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The Prevalence of Zinc Deficiency in Children with Febrile Seizure

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ABSTRACT

Introduction: A febrile seizure (FS) occurs in 2-4% of children aged 6 months to 5 years. A simple febrile seizure is the most common seizure in children. According to the evidence, both genetic and environmental factors affect the occurrence of this condition. The purpose of this study was to determine the association between zinc deficiency and sociological factors, and febrile seizures.

Methods : This case-control study evaluated 136 children at 22 Bahman Hospital of Gonabad, Iran, from July 2015 to March 2018. We selected 36 children aged 6 months to 5 years with febrile seizures as the case group and 100 febrile children without a seizure, in the same age range, as the control group. The demographic characteristics, place of residence, family history of seizures, and zinc serum level were recorded, and data were analyzed by frequency, average, and standard deviation, and Chi-square statistical tests. The odds ratios were calculated by logistic regression with a 95% confidence level. SPSS version 22.0 was used for statistical analysis.

Results: Totally, 38.8% of the cases with FS and 5.0% of the febrile children without seizure had a zinc deficiency. The serum zinc level in the case group was 75.44 ± 16.98 µgr/dL and in the control group was 100.27 ± 24.23 µgr/dL ($P < 0.001$). The odds ratio of zinc deficiency in the patients with FS compared to the febrile children without convulsion was 1.069 (1.045-1.151).

Conclusion: Children with FS are more susceptible to have zinc deficiency than those febrile but without a seizure. Therefore, zinc deficiency could be a preventable and treatable risk factor for FS.

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Introduction

Seizures can be categorized according to the type, duration, and cause of occurrence (3). Febrile seizures (FS) are usually divided into three major groups: simple febrile seizures (SFS), simple febrile seizures plus, and complex febrile seizures (CFS) (4). A febrile seizure mostly occurs within 24 hours after a fever. The prevalence of febrile seizures in children aged 6 months to 5 years is 3-4% worldwide. They can be associated with complex and abnormal neurological disorders (1). Eighteen months is the most susceptible age of a febrile seizure incidence (2).

A simple febrile seizure lasts less than 15 minutes (5). Simple febrile seizures plus stand for the occurrence of SFS more than once, without any neurological disorders. The third group is CFS with seizures of longer than 15 minutes and with multiple and focal symptoms

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(4). Simple febrile seizures are the most common in children, and recurrence occurs in one-third of affected children (6). According to the available evidence, both genetic and environmental factors affect the occurrence of this condition. Stress hormones, such as glucocorticoids and corticotrophin-releasing hormone (CRH), infect the fetal central nervous system and affect the occurrence of fever seizures as well (7). Iron deficiency is also a common, preventable, and treatable risk factor. It affects the brain and neurotransmitter metabolism, thus changing the seizure onset in children (8).Periodic diazepam or clobazam consumption and concurrent use of valproic acid or phenobarbital can prevent the recurrence of febrile seizures. Long-term use is not however recommended. Melatonin is also effective in treating hypothermia-induced seizures (9).

The most common type of focal epilepsy in adulthood is due to temporal lobe epilepsy (TLE). And, about one-third of patients do not respond to medication therapy, which is often associated with hippocampal sclerosis (HS). Febrile seizures are related to TLE and hippocampal sclerosis (10).

Hospitalization is not usually required, but in some cases with red flag symptoms, including long-term seizures, complex FS, severe neurological and infection disorders, unknown infection, a child under 18 months, and recurrent seizures, hospitalization is essential (11).

In more than 50% of children with FS experience, significant risk factors have not been recognized (12). The incidence of FS is related to genetic, environmental, and sociological factors. It is, therefore, important to identify these factors to improve the prevention, prognosis, and management of FS. This study aimed to determine the association between zinc deficiency, sociological factors, and febrile seizures. Due to the importance of febrile seizures, especially in Iran with high incidence, the aim of this study was to compare the zinc deficiency prevalence between patients with febrile seizures and those with fever but without seizure and to discuss the associated factors.

