



Investigating the correlation between serum folic acid level and febrile seizures in children: A clinical study

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ABSTRACT

Introduction: Febrile seizure (FS) is a highly frequent presenting complaint in children. It is defined as a seizure that occurs in children between 6 to 60 months related to a fever of 38°C or more without any other explanatory causes of seizure such as evidence of central nervous system (CNS) infection or a previous seizure without fever. The aim of study is to evaluate mean folic acid serum levels in febrile children with or without seizures.

Methods: The mean folic acid serum levels and demographic data of 100 children aged 6 to 60 months, admitted to the Ghaem Hospital of Mashhad, Iran in 2018-2019, were collected, where the patients with febrile seizure were considered as the case group and the febrile ones without seizure as the control group. The inclusion criteria were children aged 6 to 60 months with febrile seizures who were admitted to the pediatric ward. The exclusion criteria were having a past medical history of seizure, meningitis, or encephalitis.

Results: There were 49 febrile convulsive children (cases) and 51 febrile children without a seizure (controls). The mean serum folic acid level was 7.07 and 9.89 ng/ml for cases and controls respectively (P-value < 0.001).

Conclusion: Children with febrile seizures had significantly lower serum folic acid levels than febrile children without a seizure.

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Introduction

Febrile seizure (FS) is a highly frequent presenting complaint in children. It is defined as a seizure that occurs in children between 6 to 60 months related to a fever of 38°C or more without any other explanatory causes of seizure such as evidence of central nervous system (CNS) infection or a previous seizure without fever (1). Studies show that 2% to 5% of children experience FS (2). FS

can present as a tonic clonic, tonic, or atonic seizure. Fever is not necessarily present in the time of convulsion and can happen before or even after the seizure (3).

Febrile seizure is defined by three types: simple, complex, and status epilepticus (4). Simple is a generalized seizure episode that lasts up to 15 minutes and does not recur within 24 hours.

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Focal convulsions, a seizure occurring more than once in 24 hours or lasting more than 15 minutes, fall into the category of complex febrile seizure. A febrile seizure lasting more than 30 minutes is called a febrile status epilepticus and accounts for 25% of all childhood status epilepticus episodes (5). Although FS is a benign condition in nature, it causes a great deal of anxiety in children's caregivers (6).

There are many uncertainties about the etiology of this condition, but some studies suggest that a mixture of environmental and genetic factors orchestrate the mechanisms leading to FS. FS is most commonly seen with chickenpox, influenza, otitis media, respiratory infection, dental infection, and digestive tract infection (7). It has also been speculated and studied that changes in neurotransmitters, mutations in genes, vitamins (B12, folic acid), and trace elements, e.g., zinc, magnesium, sodium, and calcium, may have a role in the pathogenesis of febrile convulsions (8-14). Furthermore, there are studies that support that iron deficiency anemia is significantly higher in children with FS compared to febrile children without seizures (8, 13, 15). In other studies, zinc levels were reported to be significantly lower in patients with FS compared to febrile patients without convulsion (8, 14, 16). Nevertheless, only a few studies have investigated the serum folic acid level in febrile patients with and without a seizure (17-19).

Folic acid is an active agent in the nervous system. Folate deficiency causes neuropathy, depression, concentration problems, neuropsychiatric disorders, etc. (20). In the past, several studies have shown that folate has excitatory properties especially if the blood-brain barrier is compromised. In some cases of epilepsy patients under treatment with folate, seizure frequency was increased (20, 21). Previous studies on the association of folic acid and FS have each yielded interesting results, which are not in alignment with each other (17-19). In this study, we therefore aimed to evaluate and clarify the correlation between serum folic acid and FS.

