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RESEARCH ARTICLE

Comparison of first-episode psychosis and first-episode mania patients with healthy controls regarding serum vitamin B12 and folate levels

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ABSTRACT

Objective: There is information in the literature that vitamin B12 and folate play a role in the etiology of schizophrenia and bipolar disorder. On the basis of this idea, in this study, we compared patients with schizophrenia and bipolar disorder in their first episode of illness with healthy controls (HC) regarding their vitamin B12 and folate levels.

Method: In this study, vitamin B12 and folate blood levels of patients with first-episode psychosis (FEP) and first-episode mania (FEM) were compared with those of HC. Sixty-seven volunteers aged 18–65 years without any additional psychiatric or organic diseases were recruited from all three groups.

Results: According to the statistical analysis, vitamin B12 blood level was significantly lower in the FEP group than in HC (p=0.002). According to the logistic regression analyses, it was determined that vitamin B12 blood levels significantly predicted being in the FEP group (p=0.009), whereas neither vitamin B12 nor folate blood levels were associated with being in the FEM group. The predictive effect of vitamin B12 deficiency for being in the FEP group was statistically significant (p=0.002), whereas the diagnosis of vitamin B12 deficiency alone was not associated with being in the FEM group.

Conclusion: Low vitamin B12 serum levels can be seen in patients with FEP. In these patients, vitamin B12 replacement therapy may increase the effect of antipsychotic therapy.

Keywords: First-episode mania, first-episode psychosis, folate, vitamin B12

INTRODUCTION

Schizophrenia is a progressive mental disorder characterized by positive, negative, and cognitive symptoms and causes impaired social and occupational functionality (1). Cognitive symptoms may be observed before the disease is diagnosed in patients with schizophrenia. The progressive clinical course of the disease impairs the patient's functionality and may negatively affect the professional and social life of the patient (2). Genetic factors, substance use, perinatal complications, neurochemical changes, and neurodevelopmental disorders have been suggested as risk factors for schizophrenia (3).

Bipolar disorder is a mood disorder defined by depressive, manic, hypomanic, and mixed mood episodes and causes severe impairment in social,

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occupational, and family life (4). In manic episodes of bipolar disorder, symptoms such as high mood, restlessness, risky actions, decreased need for sleep, grandiosity, increased activity toward a goal, pressured speech, and flight of ideas are present (5). According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), a single manic episode is sufficient for diagnosing bipolar disorder (6). Although the etiology of bipolar disorder has not been clearly explained so far, genetic, biochemical, and psychosocial factors have been emphasized (7).

Vitamin B12, also known as cobalamin, is water soluble and cannot be synthesized in the human body (8). Vitamin B12 is involved in the erythrocyte production process, nervous system functions, and DNA synthesis in the bone marrow, and it can also be a cofactor in various enzymatic reactions (9). Memory impairment, irritability, depression, psychosis, and dementia can be seen in patients with vitamin B12 deficiency (10). Folate provides the transport of one-carbon units in one-carbon metabolism, which has an essential role in nucleic acid and amino acid metabolism. It functions as a folate substrate and coenzyme to transfer the methyl group to methionine and synthesize purines and pyrimidines. Folic acid intake is mandatory in the diet, as humans cannot synthesize para-aminobenzoic acid and bind glutamate to pteroic acid (11).

Decreased vitamin B12 and folate levels, involved in one-carbon metabolism, cause increased homocysteine concentration (12). In addition to being a molecule with toxic effects on neural and vascular development, homocysteine causes epigenetic changes by affecting the methylation of catecholamines, phospholipids, and chromatin (13). Increased levels of homocysteine and deficiencies of vitamin B12 and folate are thought to be risk factors for many diseases such as neurodevelopmental problems, heart diseases, schizophrenia, stroke, mood disorders, and cognitive weakness (14). Recent studies have reported that blood levels of vitamin B12 and folate were lower in patients with bipolar disorder and schizophrenia than in healthy controls (HC) (15–17).

The development of neuropsychiatric symptoms in vitamin B12 and folate deficiency has increased interest in these two essential vitamins. It has been hypothesized that vitamin B12 deficiency may have an important role in developing psychosis because the replacement of vitamin B12 improves the psychotic symptoms in patients with schizophrenia. Additionally, some studies have indicated that vitamin B12 levels are lower in patients with psychotic depression than in nonpsychotic depression patients (18). Moreover, low maternal folate levels are also thought to increase the risk of developing schizophrenia (19).

