

# Serum Zinc and Copper in Children with Febrile Seizures in Basrah, Iraq

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## Abstract:

**Background:** Trace elements are essential micronutrients that exist in very low concentrations in the body. They play an important role in various physiological processes and are crucial for proper functioning of the immune system. Many studies have shown that some micronutrients may have a role in febrile seizure such as selenium, zinc and copper.

**Aim:** To determine the level of serum zinc and copper in children with febrile seizures and explore their relation to selected patients' variables.

**Methods:** The study included 66 infants and children with simple febrile seizures with two control groups; a febrile control group which includes (62) children with febrile illnesses who were admitted to emergency department at Basrah Maternity and Children Hospital and Basrah General Hospital from the 1<sup>st</sup> of March to the end of October 2013, and a healthy control group which includes (58) children. Serum zinc and copper were measured for all infants and children enrolled in the study.

**Results:** Patients with febrile seizure had a significantly lower mean serum zinc level ( $8.85 \pm 3.26$ ) in comparison to febrile patients and healthy children ( $14.98 \pm 2.20$ ), ( $13.33 \pm 1.99$ ) respectively. There is no significant association between the level of serum zinc and selected variables. Serum copper level did not show a significant difference between patients with febrile seizures and control groups.

**Conclusion:** Zinc supplementation may be considered in children who are at risk of recurrent febrile seizure.

**Keywords:** Zinc, copper, febrile convulsions.

## Introduction

Febrile seizure (FS) is the most common form of seizures in children. (1) The pathophysiology of febrile seizures is still not fully understood. Several theories regarding possible metabolic changes during the rising phase of body temperature have been proposed, such as electrolyte disturbances, relative vitamin B6 deficiency, and low gamma aminobutyric acid (GABA), but these factors do not explain the seizure in the majority of cases. (2) Many studies have shown that some micronutrients may have a role in febrile seizure such as selenium, zinc and copper. (3,4) Copper (Cu) is an essential element in the synthesis and functioning of the nervous system and its deficiency may lead to several complications such as mental disorders, peripheral neuropathies and myelo- neuropathy. Severe copper deficiency may lead to seizure attack based on the important role of copper in cell physiology, such as free radical scavenging, membrane stability and prevention of paroxysmal discharge. (5) Zinc is an important micronutrient that plays important roles in growth and development, immune system response, neurological function, nerve impulse transmission, and hormone release. (6)

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Zinc can be released by electrical stimulation and may serve to modulate responses at receptors for a number of different neurotransmitters. These include both excitatory and inhibiting receptors particularly N-methyl-D-aspartate (NMDA) and Gamma aminobutyric acid (GABA) receptors. The levels of GABA depend on the level of zinc, as well as zinc is involved in the maintenance of pyridoxal phosphate concentrations by the activation of pyridoxal kinase, the lack of this enzyme results in reduced brain GABA levels. (7)

## Methods:

A case-control study has been carried out to determine level of serum zinc and copper in children with febrile seizures. Sixty six patients were recruited in the study, their ages ranged from 6-60 months; (36 males and 30 females) who were admitted to the emergency department at Basrah Maternity and Children Hospital and Basrah General Hospital from the 1st of March to the end of October 2013.

## Inclusion criteria

1- Patients with simple febrile seizures, generalized, tonic-clonic attacks lasting for a maximum of 15 min and no recurrence within a 24-hour (8)

2- Absence of central nervous system infections

Exclusion criteria )3, 9, 10, 11)