Methods

Study design

This is a case-control study conducted at the pediatric department of 22 Bahman Hospital, affiliated to Gonabad University of Medical Sciences, Gonabad, Iran, between July 2015 and March 2018. The study protocol was approved by the Ethics Committee of Gonabad University of Medical Sciences (Ethics code: IRGMJ.REC.1394.63). The study was conducted in accordance with the Declaration of Helsinki (7th revision, 2013). Written informed consent was taken from the patients' parents prior to their partake in the study. This study did not impose any additional charges to the patients, nor did it interfere with the standard process of diagnosis and treatment of the patients.

Definition

A seizure is a complicated neurological disorder associated with neuronal dysfunction, the nervous system, and abnormal electrical currents. A febrile seizure occurs when the body temperature is above 38.5 °C without primary infections of the central nervous system, such as encephalitis and meningitis.

Study population

In this prospective study, children aged 6 to 60 months with normal growth and development who were admitted to the hospital with febrile seizures for the first time were included in the case group, and those admitted with fever but no symptoms or signs of seizure were randomly included to the control group. A pediatrician was responsible for physical examinations. The children who had taken zinc supplements in the earlier one month, those who had a history of meningitis or encephalitis or had a second seizure during the hospitalization, and those who had central nervous involvements were excluded from the study.

Considering the prevalence of zinc deficiency in previous studies, the sample size for the case group was calculated to be at least 30 patients. To increase the power of the study, threefold the size of the case group was considered for the control group. Sampling was done in a six-month period and with a convenience method.

data gathering

The patients' parents were asked to fill out the demographic and baseline information questionnaire, including age, gender, place of child care (home or kindergarten), living place in the past year (urban or rural area), and a family history of seizure (in first- and second-degree members). For children who had been at least one day in kindergarten, the place of child care was considered kindergarten.A mercury thermometer under the armpit for 10 minutes was the choice for taking the temperature in all participants. However, in children older than two years old, who could not handle the armpit measurement, a digital ear thermometer was used for a few seconds. Fever was defined as a temperature of equal or higher than 38 º C under the armpit and for ear measurements during the day. In addition, a 3 cc blood sample was taken from a radial vein of participants using a 5 cc syringe with a 27 gauge needle (Elite Company), to measure the serum level of zinc. The sample

was centrifuged immediately. After the serum separation, the sample was stored at -15 ºC, then the level of zinc was measured by a Shimatzer spectrophotometer. The serum level of less than 70 µgr/dL was considered zinc deficiency, and higher levels as sufficiency.

Statistical analysis

The collected data were analyzed with SPSS (Version 22.0, IBM, Chicago, IL, USA). Quantitative variables are presented using mean ± standard deviation, and qualitative variables using frequency and percentage. The independent sample t-test, Chi-square, and Fisher's exact test were applied to compare groups. A logistic regression was applied for each variable with the group membership(case and control groups) as the target. A P-value < 0.05 was considered statistically significant.

Results

Totally, 136 patients participated in this study. The case and control groups included 36 and 100 patients respectively. The demographic and baseline data are shown in Table 1. The majority of patients had in-home child care, had a sufficient level of zinc, and did not have any family history of seizure. Although it is recommended to have the same number of patients in both groups, the low number of patients in the case group was somehow compensated with a threefold higher sample size in the control group. The mean body temperature was significantly higher and the mean level of zinc was significantly lower in the case group. The case and control groups were significantly different in terms of gender distribution, living place, family history of seizure, and the level of zinc. Note that the frequency of boys in the case group was significantly higher than in the control group . Therefore, gender was considered a confounding variable, and a stratified analysis was done between the zinc level and the case and control groups. The results showed that there was a significant association between zinc deficiency and the case and control groups, in both genders . Living in urban areas was more frequent in the case group, while living in rural areas was more frequent in the control group . A family history of seizure in the case group was significantly higher than in the controls .

The prevalence of zinc deficiency was 13.97% in the studied population, which was 7.78 times higher in the case group than in the control group .However, the case and control groups had no significant difference in terms of age and place of child care , as shown in Table 1.