These findings inferred that vitamin B12 and folate deficiencies might be associated with the etiopathogenesis of schizophrenia and bipolar disorder. Therefore, the present study aimed to compare vitamin B12 and folate levels between patients with first-episode psychosis (FEP) of schizophrenia and first-episode mania (FEM) of bipolar disorder and HC. The associations between vitamin B12 and folate deficiencies and FEP and FEM were also examined. Although many studies evaluated vitamin B12 and folate levels in patients with schizophrenia and bipolar disorder, this study is the first to compare these two groups because it was conducted in FEP and FEM patients who did not receive psychotropic medication or vitamin replacement therapy.

METHOD

Study Design and Sample

This study has a descriptive and retrospective design, and approval was obtained from the Ethics Committee of Adiyaman University Faculty of Medicine (IRB: 17/12/2019 – 2019/9-6). The protocol was approved based on the ethical standards of the Declaration of Helsinki. Written informed consent was obtained from all participants and, if any, their legal representatives/guardians following a thorough explanation of the study procedure. In this study, patients with schizophrenia and bipolar disorder, who were experiencing their first episodes, were included according to DSM-5. They were applied to Adiyaman Training and Research Hospital, Department of Psychiatry, between January 1, 2015, and December 31, 2019. In addition, the patients received inpatient treatment in the psychiatry clinic during the FEP and the FEM because of the treatment need. In this study, healthy individuals who applied to the psychiatry outpatient clinic for job examination, license application examination, and military service examination were used as the control group. People without psychiatric diagnoses were selected based on their statements and medical records. Care was taken to ensure that the control and patient groups were similar in age and gender.

Table 1: Comparison of FEP, FEM, and HC in terms of vitamin B12 and folate values

Parameter	Group	Mean±SD	One-way ANOVA		Post hoc†
			F	p	
Vitamin B12	FEP[a]	174.26±71.87	6.151	**0.03**	c>a
	FEM[b]	195.22±84.09			
	HC[c]	223.28±86.74			
Folate	FEP[a]	6.69±2.81	2.314	0.102	Not significant
	FEM[b]	7.40±3.03			
	HC[c]	7.78±3.03			

†: Tukey's HSD; FEP: First-episode psychosis; FEM: First-episode mania; HC: Healthy controls. P<0.05 statistical significance level (bold values).

The sample size was calculated as a result of the evaluation of the study by Kale et al. (17). According to the power analysis we performed, when p<0.05, power of 0.80, enrollment ratio=1, and effect size of 0.5 were accepted. The standard t-test/one-way ANOVA test was applied according to the study of Kale et al. (group 1: mean 5.40, standard deviation 3.99; group 2: mean 3.46, standard deviation 1.71; mean difference between groups: p<0.05). As a result, it was determined that at least 66 people must be in each group.

Schizophrenia and bipolar disorder patients aged 18–65 years and hospitalized in our hospital during the first episode of the illnesses were included in the study. The conclusive diagnoses of schizophrenia and bipolar disorder of these first-episode patients were confirmed after a 6-month follow-up period in our outpatient unit. Patients with epilepsy, alcohol and substance dependency, or who used psychotropic drugs before the FEP and FEM were excluded from the study (n=8 and n=6, respectively). Those who received vitamin replacement therapy before the first episode were excluded from the study (n=4). The control group was selected similar to the patient group regarding age and gender. Those with malnourishment, epilepsy, pregnancy, lactation, vitamin replacement therapy, and alcohol and substance dependence that may affect the vitamin B12 and folate levels of the control group were excluded from the study (n=6). Those with a history of psychotropic drug use were not included in the control group (n=3).

Laboratory Analyses

Venous blood examinations of the patients admitted to our inpatient unit with either FEP or FEM were performed during their hospitalization. All blood count measurements were made in Adiyaman Training and Research Hospital Biochemistry Laboratory. Serum vitamin B12 and folate levels were measured with the UniCel® DxI 800 immunoassay system (Beckman Coulter, Inc., Brea, CA, USA). The evaluation was made according to the data of Adiyaman Training and Research Hospital Biochemistry Laboratory. Serum folate levels between 2.50 and 20.00 pg/mL and serum vitamin B12 levels between 189 and 833 pg/mL were considered normal.