Methods

The present case-control study was performed to evaluate the correlation between the serum folic acid level and FS, where 100 children between 6 and 60 months were included and categorized into two groups: the case group consisting of 49 children with FS and the control group consisting of 51 febrile children who did not contract seizure during the course of their illness. Patients meeting the inclusion criteria entered this study: febrile children between 6 and 60 months of age with or without seizure who were admitted to the pediatric

ward of the Ghaem Hospital of Mashhad (Iran) in 2018-2019. Children who matched one of the following criteria were excluded: had a history of seizure or epilepsy, were confirmed cases of meningitis or encephalitis, had a co-existing condition such as heart disease, liver disease, malnutrition, or kidney disease, took a multivitamin supplement in the week before the admission, were on a vegetarian diet, and took folic acid antagonist agents.

After informing the parents of the voluntary nature of the study, signed informed consent was obtained. The study was approved by the Ethics Committee of the Mashhad University of Medical Sciences with the code IR.MUMS.MEDICAL.REC.1398.196. In all patients, 2 ml of venous blood from the arm was drawn and sent for assessment of folic acid level. Serum folic acid levels were assessed using the radioimmunoassay competitive protein binding method (RIA CPB).

The study data were analyzed in SPSS software (version 22.0). Distribution indexes were analyzed using descriptive statistics. The Kolmogorov-Smirnov test was used to assess the normality of distributions, and the parametric Student's t-test and non-parametric Mann-Whitney U test were used to compare quantitative variables between groups. In the case of a normal distribution, the Levene's test was done to assess the equality of variances. Besides, the Chi-square test was used for qualitative variables. The Student's t-test (normality and homoscedasticity conditions were met) was performed to compare the mean serum folic acid level between the two study groups. A P-value < 0.05 was considered to be statistically significant.

Results

A total of 100 children were enrolled in our study, grouped as 49 patients with FS (cases) and 51 febrile patients without a seizure (controls). The demographic and laboratory data are summarized in Table 1. As can be seen, the gender distribution between the case and control groups was not significantly different. Regarding the history of seizure in the family, even though it seems that most of the patients with FS had a positive family history, the difference was not significant either at 95%. Likewise, the mean of none of the laboratory measures was significantly different between the case and control groups.

Comparing the type of seizure (simple vs complex) in the case group, there was no significant difference in seizure type between the male and female patients (P-value = 0.11), as can be seen in Table 2. In both genders, the number of cases with simple seizure was considerably higher than the number of cases with complex seizure.

Table 1. Demographic and laboratories data for case and control groups.

	Febrile convulsing patients (cases)	Febrile without convulsion (controls)	P-value
Gender			
Boy	30	29	0.65
Girl	19	22	
History of seizure in family			
Yes	20	12	0.06
No	29	39	
Age (month)	24.57	22.66	0.35
Na (mEq /L)	138.41	138.69	0.75
K (mEq /L)	4.18	4.30	0.19
Ca (mg/dL)	9.35	9.26	0.71
Mg (mg/dL)	2.19	2.08	0.16
Glucose (mg/dL)	106.20	101.60	0.41

Table 4 shows the underlying causes of fever in two groups. The distribution of cases with different underlying causes was somehow similar in

Table 4. Underlying causes of fever in case and control groups.

	Upper respiratory tract infection	Lower respiratory tract infection	Urinary tract infection	Gastroenteritis	Other/no identifiable underlying disease
Cases	9 (18.4%)	8 (16.3%)	1 (2%)	4 (8.2%)	27 (55.1%)
Controls	9 (17.6%)	4 (7.8%)	2 (3.9%)	5 (9.8%)	31 (60.8%)
Total	18 (18%)	12 (12%)	3 (3%)	9 (9%)	58 (58%)

Note that we also compared the folic acid level in each gender group, and there was no evidence of significant difference by gender. Moreover, the seizure type did not significantly correlate with the mean folic acid levels (P-value = 0.74).

Discussion

In this study, we aimed to clarify the correlation between the incidence of febrile seizures and the folic acid level. Our results indicated that folic acid is lower in febrile convulsing patients compared to non-convulsing febrile patients. However, no significant difference in gender distribution and mean laboratory measures between the case and control groups was observed. The folic acid level between the gender groups was not significantly different either.

