

RESEARCH ARTICLE

A Case-Control Study of the Association Between Serum Copper Level and Febrile Seizures in Children

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Abstract

Objective

Febrile seizures are the most common cause of seizure in children. Identification of risk factors is very important. This study was conducted to determine the association between the serum copper level and simple febrile seizure in children.

Materials & Methods

In this study, 30 children with simple febrile seizures (case group) were compared with 30 children with febrile illness without seizures (control group) regarding serum copper level. This study was conducted in Qazvin children's hospital (Qazvin, Iran).

Results

The mean serum copper levels in the case and control groups were 141.41 ± 30.90 and 129.43 ± 18.97 mcg/dl, respectively. This difference was not significant statistically.

Conclusion

This study revealed that there is no association between serum copper levels and febrile seizures. It seems that copper deficiency is not a risk factor for febrile seizures in children.

Keywords: Febrile seizures; Copper; Children

Introduction

Seizure is the most common neurologic symptom in children. Febrile seizures are the most frequent seizure in children (1). Between 2% and 5% of neurologically healthy infants and children experience at least one usually simple febrile seizure. Febrile seizures recur in approximately 30% of those experiencing a first episode and in 50% after two or more episodes (1). Febrile seizures are age-dependent and are rare before 9 months and after 5 years of age (1-3). Several factors have been implicated in the etiopathogenesis of febrile seizures including genetic factors (1-4). Recent studies have shown that some micronutrients may have a role in febrile seizures (5-10). This question was posed that; "does copper play any role in febrile seizures?" Copper 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 myeloneuropathy (11-13). Zatta reported that severe copper deficiency may lead to seizure attacks (14). Based on the important role of copper in cell physiology, such as free radical scavenging, membrane stability and preventing paroxysmal discharges (15, 16) and also due to the limited studies in this field, this study was conducted to determine the relationship between serum copper level and febrile seizures in children.

Materials & Methods

This prospective case-control study was conducted at Qazvin children's hospital affiliated to Qazvin University of Medical Sciences (Iran) in 2009. The case group (30 patients) was selected consecutively from children who were admitted to the hospital following simple febrile seizures. The control group comprised 30 febrile children without seizure. The sample size was calculated to provide $\alpha=5\%$, $1-\alpha=95\%$, $\beta=20\%$, $1-\beta=80\%$ in statistical analysis.

The inclusion criteria for the case group were: 1-Age between 9 months and 5 years; 2- First simple febrile seizures (generalized seizure, seizure lasting less than 15 minutes); 3- Absence of central nervous system infection and electrolyte imbalance (1,17). The exclusion criteria included complex febrile seizures, no febrile convulsion, epilepsy and a neurologic deficit. The control group included healthy children without seizure who were visited in the clinic of Qazvin children's hospital due to mild febrile illness with no intervention for their problem. Children in both groups were matched in terms of age, sex, weight, height, head circumference and fever severity. Weight, height, head circumference and body temperature (axillary) were measured according to standard methods.

Blood samples were drawn in the morning between 9:00 and 11:00 am. All febrile seizure patients were at least 12 hours seizure-free before sampling time (18). Blood samples in both groups (3 cc of peripheral blood) were centrifuged and the clean serum was stored at 70°C until the time of analysis. Measurement of the serum copper was carried out by an atomic flame spectrophotometer method (19) at the Iranian Nuclear Energy Agency, Tehran. The flame spectrophotometer machine was an Australian-made Varian Spectra AA220 model. To improve accuracy, all measurements of serum copper were checked twice. The normal range of serum copper level is 70-155 $\mu\text{g/dL}$ (19).

For statistical analysis, the results were in terms of numerical indices such as frequency, mean and standard deviation. In addition, t-test and chi-square were used to compare the variables between both case and control groups. Statistical significance was set at a p value of lower than 0.05.

Ethical Considerations

The study was approved by the ethics committee of the research department in Qazvin University of Medical Sciences (project thesis no: 186). All parents were given information about the research method in a simple language. The children were included in the study when their parents agreed and signed the informed consent form.

Results

In the case group, 18 of the cases were male and 12 female and in the control group, 16 were male and the remainder were female ($p=0.43$). The minimum and maximum ages in the case and control groups were 9 and 60 months, respectively. There was no statistically significant difference between the groups in terms of age, weight, height, head circumference and body temperature ($p>0.05$) (Table 1). There was no significant differences between case and control groups regarding concentrations of serum copper levels ($p=0.055$) (Table 2). There was no statistically significant difference between serum copper levels in the groups with the standard value. In addition, none of the children in any of the groups had serum copper levels less than 70 $\mu\text{g/dl}$ (hypocupremia) ($p=0.103$) (Table 3). The concentration of serum copper levels in the two groups regarding sex is demonstrated in Table 4 ($p>0.05$).

