Significant.

**Figure (1): Serum zinc levels between both groups**

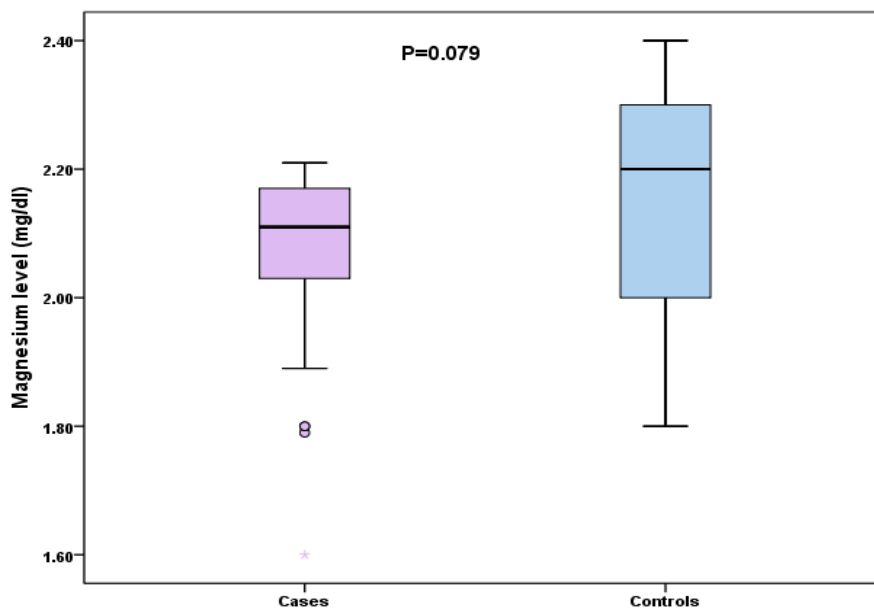


Figure (2): Serum magnesium levels between both groups

Table 3, Figures 1 & 2 shows the mean serum zinc level in children with febrile convulsion was found to be lower than that of febrile children without convulsion with

statistically significant difference. The serum Mg level didn't show significant difference between case and control groups.

Table (4): Gender distribution of serum zinc and magnesium levels among cases

Variables	Male (n=28)	Female (n=22)	P- value ¹
	Mean±SD	Mean±SD	
Zinc level (µg/dl)	58.65 ± 8.44	51.12 ± 15.31	0.080
Magnesium level (mg/dl)	2.07 ± 0.17	2.10 ± 0.16	0.248

¹: Kruskal-Wallis test.

This table demonstrates the mean serum Zn and Mg levels and did not show significant

differences between boys and girls.

DISCUSSION

Febrile convulsion is a common neurological problem in children. The exact pathogenesis is unknown, but however its occurrence is influenced by genetic and environmental factors. (4) Different hypothesis were suggested to explain the relation between changes in trace elements and neurotransmitters in biological fluids with febrile seizures. **(Mishra et al, 2007).**

Several trace elements play important roles in redox reactions, stabilization of cell membranes and neurotransmitter receptor interaction. **(Akbar et al 2012)** Zinc is a component of many enzymes involved in many proteins, lipids and carbohydrates metabolism. **(Namakin et al 2016)** It is a co-factor of glutamic acid decarboxylase which a rate limiting enzyme in the synthesis of the inhibitory neurotransmitter gamma aminobutyric acid (GABA). Magnesium counteracts the stimulatory effects of Calcium on synaptic transmission by exerting a voltage dependent blockage of N-methyl-D-aspartate (NMDA) receptor channel. **(Salehiomran & Mahzari, 2013).**

In the present study, we investigated the serum zinc and magnesium in children with febrile convulsion in comparison

with the febrile children without convulsion. Similar to most of the previous studies in this issue we have compared the mean serum zinc and magnesium levels between cases and controls.

We found that the males predominated, with a male to female ratio of 1.27:1. This was similar to the ratio reported by other studies which ranged from (1.4 - 1.7):1. **(Salehiomran & Mahzari, 2013).**

No statistically significant difference was found in the age, gender distribution and nutritional status between the case and control groups. Namakin et al and Mahyar et al also reported the similar findings. **(Namakin et al 2016), (Mahyar et al 2008).**

The mean zinc level in children with febrile convulsion was found to be significantly lower than the mean zinc level of febrile children without convulsion. Similar findings have been reported by other studies. **(Aly et al, 2014) (Srinivasa & Manjunath, 2014) (Joshi & Shetty, 2014).**

Serum Mg level in our study didn't show significant difference between case and control groups, which is similar to studies done by **Donaldson et al and Khosroshahi et al. (Donaldson et al, 2008) (Khosroshahi et al 2015),** but it was inconsistent with

works by **Talebian et al and Derakhshan et al** which found difference between them. (**Talebian et al., 2009**) (**Derakhshan et al., 2010**).

The serum Zn levels are different for male and female children at different ages. (**Nasehi et al., 2015**) Our results showed no significant gender difference among the cases regarding serum Zn levels. Similarly, **Ehsanipour et al.** found Zn serum levels in girls was insignificantly lower than for boys (84.12 Vs 87.56 mg/l). (**Ehsanipour et al, 2009**).

It is important to interpret our results in the context of potential study limitations, as we couldn't assess the CSF zinc level. Zinc is essential for body enzymes that modulates CNS activities. CSF hypozincemia activates Nmethyl-D-aspartate receptors or disinhibits GABAergic action, thus resulting in febrile convulsion. (**Mollah et al, 2011**) However, findings by **Garty et al.** do not support the hypothesis that febrile convulsions are related to reduced CSF zinc concentration. (**Garty et al 1995**).

CONCLUSIONS

Serum zinc was significantly lower in children with febrile convulsion in comparison with control group. As regard the magnesium level we found no

difference but as there are discrepancies among different studies, it seems reasonable to further investigate these issues with larger sample sizes or different methodologies to show how zinc level plays role in the pathophysiology of febrile seizure and whether zinc supplementation could be effective in preventing febrile seizures and the role of Mg in inducing convulsion in febrile children.

RECOMMENDATION

According to our study, we recommend measuring serum zinc in children with febrile convulsion to ensure absence of any deficiency and supplement zinc for those with zinc deficiency to prevent recurrence of febrile seizure.

LIMITATIONS

The study was done on a small group of children and in one center and need to be verified by more studies in different centers and larger number of patients.

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