Folate is found in green vegetables, fruits, and animal sources like liver (22). To date, many studies discussed the cause and pathogenesis of FS. In a study done by Abdel Hameed et al., it was suggested that zinc and iron deficiency can be the potential causes of FS in children (8). Other studies have also reported that iron deficiency anemia was significantly higher in febrile convulsing children

Table 2. Distribution of gender with seizure type in the case group.

	Complex seizure	Simple seizure	P-value
Boy	9 (81.8%)	21 (55.3%)	0.11*
Girl	2 (18.2%)	17 (44.7%)	
Total	11 (22.4%)	38 (77.6%)	

Table 3 shows the folic acid levels in the case and control groups. As can be seen, the mean folic acid level in cases and controls was 7.07 ng/mL and 9.89 ng/mL respectively, and the difference is statistically significant (P-value < 0.001).

Table 3. Comparing the mean serum folic acid levels in cases vs controls.

	Controls	Cases	P-value
Mean serum folic acid*	9.89 (± 4.01)	7.07 (± 3.32)	< 0.001

* nanograms per milliliter

cases and controls, and no statistically significant difference was observed between the two groups (P-value = 0.73).

compared to children who did not have a seizure in the course of their fever (15, 23, 24).

A few studies showed that low cobalamin levels and higher folate levels may be associated with seizures in febrile children, but the association is not fully understood yet. Osifo et al. researched the association of folic acid and febrile seizures in children between 8 and 60 months with fever (17). In this study, they reported that serum and red blood cell folic acid levels were higher in convulsing febrile children compared to non-convulsing febrile children (17). Ergo, they suggested that folic acid concentration in serum and red blood cells may be the cause of seizure in febrile children. In another study, Osifo et al. compared B12 and folic acid levels in 40 febrile patients and healthy children as a control group (18). They found that B12 levels were significantly lower in febrile children and especially lower in the febrile convulsing subgroup (18). Moreover, the mean B12 level in the cerebrospinal fluid (CSF) was not different between groups. It was also stated that folic acid levels were higher in febrile patients with the highest levels in the FS group. But, no significant difference between CSF levels in the febrile convulsing and

non-convulsing groups was seen (18). Note that in the present study, we only assessed the serum level of folic acid.

In contrast with these findings, our study showed that folic acid levels are significantly lower in febrile convulsing children compared to children with fever who did not contract seizure. It may be due to the fact that folic acid is an essential component in DNA replication and has been found to be a key element in nervous system development and functions such as synaptic modulation (20).

Ozkale et al. performed a similar study in 2015 on 104 children with FS and 75 febrile children without seizure as the control group in order to evaluate how B12, folic acid, and homocysteine levels were associated with FS (19). In the Ozkale study, 87.5% of convulsing patients were reported to have simple seizure whereas, in our study, 77.5% and 22.5% were reported to have simple and complex seizures respectively. They concluded that B12 deficiency did not significantly differ in case and control groups, but B12 levels were significantly lower in the case group (P-value < 0.05) (19). On the other hand, homocysteine and folic acid levels were not different between cases and controls.

In the Ozkale study, the folic acid levels were lower in low-grade fever (37.5 °C to 39 °C) and in patients with three or more episodes of seizure (19). Therefore, they concluded that lower folic acid levels are related to the recurrence of FS besides a lower threshold for seizure with fever.

As discussed, while some articles' findings are consistent with our results, some reported different results or similarly mentioned a lower serum level of folic acid in FS patients but the difference between the case and control groups was not significant. The difference in results may be related to the sample size and the characteristics of the studied population such as the severity of fever and unknown underlying conditions. Further studies with a larger population size and more controlled characteristics are therefore recommended.

Limitations

While based on previous articles statistical analysis suggested having around 60 patients in each group for 95% confidence and 80% power, we were restricted to 50 patients in each group due to the limited number of eligible patients and time. Besides, we only assessed the serum level of folic acid while some articles also evaluated the cerebrospinal fluid level.

Conclusion

Our findings indicate that in contrast to some existing results, the serum folic acid levels are sig-

nificantly lower in febrile children who contract seizure in course of their illness.

Conflict of Interest

The authors declare no conflict of interest.

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