Statistical Analyses

IBM SPSS (Statistical Package for the Social Sciences) version 22.0 program was used for statistical analysis. Descriptive statistics and continuous variables were given as mean±standard deviation, and categorical variables were frequency and percentage. The normal distribution of the data, kurtosis, and skewness values were evaluated with the Shapiro–Wilk test, and Levene's test was used for the homogeneous distribution of the data. A one-way ANOVA test was used to compare continuous variables of the groups. Tukey's HSD test, one of the post hoc analyses, was used to determine the differences between the groups. The Chi-squared analysis was used to determine the difference in the prevalence of vitamin B12 deficiency between the groups. The logistic regression analysis was used to examine vitamin levels as potential predictors of being in the FEP or FEM groups. The statistical significance level was accepted as p<0.05 for all values.

RESULTS

Sociodemographic Data

The sample of the study included 67 (37 M, 30 F) FEP patients, 67 (35 M, 32 F) FEM patients, and 67 (33 M, 34 F) HC. The mean age of males with FEP was 24.62±4.49 years, and the mean age of females with FEP was 30.46±11.80 years. The mean age of males with FEM was 27.11±6.86 years, and the mean age of

Table 2: Comparison of FEP, FEM, and HC by gender in terms of vitamin B12 and folate values

Gender	Parameter	Group	Mean±SD	One-way ANOVA		Post hoc†
				F	p	
Male	Vitamin B12	FEP[a]	164.32±54.47	4.557	**0.013**	c>a
		FEM[b]	177.89±77.11			
		HC[c]	216.70±89.92			
	Folate	FEP[a]	6.24±1.64	3.124	**0.048**	c>a
		FEM[b]	6.61±2.99			
		HC[c]	7.67±2.61			
Female	Vitamin B12	FEP[a]	186.53±88.27	1.992	0.142	Not significant
		FEM[b]	214.19±88.45			
		HC[c]	229.68±84.39			
	Folate	FEP[a]	7.25±3.76	0.734	0.483	
		FEM[b]	8.28±2.86			
		HC[c]	7.87±3.42			

†: Tukey's HSD; FEP: First-episode psychosis; FEM: First-episode mania; HC: Healthy controls. P<0.05 statistical significance level (bold values).

females with FEM was 27.66±8.17 years. The mean age of males in the HC was 26.90±8.14 years, and the mean age of females in the HC was 27.82±9.58 years. In the FEP group, the mean age of men was significantly younger than that of women (p=0.015). The FEP, FEM, and HC mean ages were 27.23±8.98, 27.38±7.48, and 27.37±8.85 years, respectively. There was no significant difference between the three groups regarding age (p=0.994).

Vitamin B12 and Folate Levels

Table 1 shows the mean and standard deviations of vitamin B12 and folate blood levels and the comparison of vitamin B12 and folate blood levels of the FEP, FEM, and HC groups. There was a significant difference between the groups in vitamin B12 levels (p=0.03). According to results of the post hoc analysis, vitamin B12 levels were significantly lower in the FEP group than in HC (p=0.002). There was no difference between the groups regarding folate levels (p=0.102).

The vitamin B12 and folate levels in FEP, FEM, and HC are based on gender and are compared in Table 2. Vitamin B12 and folate levels were significantly lower in male FEP patients than in healthy men (p=0.012 and p=0.045).

The frequency of vitamin B12 deficiency was 71.6% (n=48) in the FEP group, 58.2% (n=39) in the FEM group, and 38.8% (n=26) in the HC group. While folate deficiency was not detected in FEP and HC groups, only 1 patient (1.49%) in the FEM group had folate deficiency.

Table 3: Comparison of the groups in terms of prevalence of vitamin B12 deficiency

Group I	Group II	χ^2	p
FEP	FEM	2.654	0.103
	HC	14.607	<**0.001**
FEM	FEP	2.654	0.103
	HC	5.049	**0.025**

χ^2: Pearson's Chi-squared; FEP: First-episode psychosis; FEM: First-episode mania; HC: Healthy controls. P<0.05 statistical significance level (bold values).

The frequency of vitamin B12 deficiency in FEP, FEM, and HC groups is shown in Table 3. The frequency of vitamin B12 deficiency showed a significant difference between the groups (p=0.001). The frequency of vitamin B12 deficiency was significantly higher in the FEP group than in the HC group (p<0.001). In addition, the frequency of vitamin B12 deficiency in FEM patients was significantly higher than in HC (p=0.025). There was no significant difference in the frequency of vitamin B12 deficiency between the FEP and FEM groups (p=0.103).