Discussion

Although several studies have been conducted about identifying risk factors for febrile seizures, as far as my knowledge and literature review is concerned, the studies that have been carried out regarding the role of copper in this convulsive disorder are rare (3, 20). Copper deficiency is rather uncommon in humans due to its very low daily requirement and easy consumption. Legumes, meats and nuts are suppliers of this element. It is absorbed through the stomach mucosa and the proximal duodenum. With the abundant supply of dietary copper, acquired copper deficiency is relatively scarce compared with other causes of neurologic deficits (21). Copper is an essential micronutrient which is vital for the function of many cellular enzymes (11). Copper cooperates as a catalytic cofactor in the chemistry of redox enzymes, mitochondrial respiration, iron

absorption and free radical scavenging (11,15). Zatta et al.'s study on animals revealed that severe copper deficiency may lead to seizure (14). Ilhan et al. showed that there was a statistically significant increase in the serum copper level in epileptic patients compared to controls (22). It is believed that the role of copper in the induction of seizure may be related to its inhibitory activity against Mg-ATPase and Na-K ATPase enzymes in the hippocampus and hypothalamus. This process disrupts the mechanisms which maintain the correct intra neuronal sodium and potassium ratio. Finally, this disruption results in membrane instability and paroxysmal discharges (16). Mishra et al. revealed that the copper level of cerebrospinal fluid in patients with febrile seizures is significantly less than the control groups. Besides, they found that there was no significant change in serum copper levels between the groups. In addition, there was no significant correlation between copper levels in the cerebrospinal fluid and serum. They concluded that the decrease in CSF copper level in febrile seizures may be a co-precipitating event in the occurrence of seizures (20). Amiri et al. reported that there was no significant difference between febrile seizures and control groups regarding serum copper levels (8). The results of our study were similar

to Mishra and Amiri studies. Although the studies concerning the role of serum copper in febrile seizures are rare, our findings and previous limited researches show that copper deficiency probably has no role in febrile seizures. Thus, it seems that the measurement of serum copper level in febrile seizure patients is not indicated. It is noteworthy that this conclusion applies only to our study. One of the limitations of the present study was lack of CSF copper measurement. Further investigations with larger samples and CSF copper measurements are warranted.

In conclusion, this study revealed that there is no association between copper deficiency and febrile seizures. It seems that copper deficiency is not a risk factor for febrile seizures in children.

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Financial Disclosure

None declared.

Table 1. Comparison of Variables in Case and Control Groups

Variables	Mean (±SD) Case	Mean (±SD) Control	Range	P
Age (mo)	32.23 (±15.38)	31.60 (±15.60)	49 48	0.87
Weight (kg)	12.76 (± 2.15)	12.65 (±2.29)	8 7.7	0.54
Height (cm)	89.50 (±11.45)	89.41 (±10. 67)	34.50 36.80	0.62
Head circumference (cm)	49.63 (±3.46)	49.48 (±3. 31)	10.50 10.60	0.91
Temperature ° C	38.62 (± 0.34)	38.68 (±0.36)	1.30 1.60	0.49

Association Between Febrile Seizures and Serum Copper Level

Table 2. Comparison of Serum Copper Level in Case and Control Groups

Serum Copper Groups ($\mu\text{g/dL}$)	Mean \pm SD	Minimum	Maximum	Range	P
Case	142.20 \pm 30.40	99	195.5	96.50	0.055
Control	129.43 \pm 18.97	94	182	88	

Table 3. Comparison of Serum Copper Level in Groups with Standard Value

Serum Copper ($\mu\text{g/dL}$)	Case n(%)	Control n(%)
<70	0(0)	0(0)
70 -140	16(53.3)	23(76.7)
>140	14(46.7)	7(23.3)
Total	30(100)	30(100)

P=0.103

Table 4. Comparison of Serum Copper Level Between Genders in Case and Control Groups

Serum Copper Groups ($\mu\text{g/dL}$)	Male (mean \pm SD)	Female (mean \pm SD)	P
Case	148 \pm 30.5	135.7 \pm 29.9	0.277
Control	129.1 \pm 20.1	130 \pm 17.7	0.904

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