The multiple logistic regression analysis showed that the level of zinc was 1.069 times higher in the control group than in the case group. In addition, a family history of seizure and living place were also significantly different between the two groups . However, temperature and gender had no significant difference, as can be seen in Table 2.

Table 1: Demographic and base line information between case and control groups

Variables		Case (n=36)	Control (n=100)	p-valuea
Age (months)		17.73±26.83	17.55±27.46	0.855
Temperature (ºC)		0.99±38.77	1.04±38.28	0.017
Level of Zinc (µgr/dL)		16.98±75.44	24.23±100.27	<0.001
Gender	Boy	25(69.4)	42(42)	0.006
	Girl	11(30.6)	58(58)	
Living place	Rural area	16(44.4)	84(84)	<0.001
	Urban area	20(55.6)	16(16)	
Place of childcare	Home	25(69.4)	71(71)	0.861
	kindergarten	11(30.6)	29(29)	
Family history of seizure	Positive	17(47.2)	1(1)	<0.001[b]
	Negative	19(52.8)	99(99)	
Zinc range	Sufficient	22(61.1)	95(95)	<0.001
	Deficient	14(38.9)	5(5)	
Boys	Sufficient	14(38.9)	40(40)	<0.001[c]
	Deficient	11(30.6)	2(2)	
Girls	Sufficient	8(22.2)	55(55)	
	Deficient	3(8.3)	3(3)	

Data was described using mean ± SD or frequency (percent). ap-value refers to the difference of each variables between case and control groups. brefers to the analysis based on Fisher's Exact test. crefers to the analysis based on Cochran–Mantel–Haenszel test

Table 2: Multiple logistic regression of each variable between case and control groups

Variables	OR(CI)	p-value*
Temperature (ºC)	1.236-0.342)0.639)	0.189
Level of Zinc (µgr/dL)	1.151-1.045)1.069)	<0.001
Gender	1.544-0.091)0.319)	0.174
Family history of seizure	0.27-0.000)0.011)	<0.001
Living place	-56.394)6.562 1.881)	<0.001

OR: Odds Ratio; CI: Confidence Interval.

Discussion

The present study showed that the prevalence of febrile seizures was associated with gender, living place, temperature, family history of seizure, and the serum level of zinc. In this regard, the frequency of zinc deficiency was higher in patients with febrile seizures compared to febrile patients without seizure, before and after adjusting for gender.

Zinc plays a vital role in the neuronal terminals of the hippocampus and amygdala by producing pyridoxal phosphate and affecting glutamatergic, gamma-aminobutyric acidergic (GABAergic), and glycinergic synapses (13).

Glutamic acid decarboxylase (GAD) acts as a major inhibitory neurotransmitter in the synthesis of gamma-aminobutyric acid (GABA) (14). A study by Ganesh R. and Janakiraman L. on 38 children with febrile convulsion and 38 children as a control group, aged between 3 months and 5 years, indicated that a serum zinc deficiency was significantly more prevalent in their case group than in the control group (15). Another study has reported that there is a correlation between disruption in Zn2+ homeostasis and fever seizure (16).

In studies by Papierkowski A., Mollah M.A., and Gündüz Z. et al., the mean serum zinc level in the febrile convulsion group was significantly lower than in the control group, which indicates the role of zinc in febrile seizure. Comparing the groups in terms of age and gender, no significant difference was found, similar to our study (17-19). Abdel Hameed Z.A. et al. (20), in a study on 100 infants in Egypt, observed that temperature had no significant difference between the case and control groups. But Berg A.T. (21), Ahmed B.W. (22), and our study showed the importance of temperature in febrile seizure. The geographic area can be the cause of this difference. Duangpetsang J. in a study from 2014 to 2017 reported that a high fever with electrolyte disturbance hyponatremia has an important role in FS (23). Sharifi R. et al., in a study in 2007-2014, showed the importance of family history in febrile seizure (24), which is similar to our results.

Conclusion

The findings of this study show that zinc deficiency is significantly associated with the occurrence of febrile seizures. Zinc supplementation in children can therefore be helpful for the prevention and treatment of FS.

Conflict of interest

The authors declare no conflicts of interest.

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