1- Age younger than 6 months or older than 60 months. 2- History of previous febrile seizure attack(s). 3- Epilepsy and neurologic conditions e.g. (Cerebral palsy). 4- Moderate or severe malnutrition, acute or chronic diarrhea, patients taking zinc supplements for therapeutic purposes within 3 months prior to the study .5- History of chronic diseases such as celiac disease, chronic kidney disease, sickle cell disease and diabetes mellitus. Control groups include: Febrile patients group included 58 febrile infants and children who were seen in the outpatient clinic or emergency department of the same hospitals, because of febrile illnesses as upper respiratory tract infection (URTI), pneumonia, urinary tract infection; no central nervous system infection or history of seizure. Healthy children group included 62 healthy infants and children consulting at Al-Razi and Al-Seef primary health care centers for immunization and routine child health visit. A special questionnaire was designed for the purpose of the study to collect the following information: Identity includes name, age, sex and residence. Presenting symptoms of seizure onset and duration (measured in minutes based on parents' observation record); Fever onset, duration and classified into: low grade fever ( 37.5 -38.3 °C), moderate grade fever (38.4-38.9 °C), high grade fever (39-40 °C) and hyperpyrexia (>40 °C).(12) Past history of recurrent febrile seizure, Immunization history of recent vaccination within 72 hours, Family history of febrile seizure or epilepsy, (13) Drugs history of oral diazepam, anti-epileptics drug and zinc supplement All patients underwent general and systemic examination, vital signs were measured and anthropometric measurement; weight and height/length were assessed and applied to appropriate charts. An approval from the ethical committee at Basra Medical College and the research committee at Basrah Health Directorate was obtained as well as an informed consent from the parents for all infants and children recruited in the study. Serum Zinc and Copper measurements: Two milliliters of whole blood was collected from the patients during the first 6 hours after admission to hospital and at the time of interview regarding the control groups. (14) The serum was separated and stored at -10°C. Zinc and copper levels were measured by spectrophotometry machine (CE Cell 1011 France made). The normal value for serum zinc is 10.7-17.6 mmol/l, for copper is 0.47-2.36 mmol/l in children up to 10 years), according to the test kit label.

#### Statistical analysis:

Data was analyzed using SPSS program V.17 Expressed by mean  $\pm$  Standard Deviation. A comparison of proportions was performed using Chi-Square test. T-test and one-way analysis of variance (ANOVA) was used to compare means. Logistic regression analysis was done to study relation of different variables and for some variables the odd ratio (OR) and 95% confidence interval (CI) were calculated. For all tests P-value of <0.05 was considered as statistically significant.

#### Results:

A total of 66 children with febrile seizures (FS) were included in the study (mean age was  $24.6 \pm 13.19$  months) . Sixty two healthy children (mean age was  $25.1 \pm 13.7$  months) and 58 febrile children (mean age was  $23.8 \pm 13$  months) were included as controls. The age and sex distribution of the children in the study and control groups showed no significant difference (P value >0.05) as shown in Table 1. Despite higher frequency of upper respiratory tract infections (URTI) and pneumonia seen in patients with febrile seizures and febrile control group, the result were not statistically significant, (P value > 0.05). Although urinary tract infection (UTI) and other causes are seen more frequently in the febrile control group than febrile seizure patients, the result is not significant (P-value > 0.05) as shown in Table 2. Children with febrile seizure had a lower mean serum zinc level ( $8.85 \pm 3.26$ ) in comparison to febrile patients and healthy control group ( $14.98 \pm 2.20$ ) and ( $13.33 \pm 1.99$ ) respectively with statistically significant result (P value < 0.05). No significant differences were detected between febrile and healthy control groups (P value >0.05). The mean serum copper level showed no statistically significant difference between patients with the febrile seizure and control groups (P value >0.05) as presented in Table 3. Table 4 shows no significant correlation between the mean serum zinc level and selected variables of infants and children with febrile seizure such as age, sex, weight and height/length (P value >0.05). Low mean serum zinc level ( $8.02 \pm 2.85$  and  $8.19 \pm 3.03$ ) is seen in children with high grade fever, and those with history of recurrent febrile seizure respectively, with no statistical significance. The mean serum zinc level showed no significant association to family history of febrile seizure. Children with pneumonia had low mean serum zinc level ( $7.62 \pm 2.73$ ) compared to children with other associated illnesses such as URTI or UTI , the difference is not statistically significant (P value > 0.05). There was no significant correlation of studied variables of children with febrile seizure as (age, sex, weight, height, temperature, family history, frequency of FS and diagnosis) with low serum zinc level.

