



Serum Vitamin B12 Level of Children and Its Clinical Relationship with Febrile Seizures

Çocuklarda Vitamin B12 Kan Düzeyi ve Ateşli Nöbetlerle Klinik İlişkisi

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Abstract

Objective: In the present study, our aim was to investigate the correlation between vitamin B12 levels and febrile seizures (FS) in the pediatric population.

Method: The study included a total of 104 patients, comprising 50 children who were admitted with FS and 54 healthy children who served as the control group. Demographic characteristics, seizure types, biochemical parameters (glucose, Na, K, Ca, Mg, P), infection markers (C-reactive protein, procalcitonin) and the serum levels of vitamin B12 in the patients were retrospectively examined by reviewing the records in the hospital database.

Results: Demographic parameters were similar between groups. The median age of the children in the FS group was 21.6±11.6 months. The mean temperature of the patients measured by tympanic thermometer during the seizure was 38.3±0.29, 76% of the patients presented with simple FS, 22% with complex FS. In the etiology, upper respiratory tract infections was defined as the most common (72%) cause. The serum vitamin B12, sodium, potassium, calcium, magnesium, phosphorus and platelet values of the febrile convulsion group were statistically lower than the control group.

Conclusion: In the course of our research, we observed a significant decrease in vitamin B12 levels among the FS group compared to the control group. These findings suggest that low levels of vitamin B12 may contribute to an elevated risk of FS.

Keywords: Child, febrile seizures, vitamin B12

Öz

Amaç: Çalışmamızda çocuklarda febril konvülsiyon (FK) ile vitamin B12 düzeyleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Yöntem: Çalışmaya FK ile başvuran 50 çocuk ve kontrol grubu olarak 54 sağlıklı çocuk olmak üzere 104 hasta dahil edildi. Hastaların demografik özellikleri, nöbet tipleri, biyokimyasal parametreler (glikoz, Na, K, Ca, Mg, P), enfeksiyon belirteçleri (C-reaktif protein, prokalsitonin) ve serum vitamin B12 düzeyleri hastane veri tabanından retrospektif olarak incelendi.

Bulgular: Demografik parametreler gruplar arasında benzerdi. FK grubunda ortalama yaş 21,6±11,6 aydı. Hastaların nöbet sırasında timpanik termometre ile ölçülen ortalama ateşi 38,3±0,29 olup, hastaların %76'sı basit FK, %22'si kompleks FK ile başvurdu. Etiyolojide en sık (%72) üst solunum yolu enfeksiyonu olarak tanımlandı. FK geçiren grubun serum vitamin B12, sodyum, potasyum, kalsiyum, magnezyum, fosfor ve trombosit değerleri kontrol grubuna göre istatistiksel olarak düşüktü.

Sonuç: Yaptığımız çalışmada, FK grubunda vitamin B12 düzeyleri, kontrol grubuna göre anlamlı olarak düşük bulunmuştur. Düşük B12 vitamini düzeylerinin artmış FK riskine katkıda bulunabileceğini düşünüyoruz.

Anahtar kelimeler: Çocuk, febril konvülsiyon, vitamin B12

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Introduction

According to the International League Against Epilepsy (ILAE), febrile seizure (FS) is defined as a seizure associated with a febrile illness without the presence of central nervous system (CNS) infection or a specific cause (such as acute electrolyte imbalance, metabolic disorder, trauma, intoxication) in children aged 6 months to 5 years who have not experienced prior afebrile seizures (1-3). FSs are acknowledged the most prevalent neurological disorder in the pediatric population (3,4). The frequency and occurrence of FS demonstrate heterogeneity, contingent upon geographical, socio-economic, and genetic factors. In studies conducted internationally, it has been reported that around 2-5% of neurologically healthy children experience at least one FS during their childhood (1,5,6). In a study conducted in our country, FS rate was reported as between 2.6% and 5.8% (4). FSs are observed to be more frequent in boys compared to girls, and they are most commonly observed between the ages of 12 and 18 months (1,4).