The predictive potential of vitamin B12 and folate blood levels for being in either the FEP (FEP vs. HC) or the FEM (FEM vs HC) group was examined with logistic regression analyses shown in Tables 4 and 5, respectively. According to the logistic regression analyses, it was determined that vitamin B12 blood levels significantly predicted being in the FEP group (p=0.009; OR: 1.006; 95% CI: 1.001–1.010; Nagelkerke R^2 of 0.082), whereas neither vitamin B12 nor folate blood levels were associated with being in the FEM group.

Table 4: Predictive effects of vitamin B12 and folate levels in patients with FEP

Group	Independent variable	B	Wald	df	Odds ratio	p	95% Confidence interval	
							Lower	Higher
FEP	Vitamin B12 level	0.006	6.850	1	1.006	**0.009**	1.001	1.010
	Folate level	0.103	3.245	1	1.019	0.072	0.991	1.240
	Constant	-1.125	3.851	1	0.325	0.050		

Logistic regression analysis was used. Nagelkerke R^2 of the model: 0.082; χ^2: 12.224, and the overall percentage for the model is 66.7%; FEP: First-episode psychosis. P<0.05 statistical significance level (bold values).

Table 5: Predictive effects of vitamin B12 and folate levels in patients with FEM

Group	Independent variable	B	Wald	df	Odds ratio	p	95% Confidence interval	
							Lower	Higher
FEM	Vitamin B12 level	0.001	0.100	1	1.006	0.752	0.997	1.004
	Folate level	-0.020	0.166	1	1.019	0.684	0.888	1.081
	Constant	0.728	1.999	1	0.157	2.071		

Logistic regression analysis was used. Nagelkerke R^2 of the model: 0.002; χ^2: 0.247, and the overall percentage for the model is 66.7%. FEM: First-episode mania.

Table 6: Predictive effect of diagnosis of vitamin B12 deficiency in patients with FEP

Group	Independent variable	B	Wald	df	Odds ratio	p	95% Confidence interval	
							Lower	Higher
FEP	Vitamin B12 deficiency	0.986	9.417	1	2.682	**0.002**	1.428	5.036
	Constant	0.303	2.538	1	1.354	0.111		

Logistic regression analysis was used. Negelkerke R^2 of the model: 0.067; χ^2: 9.979, and the overall percentage for the model is 66.7%. FEP: First-episode psychosis. P<0.05 statistical significance level (bold values).

Table 7: Predictive effect of diagnosis of vitamin B12 deficiency in patients with FEM

Group	Independent variable	B	Wald	df	Odds ratio	p	95% Confidence interval	
							Lower	Higher
FEM	Vitamin B12 deficiency	0.122	0.162	1	1.129	0.688	0.624	2.043
	Constant	0.641	10.478	1	1.897	0.001		

Logistic regression analysis was used. Negelkerke R^2 of the model: 0.001; χ^2: 0.162, and the overall percentage for the model is 66.7%. FEM: First-episode mania.

The predictive potential of the diagnosis of vitamin B12 deficiency for being in either the FEP (FEP vs HC) or the FEM (FEM vs HC) group was examined with logistic regression analyses shown in Tables 6 and 7, respectively. The predictive effect of vitamin B12 deficiency for being in the FEP group was statistically significant (p=0.002; OR: 2.682; 95% CI: 1.428–5.036; Nagelkerke R^2 of 0.067), whereas the diagnosis of vitamin B12 deficiency alone was not associated with being in the FEM group.

DISCUSSION

According to our knowledge, this study is the first to compare vitamin B12 and folate levels between patients with FEP of schizophrenia and patients with FEM of bipolar disorder and HC. The main findings of the present study showed that (i) vitamin B12 deficiency and low levels of vitamin B12 predicted for being in the schizophrenia-FEP group, (ii) the

frequency of vitamin B12 deficiency was found higher in individuals with FEP of schizophrenia than in HC, (iii) the frequency of vitamin B12 deficiency was found higher in individuals with FEM of bipolar disorder than in HC, and (iv) the folate levels of the male participants with FEP of schizophrenia were lower than those of HC.

