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Serum Vitamin C Levels: A Comparison between Febrile Children with or without Seizure

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ABSTRACT

Introduction: An imbalance has been reported in the oxidant-antioxidant system of infants with febrile convulsion. This study aimed to compare serum vitamin C levels between febrile children with or without seizures.

Methods: This multicenter case-control study was conducted on febrile infants and children referred to Mashhad University of Medical Sciences pediatric emergency wards. The subjects were equally divided into two febrile groups of case (with seizures) and control (without seizures). A visible spectrophotometer was used to determine the total vitamin C level.

Results: In total, 100 febrile children were included in the study. Based on the results, there was no statistically significant difference between the two groups in terms of age, gender, and family history of febrile convulsion (FC) (P>0.05). The mean vitamin C levels in the case and control groups were 42.73±7.2 and 78.59±11.1 µg/l, respectively. There was a significant difference between the groups regarding the vitamin C level (P<0.001). Regression analysis revealed that age (P=0.74), gender (P=0.66), and family history of febrile convulsion (P=0.52) had not any correlation with vitamin C levels. On the other hand, vitamin C levels were associated with FC (P=0.001).

Conclusion: The serum levels of vitamin C were lower in children with febrile seizures than in the control group. Thus, reduced vitamin C levels can be considered a predisposing factor for FC.

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Introduction

Febrile seizures are the most common seizures among the pediatric population. Typically, this condition occurs in those between 6 months and 5 years of age (1-3). The incidence of febrile seizures has been estimated to be 2%-4%; however, it is more common in Asian countries (4, 5). The mechanism of febrile seizure is still unknown, and many risk factors seem to be involved (6). The autosomal pattern is often inherited and has been identified in some families. Genetic predisposition and changes in the levels of neurotransmitters are introduced as the main factor in the pathogenesis of febrile seizures (7). Different hypotheses have been proposed focusing on oxidative stress and the changes in trace elements in biological body fluids, which may have a major part in the pathogenesis of febrile seizure (8). The balance between reactive oxidant species and antioxidant defense mechanisms alternates during oxidative stress (9). Increased lipid

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peroxidation by the significant free radicals leads to the disruption of cell membranes and, consequently, febrile seizures (10). Plasma levels of inflammatory factors and prostaglandins increase during fever, which increases the level of free radicals in the body (11). Vitamin B6 deficiency, electrolyte disturbances, and reduced serum and cerebrospinal fluid zinc levels are possible factors involved in febrile seizure (12). The other potential factor is low levels of gamma-aminobutyric acid (GABA) (8).

Vitamin C is a water-soluble essential vitamin with a principal neuroprotective function. This vitamin protects intracellular structures against oxidative damage, and its neurological antioxidant role has been proven (13). Besides, the optimal level reduction of vitamin C leads to cellular damage and neurotransmitter disparities (14, 15).

To our knowledge, very few studies have investigated the correlation between febrile seizure and serum vitamin C levels (16). Due to the effects of vitamin C on the body's immune system against oxidative stress and its possible role in the pathogenesis of febrile seizure, this study aimed to compare febrile children with or without seizure regarding vitamin C levels in blood samples.

Materials and Method

This multicenter case-control study was performed on febrile patients aged 6 months to 5 years (60 months) who were referred to the emergency ward of the Ghaem, Doctor Sheikh, Akbar, and Imam Reza hospitals, Mashhad, Iran.

Inclusion and Exclusion Criteria

Febrile infants and children aged 6 months to 5 years were included in this study. Fever was defined as a temperature ≥38°C. Those with underlying neurological or metabolic diseases, psychomotor retardation, CNS infection, and history of previous seizures (17) were excluded from the study.

Study Design

In total, 100 infants and children were selected using the available sampling method, and they were divided into two groups of case (febrile seizures) and control (febrile without seizures). It is worth mentioning that the two groups were matched in terms of age and gender. The demographic characteristics covering such information as age, gender, duration of illness, and family history of febrile seizure were gathered from the medical records of the selected samples.

Serum and Kit Preparation

After admission, a 2 cc blood sample was taken from all subjects to measure serum levels of vitamin C. The samples were transferred to the Immunology Laboratory affiliated with the Ghaem Hospital, Mashhad, Iran. Instruments and materials used in this study included samplers and sampler tips in different sizes, microtubes 1.5 ml, deionized or distilled water, hot air ovens or Bain Marie (37°C), shakers, centrifuge 15000 g, a plate reader with a wavelength of 530500- nm, and a protein measuring kit for normalization (KBCA96). A visible spectrophotometer was used to determine the total vitamin C level. A spectrophotometer can be used to study the absorption spectra of different materials (18-20).

Statistical Analysis

The data were analyzed in SPSS software (version 20), and appropriate statistical indicators were used to describe the data. The Kolmogorov-Smirnov/Lilliefors test was utilized to assess the data normality. The t-test and its nonparametric equivalence were employed for quantitative analyses. Moreover, the Chi-square test was used for qualitative analysis. A p-value less than 0.05 was considered statistically significant.

Ethical Considerations

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (No: 951826; code: 226). In line with the principles of research ethics, informed consent was obtained from the parents of all cases. No additional costs were imposed on the patients, and the parents were assured that their information would remain confidential and that they could withdraw from the study at any time.