FSs may be classified according to their physical characteristics, duration (simple or complex), and their recurrence rate (1). FSs can be categorized into three groups: simple FS, complex FS, and febrile status epilepticus. A simple FS is characterized by a generalized, typically tonic-clonic, seizure that is induced by fever and lasts for a maximum of 15 minutes. It does not recur within 24 hours. A complex FS is a seizure lasting longer than 15 minutes which is focal and/or recurrent within 24 hours. Febrile status epilepticus is defined as a prolonged febrile seizure lasting for more than 30 minutes, or recurring within 30 minutes without the return of consciousness (1,7). Viral infections account for approximately 80% of the cases of fever that lead to FS (7,8). Roseola infantum (exanthem subitum), influenza A and human coronavirus HKU1 have been identified as the most significant viral infections associated with an increased risk of FS. These viral infections play a notable role in triggering FS in susceptible individuals, particularly young children (1,5,9). In addition it has been documented that the incidence of FS exhibits a transient elevation within a few days following the administration of specific vaccines; namely combined diphtheria-tetanus toxoids-whole cell pertussis and measles vaccines (1,10). Other significant etiologies of FS include viral upper respiratory tract infections (URTIs), pharyngitis, otitis media, and gastroenteritis (1,5). Moreover, research findings have indicated that deficiencies in vitamin B12, folic acid, selenium, calcium, and magnesium have been associated with an elevated risk of febrile seizures (11-15).

Vitamin B12 plays a vital role in neural myelination, synaptogenesis, and neurotransmitter synthesis, all of which have potential implications for cognitive development (14-16). Vitamin B12 deficiency in early childhood has been associated with many factors that negatively affect the child's neurological development, including impaired cognitive development (14). Absolutely, apart from its role in neural myelination, synaptogenesis, and neurotransmitter synthesis, vitamin B12 also plays a crucial role in various other biological processes. These include DNA synthesis, where it is essential for the formation of nucleotides, and methylation reactions, which are vital for regulating gene expression and other cellular functions (16,17). Studies on FS have reported that children with FS have lower serum vitamin B12 levels and lower folic acid levels may lead to recurrence of FSs (13,18). In the present study, our main objective was to explore whether there is an association between low serum vitamin B12 levels and FS in children who were referred to the pediatric outpatient clinic for this condition. Additionally, we aimed to determine if the serum vitamin B12 level can be considered a potential risk factor for the occurrence of FSs in this particular population.

Materials and Methods

Between January 2021 and December 2021, a total of 50 pediatric patients with a recent history of FS who presented at the Pediatric Outpatient Clinic of University of Health Sciences Turkey, İstanbul Bağcilar Training and Research Hospital, were enrolled in the study, along with 54 healthy children who had no previous history of FS and attended the pediatric outpatient clinic for routine check-ups. Between January 2021 and December 2021, 50 pediatric patients with a history of FS who applied to the University of Health Sciences Turkey, İstanbul Bağcilar Training and Research Hospital Pediatric Outpatient Clinic and 54 healthy children who had no history of FS before and applied to the Pediatric outpatient clinic for routine control were included in the study. Our study was approved by İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (dated: 04/10/2021, number: E-10840098-772.02-4983). Our study was carried out in accordance with the Helsinki criteria. While the accepted reference value for serum vitamin B12 level is 180-1165 pg/dL (13), the observed vitamin B12 levels in our patients were notably higher at 400 pg/dL. However, intriguingly, within the FS subgroup, the serum vitamin B12 levels were found to be significantly lower compared to the control group.

The patients included in the study were between 6 months and 5 years old. The patients were grouped according to their gender as boys and girls. Simple FS was defined as primary generalized, tonic-clonic seizures lasting less than 15 minutes and not recurring within 24 hours. Sizuers with focal onset, lasting longer than 15 minutes or recurring within 24 hours, with at least one of the following features were defined as complex FS. Febrile status epilepticus is defined as a prolonged febrile seizure lasting for more than 30 minutes, or recurring within 30 minutes without the return of consciousness (1,7,19). Patients with CNS infection or chronic neurological disease, electrolyte imbalance, metabolic disorder, intoxication or trauma and patients who received vitamin B12 supplements were excluded from the study.