Although many studies have reported that vitamin B12 levels are lower in patients with schizophrenia than in HC (15,17,20–22), the association between vitamin B12 deficiency and schizophrenia is unclear. The results of this study have shown that vitamin B12 deficiency and low levels of vitamin B12 are associated with FEP. It can be explained by the role of vitamin B12 in homocysteine metabolism. Vitamin B12 is critical in converting homocysteine to methionine as a cofactor. As a result of low vitamin B12 levels, homocysteine cannot convert to methionine, and homocysteine levels increase in the brain. An increase in homocysteine levels stimulates glutamate receptors and decreases the tolerance of neurons against oxidative stress reactions. These reactions may lead to neurodegenerative processes related to the pathogenesis of schizophrenia. Additionally, it has been shown that a higher level of homocysteine is associated with deterioration of the neuronal membranes in the central nervous system by disruption of methylation. Namely, it can be said that low vitamin B12 levels negatively affect the neuroprotective mechanisms of one-carbon metabolism (17).

Another finding of the present study was that the frequency of vitamin B12 deficiency was higher in FEP patients (71.6%) and FEM patients (58.2%) than in HCs (38.8%). In a study conducted by Lerner et al. (21), it has been reported that the frequency of vitamin B12 deficiency is higher in patients with schizophrenia (50.8%) than in HC (25%). Yazici et al. (22) have reported that the frequency of vitamin B12 deficiency (<200 pg/mL) is 45.5% in patients with schizophrenia and 11.5% in HC. It seems that the present study's finding is similar to previous studies. Thus, it can be said that vitamin B12 deficiency is higher in patients with schizophrenia than in healthy individuals. Ozbek et al. (15) found that vitamin B12 levels in bipolar disorder patients were lower than in HC and reported that vitamin B12 levels could be used as a predictor in bipolar disorder.

On the other hand, the present study has shown no significant difference in folate deficiency between the patients and HC. However, some studies have indicated that folate deficiency is higher in patients with schizophrenia or bipolar disorder than in HC (15,17,21–24). A study conducted in Turkey found that the frequency of folate deficiency or low level of folate is higher in patients with schizophrenia than in HC (22). Kale et al. (17) found that serum folate levels were significantly lower in patients with FEP than in HC. Yazici et al. (25), in their study comparing schizophrenia patients with acute episodes and remission and the control group, found that vitamin B12 and folate levels were higher in patients with schizophrenia. Still, they attributed this to vitamin replacement therapy. The differences in the samples can explain these controversial findings. Namely, the present study sample consists of drug-naive patients, and the patients are not exposed to possible folate reducing the effect of antipsychotics. Some studies have indicated that antipsychotic agents can reduce serum folate levels (26). Misiak et al. (27) have reported that higher doses of olanzapine administration are associated with lower folate levels in patients with schizophrenia. In a study by Eren et al. (26), it has been shown that higher doses of typical antipsychotics were related to lower folate levels.

In a study conducted in a nonpsychiatric population, folate levels were lower in men than in women (28). In our study, folate levels were lower in FEP and FEM patients than in HC. However, when FEP and FEM patients were analyzed separately, this difference was only statistically significant in male FEP patients compared with male HC patients. The low folate levels in male FEP patients may be related to the role of folate in the homocysteine mechanism.

Regarding the results of our study and the literature, it is challenging to accept vitamin B12 deficiency as a single risk factor for the development of schizophrenia. However, based on our results, it can be argued that FEP is more associated with vitamin B12 deficiency than FEM.

This study has limitations in some respects. The most important limitation of this study was the inaccessibility of some information due to its retrospective nature. For example, the nutritional habits of patients and HC could not be evaluated. Diseases that may cause vitamin B12 deficiency, such as intrinsic factor deficiency, transcobalamin II deficiency, atrophic gastritis, helicobacter pylori-associated gastritis, and achlorhydria, could not be excluded. The severity of the diseases could not be evaluated; however, the severity may be related to vitamin B12 and folate levels. Although a significant association was found between low vitamin B12 levels and FEP, our results explained only a small part of this patient population.

In conclusion, our results suggest that lower levels of vitamin B12 may be suggestive of FEP, and further studies should be conducted on whether vitamin B12 replacement therapy increase the effect of antipsychotic therapy in the early stages of schizophrenia.

Contribution Categories		Author Initials
Category 1	Concept/Design	B.H.A.
	Data acquisition	Y.K.
	Data analysis/Interpretation	Y.K., B.H.A.
Category 2	Drafting manuscript	Y.K.
	Critical revision of manuscript	B.H.A.
Category 3	Final approval and accountability	Y.K., B.H.A.

Ethical Approval: Ethics Committee of Adiyaman University Faculty of Medicine approved the study protocol (IRB: 17/12/2019 – 2019/9-6).

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