Results

In total, 100 febrile infants and children were equally divided into two groups of case and control with mean ages of 30.18±13.4 and 29.6±13.7 months, respectively. It is worth mentioning that there was no significant difference between the two groups in this regard (P=0.82). Table 1 summarizes the distribution of demographic characteristics, including gender and family history of febrile seizure, in the two groups. No statistically significant difference was observed between the two groups in terms of gender (P=0.67) and family history of febrile seizure (P=0.39). It was found that the mean values of vitamin C levels in the case and control groups were 42.73±7.2 **µg/l** and 78.59±11.1 µg/l, respectively, which differed significantly (P<0.001). The mean values of vitamin C levels were 62.06±21.07 µg/l and 59.17±20.96 µg/l in

Table 1: Distribution of demographic characteristics including gender and family history of febrile seizure in two groups

Variables No		Case group N=50		Control group N=50		P-value
		%	No	%		
Gender	Male	34	68	32	64	0.67
	Female	16	32	18	36	
Family history of febrile seizures	Yes	28	56	22	44	0.39
	No	22	44	28	56	

Table 2: Comparison of vitamin C levels between female in the two groups and male in the two groups

		Number	Mean	Standard Deviation	P-value
Vitamin C levels in *Female*	Control	18	79.75	9.56	<0.001
	Case	16	42.59	6.28	
Vitamin C levels in *Male*	Control	32	77.93	11.67	<0.001
	Case	34	42.80	7.64	

female and male children, respectively, and the assessment of the relationship between gender and vitamin C levels showed no significant difference between males and females (P>0.05). However, as illustrated in Table 2, there was a significant difference between males and females regarding vitamin C levels in both case and control groups (P<0.001).

It was also observed that the mean values of vitamin C levels were 43.48±7.01 µg/l and 41.79±7.5 **µg**/l in children with and without family history of febrile seizure in the case group, respectively, and the difference was not significant (P=0.85). As shown in Table 3, regression analysis showed that age (P=0.74), gender (P=0.66), and family history of febrile seizure (P=0.52) did not correlate with vitamin C levels. However, vitamin C levels were significantly associated with FC (P=0.001).

Discussion

Oxidative stress plays a vital role in the pathophysiology of neurological disorders, such as epileptic seizures and neurodegenerative disorders (21). The equilibrium between reactive oxidant species and antioxidant defense mechanisms changes during oxidative stress.

Table 3: Regression analysis of relationship between vitamin C serum levels and febrile convulsion, age, gender and family history of febrile seizure

Model	β	SE	Beta	P value
Febrile convulsion	0.91	0.02	0.36	0.001
Age	0.01	0.001	>0.005	0.74
Gender	-0.21	0.02	-0.009	0.66
Family history of febrile seizure	0.03	0.02	0.01	0.52

Febrile seizures can occur due to an imbalance in the oxidant-antioxidant systems, which seriously upsets the balance of free radicals and antioxidants in the body (9). Vitamins C, E, and A, uric acid, and bilirubin are well-known antioxidants contributing to the body's defensive system (16). Moreover, vitamin C is of utmost importance in detoxifying the human body system and protects against cell damage caused by free radicals (22).

Our findings showed a lower level of vitamin C in infants and children with febrile seizures compared to controls. Thus, lower serum vitamin C levels may be considered a predisposing factor in febrile seizure. Consistent with our results, in a case-control study carried out by Kumar et al. in 2017, serum levels of vitamin C were measured in two groups of children with febrile convulsions and healthy ones. The mean values of vitamin C levels in the case and control groups were 48±10 and 88±14 **µg**/l, respectively. Significantly lower levels of vitamin C were found in children with febrile seizures (P<0.001). They stated that oxidative stress was one of the mechanisms for febrile convulsion and that FC could occur due to dimness in the antioxidant system (16). Likewise, another case-control study was performed by Das et al. to investigate the serum levels of malondialdehyde, vitamin C, and trace elements in adult epileptic patients and healthy ones. A higher value of malondialdehyde and a lower level of vitamin C were observed in the cases. They revealed that antioxidants such as vitamin C, zinc, and copper played an essential role in the pathogenesis of epilepsy (23), which was in line with the findings of previously conducted studies (24, 25).

Furthermore, Vitamin C as an antioxidant can potentially control febrile seizures. Based on one animal study conducted by Ullah et

al., vitamin C has anticonvulsant effects. They showed that vitamin C supplementation led to reduced polyspike and epileptiform discharges. They recommended vitamin C as a potential therapeutic option for epilepsy (26).

Conclusion

In summary, an imbalance has been reported in the oxidant-antioxidant system of children with febrile seizures. Antioxidants such as vitamin C can reduce febrile seizure manifestations and change biochemical markers, such as oxidative stress. Based on this study's results, serum levels of vitamin C in infants and children with febrile seizures were lower than those in the control group. Therefore, lower levels of vitamin C could be considered a predisposing factor in the pathogenesis of febrile convulsion.

Limitations and Suggestions

Further studies should be conducted using a larger sample size. We recommend future research to clarify the exact role of vitamin C in the pathogenesis of febrile seizure. Administering vitamin C prophylaxis to febrile children under five years to minimize the risk of seizures is another valuable area for future research.

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