According to these criteria, 104 patients, including 50 children admitted with FS and 54 children without any seizure in the similar age group were included in our study. Demographic characteristics, seizure types, biochemical parameters (glucose, Na, K, Ca, Mg, P), infection markers [C-reactive protein (CRP), procalcitonin (PCT)] and serum vitamin B12 levels of the patients were retrospectively scanned from the hospital database and recorded in an Excel file.

Serum glucose, sodium, potassium, magnesium, phosphorus, calcium and vitamin B12 levels were determined using the Hitachi 7600-020 automatic biochemical analyzer. Serum PCT was determined with the Swiss Roche Cobas E601 electrochemiluminescence immunoassay analyzer. Calibration solution, reagents and quality control products were all supplied by Roche.

Statistical Analysis

The data were evaluated in the statistical package program of IBM SPSS Statistics Standard Concurrent User V 26 (IBM Corp., Armonk, New York, USA). Descriptive statistics were expressed as number of units (n), percent (%), mean ± standard deviation, median (M), minimum, maximum and interquartile range. The normal distribution of the data of numerical variables was evaluated with the Shapiro-Wilk normality test. Comparisons of the two groups for numerical variables were made with the t-test for independent samples if the data were normally distributed, and with the Mann-Whitney U test if they were non-normally distributed. Focus of fever between groups was compared by using One-Way Analysis of Variance if the data were normally distributed, and Kruskal-Wallis analysis if the data were non-normally distributed. In case the One-Way Analysis of Variance

result was found to be significant, Tukey test was used as a (post-hoc) multiple comparison test. Pearson chi-square and Fisher's Exact tests were used to compare the groups according to gender. A p-value of <0.05 was considered statistically significant.

Results

Based on the data presented in Table 1, the study comprised a total of 104 patients, with 50 patients included in the FS group and 54 patients in the control group. In the FS group, the number of male patients was 36, accounting for 72.0% of the group. In contrast, the control group had 30 male patients, representing 55.6% of the group. The difference in the proportion of male patients between the two groups was not statistically significant (p>0.05). The median age was 21.6±11.6 months in the febrile convulsion group and 20.5±11.2 months in the control group. There is no statistical difference between the study population and control group regarding age of the subjects (p>0.05).

Considering the descriptive characteristics of the patients presenting with FS according to Table 2, 76% (n=38) of the patients presented with simple FS, 22% (n=11) with complex FS, and 1 patient corresponding to 2% with febrile status epilepticus. When the focus of fever was examined, URTIs was determined in 72% (n=36), acute gastroenteritis in 14% (n=7), and other causes of fever in 12% (n=6) of the patients.

Table 3 presents the means of various blood indices, biochemical parameters (glucose, Na, K, Ca, Mg, P), infection markers (CRP, PCT) and serum vitamin B12 levels for the FS group, along with a comparison to the corresponding means of the control group.

According to the table, there was no significant difference observed between the hemoglobin (Hb) values of the FS

Table 1. Comparison of descriptive characteristics of the groups

	Groups		Test statistics	
	Febrile convulsion n=50	Control n=54	Test value	p-value
Gender, n (%)			3.028 [†]	0.104
Male	36 (72.0)	30 (55.6)		
Female	14 (28.0)	24 (44.4)		
Age, (years)			0.765 [*]	0.444
Mean ± SD	21.6±11.6	20.5±11.2		
M (min-max)	17.5 (8-58)	17.0 (8-51)		

SD: Standard deviation, M: Median, †: Chi-square test, *: Mann-Whitney U test

and control groups ($p>0.05$). However, the leukocyte [white blood cell (WBC)] count showed a statistically significant difference, with higher values in the FS group compared to the control group ($p<0.05$). Moreover, the infection markers, CRP, PCT, and glucose levels in the FS group were significantly higher than those in the control group ($p<0.001$).

The vitamin B12 ($p<0.05$), sodium, potassium, calcium, magnesium, phosphorus and PLT values of the FS group were statistically lower than the control group (Table 3).

According to Table 4, there is no statistical difference between the descriptive features and laboratory values of the simple and complex FS groups ($p>0.05$).

Discussion

FS is a convulsive disorder that is common in childhood and its underlying causes have not been fully explained. It is defined as a convulsion occurring during a febrile illness in patients without neurological infection, metabolic disorder or a history of FSs (2,20). Studies on FS have emphasized that children with FSs have lower serum vitamin B12 levels (13). In our research, we observed that the vitamin B12 levels were notably lower in the FS group when compared to the control group.