**Table 1: Age and sex distribution of patients and control groups**

Variable	Febrile Seizure group		Control groups		P-value
	No.	(%)	group No.	Febrile patients (%)	
Age (months)	6-12	15 (22.7)	17 (27.5)	9 (15.5)	0.87 **
	13-24	26 (39.4)	18 (29.0)	28 (48.3)	
	25-48	20 (30.3)	23 (37.0)	15 (25.9)	
	49-60	5 (7.6)	4 (6.5)	6 (10.3)	
Sex	Males	36 (54.5)	34 (54.8)	31 (53.4)	0.98 *
	Females	30 (45.5)	28 (45.2)	27 (46.6)	
Total (186)	66		62	58	

**Table 2: Diagnosis in patients with febrile seizure and febrile control group**

Diagnosis	Febrile seizure		Febrile control group		P value*
	No.	%	No.	%	
URTI	31	47.0	23	39.6	0.276
Pneumonia	24	36.4	15	25.9	0.150
UTI	6	9.1	11	19	0.225
Others	5	7.5	9	15.5	0.282

\*Chi square test was used to measure P-value for all variables

**Table 3: Mean serum zinc and copper among patients with febrile seizures and controls**

Variable	Control groups			P value‡
	Febrile group Mean(±SD)	Febrile group Mean(±SD)	Healthy group Mean(±SD)	
Zinc	8.85 ±3.26	14.98 ±2.20	13.33 ±1.99	<0.005** 0.182 *
Copper	1.98 ±0.25	1.94 ±0.26	1.88 ±0.43	0.27

‡ ANOVA was used to measure P- value for all variables

P\*\* patient with FS and control groups (febrile group and/or healthy group)

P\* febrile patient and healthy control groups

**Table 4: Serum zinc in relation to selected characteristics of patients with febrile seizures**

Variable		Mean Serum Zn	P value**
Age (months)	6- 12	9.24 ± 2.37	0.54**
	13-24	8.73 ± 3.69	
	25-48	8.93 ± 2.87	
	49-60	6.96 ± 1.4	
Sex	Males	8.95±3.29	0.61 *
	Females	8.57±2.78	
Weight (Kg)	6-12	8.20±3.02	0.41 **
	13-18	9.23±3.10	
	19-24	8.53±2.84	
Height (cm)	60-75	9.42±1.93	0.32**
	76-90	8.20±3.04	
	91-119	9.28±3.80	
Grade of Fever	Low	10.75±0.35	0.13**
	Moderate	10.07±4.20	
	High	8.02 ± 2.85	
Frequency of FS	First attack	9.56 ± 3.41	0.44 *
	Recurrent	8.19 ± 3.03	
Family history of FS	Negative	8.20 ± 3.02	0.34 *
	Positive	9.23 ± 3.10	
Causes of fever	URTI	9.32 ± 2.90	0.135 **
	pneumonia	7.62 ± 2.73	
	UTI	9.88 ± 4.77	
	Other	9.60 ±1.95	

\* t- test

\*\* ANOVA

### Discussion:

Febrile seizure (FS) is the most common brain related disease in children. (15) Several studies have indicated that multiple factors can be involved in the pathogenesis of febrile seizure. This study was designed to explore whether zinc and copper have any role in developing febrile seizure. A higher frequency of respiratory tract infections was seen in patients with FS and febrile control group; which is in agreement with a study carried out by Al-Zwaini from Iraq, where upper and lower respiratory tract infections constituted 67% of febrile illnesses in children with febrile seizure. (16) In contrast Aliabad et al, (17) found that only 20% of children with febrile seizures had upper or lower respiratory tract infections. The current study showed that the mean serum zinc level was significantly lower in children