In the current investigation, we found no statistically significant difference in terms of gender and age distribution between the FS group and the control group.

Table 2. Descriptive characteristics of febrile convulsion group (n=50)

Gender, n (%)	
Male	36 (72.0)
Female	14 (28.0)
Age, (years)	
Mean \pm SD	21.6 \pm 11.6
M (min-max)	17.5 (8-58)
Fever, (celcius)	
Mean \pm SD	38.30 \pm 0.29
M (min-max)	38.30 (38.00-39.80)
Seizure classification, n (%)	
Simple	38 (76.0)
Complex	11 (22.0)
Status	1 (2.0)
Focus of fever, n (%)	
AGE	7 (14.0)
URTI	36 (72.0)
Teething	6 (12.0)

Sd: Standard deviation, M: Median

In the FS group, there were 36 male patients, accounting for 72% of the group and 14 female patients, representing 28% of the group. In concordance with our study, male predominance was reported in other studies (21,22).

Table 3. Comparison of laboratory values between groups

	Groups		Test statistics	
	Febrile seizures n=50	Control n=54	Test value	p-value
Hb	11.46 \pm 1.05	11.27 \pm 1.03	0.914 [†]	0.363
Sodium	134.92 \pm 2.54	137.85 \pm 1.82	6.701 [†]	<0.001
Potassium	4.41 \pm 0.46	4.60 \pm 0.36	2.389 [†]	0.019
Calcium	9.41 \pm 0.51	10.03 \pm 0.45	6.619 [†]	<0.001
Magnesium	2.026 \pm 0.150	2.116 \pm 0.194	2.623 [†]	0.010
Phosphorus	5.13 \pm 0.58	5.36 \pm 0.51	2.092 [†]	0.039
WBC	10.560 (6.437)	8.945 (4.665)	2.394	0.017
PLT ($\times 10^3$)	280.5 (135.2)	318.0 (132.0)	2.189	0.029
CRP	4.85 (15.93)	0.43 (1.53)	5.264	<0.001
Procalcitonin	0.14 (0.17)	0.05 (0.09)	4.934	<0.001
Glucose	111.5 (31.0)	84.5 (9.2)	6.607	<0.001
Vitamin B12	401 (175)	441 (228)	1041 [*]	0.044

Data are expressed as mean \pm standard deviation or median (interquartile range) values. [†]: Independent samples t-test, ^{*}: Mann-Whitney U test, Hb: Hemoglobin, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein, Normal ranges: Vitamin B12 180-1165 pg/mL (13)

Table 4. Comparison of descriptive characteristics and laboratory values according to seizure classification

	Groups		Test statistics	
	Simple n=38	Complex n=11	Test value	p-value
Gender, n (%)				
Male	28 (73.7)	8 (72.7)	0.004	>0.999
Female	10 (26.3)	3 (27.3)		
Age	17.0 (10.5)	18.0 (12.0)	0.552 [*]	0.581
Hb	11.45 \pm 0.83	11.49 \pm 1.71	0.089 [†]	0.929
Na	134.84 \pm 2.72	135.00 \pm 2.00	0.179 [†]	0.859
K	4.36 \pm 0.42	4.40 \pm 0.27	0.288 [†]	0.775
Ca	9.34 \pm 0.51	9.54 \pm 0.31	1.197 [†]	0.237
Mg	2.03 \pm 0.14	1.98 \pm 0.16	0.948 [†]	0.348
Phosphorus	5.11 \pm 0.54	5.07 \pm 0.55	0.190 [†]	0.850
WBC	10.560 (6.325)	10.030 (8.272)	0.264 [*]	0.792
PLT ($\times 10^3$)	289 (124.5)	280 (185.2)	0.048 [*]	0.962
CRP	4.47 (17.08)	3.78 (12.18)	0.383 [*]	0.701
Procalcitonin	0.12 (0.25)	0.23 (0.14)	0.336 [*]	0.737
Glucose	112.0 (29.0)	115.5 (39.0)	0.647 [*]	0.517
B12	425 \pm 158	335 \pm 120	1.75 [†]	0.087

Data are expressed as mean \pm standard deviation or median (interquartile range) values. [†]: Independent samples t-test, ^{*}: Mann-Whitney U test, WBC: White blood cell, PLT: Platelet, CRP: C-reactive protein

In our research, we observed that the median age of patients referred to the pediatric emergency department with FS was 21.6 ± 11.6 months, which aligns with the findings reported in the existing literature (1,4,7,12). Indeed the accepted body temperature threshold for FS has been reported as 38°C in certain studies, while in others, it is considered to be 38.5°C and above (4). In the study of Sfaihi et al. (23) on 482 cases, he stated that the mean body temperature was above 39°C when the patients with FS referred to the hospital. In a study of 457 cases by Canpolat et al. (4) in our country, the body temperature was below 39°C in 24.7% of the cases and above 39°C in 75.3% of the cases. In our study, the mean fever value in patients with FS was 38.3°C ($38.00\text{-}39.80^\circ\text{C}$) (4). In accordance with our study 80-85% of cases referring to the emergency department with FS have simple FS and 10-15% have complicated FS (4,24,25). FSs are associated with viral infections in around 80% of patients who experience them. Additionally, certain infections, such as URIs, pharyngitis, acute otitis media, lower respiratory tract infection, urinary tract infection, and acute gastroenteritis, have been identified as potential precipitating factors for FS. These infections can trigger the onset of FS in susceptible individuals, especially in young children (24,26,27). Consistent with the literature, URIs were in the first place in our study ($n=36$, 72%), followed by acute gastroenteritis ($n=7$, 14%), urinary tract infections ($n=1$, 2%) and other factors (teething..) ($n=6$, 12%) (1,4,13,28).

Upon comparison of the laboratory parameters between the FS group and the control group, no statistically significant difference was found in terms of Hb values. Similarly to our study in two studies conducted in our country, no difference was found in Hb values between the groups (13,22).

WBC, CRP, PCT and glucose values of the group referring with FS were statistically higher than the control group. It was thought that the increase in glucose level compared to the control group may be due to stress, and the results were found to be similar with other studies (29,30). However, sodium, potassium, calcium, magnesium, phosphorus and PLT values were statistically lower than the control group. In parallel with our study, low platelet levels were found in children referring with FS elsewhere (8). In addition, studies have emphasized low electrolyte values in children referring with FS, and it has been reported that low levels of sodium, calcium, and magnesium may be encountered, similar to our study (11,12).

Vitamin B12 is vital for humans, especially for the central nervous system. Vitamin B12 deficiency in early childhood has been associated with many factors that negatively affect the child's neurological development, including impaired cognitive development (14). In our study, vitamin B12 values were statistically lower in patients who referred to the pediatric outpatient clinic with FS compared to the control group. Similarly in the studies performed, vitamin B12 levels were found to be lower than the control group in patients presenting with FS and the study suggested that low vitamin B12 levels might be involved in the etiopathogenesis of FS (13,22).

In this present study, there is no statistical difference between the descriptive features and laboratory values of the simple FS and complex FS groups. In a study conducted in our country with a small sample size, it was stated that there were differences in Hb between the groups, while no statistical difference was found in our study (31).

Study Limitations

The limitations of our study are it is being retrospective, single-center and the number of patients is small. In addition, because it is retrospective, the family history of the patients and the causes that may increase the risk of recurrence could not be fully questioned. There is a need for multicenter, larger studies on the precise role of B12 deficiency in febrile seizures.

Conclusion

76% of our patients were simple FS and 22% were complicated FS. URIs were the most common underlying cause. The observation that vitamin B12 levels were significantly lower in the group presenting with FS compared to the control group suggest that low vitamin B12 levels may play a role in the increased risk of FS.

Ethics

Ethics Committee Approval: Our study was approved by İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee (dated: 04/10/2021, number: E-10840098-772.02-4983).

Informed Consent: Informed consent was obtained

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: O.Y., M.T.K., M.E., A.Ö., Design: O.Y., M.T.K., M.E., H.S.S., Ö.B., Data Collection or Processing: O.Y., H.S.S., A.Ö.,

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