with febrile seizure compared to the control group. This observation is consistent with studies by Ganesh et al from India (2006), (7) Ehsanipour et al from Iran (2009) (9) and Lee et al from Korea (2012). (18) No significant difference was found regarding the level of serum zinc in relation to age, sex, anthropometric measurements, grade of fever, in consistence with other studies. (7, 9, 18) In addition, no significant difference in mean serum zinc levels was found in relation to family history of febrile seizure, number of convulsions, in agreement with İhsan et al from Istanbul (19). The reason for lower serum zinc levels in patients with febrile seizure is not known. However, fever and acute infections may have some role in developing such conditions. It is believed that the release of tumor necrosis factor (TNF) and interleukin during fever or tissue injury may result in the reduction of serum zinc level (20) Izumi et al (21) and Pallain et al (22) proposed that hypozincemia trigger the N-methyl-D-aspartate (NMDA) receptor which is one of the members of glutamate family receptor, and it may play an important role in the initiation of epileptic discharge. This study did not observe any reduction in the serum zinc levels in children who had fever without seizure. Patients with febrile seizures and pneumonia had lower serum zinc level than children with URTI or UTI, but not significantly so. Many authors have confirmed that routine zinc supplementation for more than three months has a positive effect on reducing the duration of acute lower respiratory tract infections among children in developing countries. (6) On the other hand, a the study conducted by Cho et al. Pusan Hospital in Korea, reported no significant difference between the mean serum zinc level in children with febrile seizures and that of control group, possibly because of the small sample size patients (11) included in their study. (23) A study carried out on 310 children with FS, by Sadeghzadeh et al in Iran did not show a significant correlation between serum zinc level and febrile seizure. (24) Studies carried out to assess the role of copper in febrile seizures are few. (25, 26) Copper deficiency is rather uncommon in humans due to its very low daily requirement and easy consumption in a variety of food items such as legumes, meats and nuts. The current study showed that only (10.6%) of patients had a positive family history of FS, because of enrolment of first degree relatives only in the family history of studied children, (13) in comparison to the higher result which varied from 25% to 40% from other studies. (27) High grade fever was recorded in 80% of patients with FS; other studies demonstrated that the height of temperature was a significant independent risk factor for FS. (28) Other studies found that temperatures more than 38.5°C, are related to recurrent FS with focal features. (27) Serum copper level was not significantly different in FS group compared to the control group. A similar result was found by Mahyar et al. (25) Although studies on the role of serum copper in febrile convulsions are rare, current findings and previous limited research showed that copper probably has no

role in febrile seizures. From this study, it can be concluded that children with febrile seizures have low serum zinc level and possibly zinc supplementation can be considered in patients who are at risk of recurrent febrile seizure.

#### Authors' contribution:

Dr. Basher Abdullah Jaber ; corresponding author

Prof. Sawsan Issa Habeeb; supervisor

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## مستوى الزنك والنحاس عند الاطفال المصابين بالصرع الحراري

### الخلاصة:

**خلفية البحث:** ان المغذيات الدقيقة الأساسية الموجودة في تراكيز منخفضة جدا في الجسم مثل السيلينيوم والزنك والنحاس تلعب دوراً مهماً في العمليات الفسيولوجية المختلفة وتعتبر أساساً في الأداء السليم لجهاز المناعة وقد أظهرت العديد من الدراسات أن هذه المغذيات الدقيقة قد يكون لها دور في الصرع الحراري عند الأطفال.

**الهدف:** تحديد مستوى الزنك والنحاس في الدم لدى الأطفال الذين يعانون من الصرع الحراري ودراسة العلاقة مع بعض المتغيرات لدى المرضى .

**المنهجية:** شملت الدراسة 66 رضيعاً وطفلاً يعانون من نوبات صرع حراري بسيط ومجموعتان ضابقتان؛ وتشمل مجموعة الاطفال الذين يعانون من حمى ومجموعة الاطفال الاصحاء. تم قياس مستوى الزنك والنحاس في المصل لجميع الرضع والأطفال المسجلين في الدراسة.

**النتائج:** المرضى الذين يعانون من نوبة الصرع الحراري لديهم مستوى منخفض بشكل ملحوظ من الزنك في المصل ( $3.26 \pm 8.85$ ) بالمقارنة مع مجموعتي الضبط "مرضى الحمى والأطفال الأصحاء" ( $2.2 \pm 14.98$ )، ( $1.99 \pm 13.33$ ) على التوالي. لا يوجد ارتباط ذو دلالة إحصائية بين مستوى الزنك في المصل مع متغيرات المرضى المحددة. لم يُظهر مستوى النحاس في مصل الدم فرقاً معنوياً بين المرضى الذين يعانون من نوبات الصرع ومجموعات الضبط.

**الاستنتاج:** يمكن ادخال مكملات الزنك في علاج الأطفال الذين هم عرضة لخطر نوبات الصرع الحراري المتكرر.

**الكلمات المفتاحية:** الزنك, النحاس, الصرع الحراري.