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Research Article

Prevalence of Vitamin B12 and Folic Acid Deficiency in Patients with Severe Mental Disorders Admitted to Acute Psychiatric Unit and Review of the Literature

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Abstract

Introduction: Diet is increasingly recognized as a potentially modifiable factor influencing the development and treatment of psychiatric disorders. Vitamin B12 and folic acid deficiencies may have a significant causal contribution in the development and mental illnesses exacerbations.

Objectives: The main objective was to study the prevalence of vitamin B12 and folic acid deficiency in a group of psychiatric inpatients and to compare it with another cohort of Internal Medicine department. Also, a review of other nutritional epidemiological studies of psychiatric inpatients is carried out.

Methods: We conducted a cross-sectional descriptive study evaluating the prevalence of vitamin B12 and folic acid deficiency in newly psychiatric patients aged 18 years or more admitted to the acute hospitalization unit. Patients presenting a serum creatinine ≥2 mg/dL, advanced chronic liver disease, cognitive impairment, discharged or deceased with 48 hours after hospital admission were excluded. Matched controls were obtained from Internal Medicine department. Deficiency was considered with plasmatic levels lower to 200 pg/ml and 2.76 ng/ml for vitamin B12 and folic acid, respectively.

Results: 140 patients were included in the study, 70 patients of the Psychiatric unit and 70 patients of the Internal Medicine department. In total, 8 patients (11.4%) of the psychiatric cohort had vitamin B12 deficiency while folic acid deficiency was found in 27 (38.6%). The prevalence of these deficiencies obtained in the Internal Medicine cohort was identical. Mean values of cobalamin in controls were significantly higher than in psychiatric patients (p = 0.0381). Low folate levels were significantly associated with alcohol consumption and a correlation between elevated folate levels with age, female sex, and food disorder (n = 2) was obtained.

Conclusions: Vitamin B12 and folic acid deficiencies are prevalent among psychiatric inpatients, and there were no differences with respect to patients admitted to Internal Medicine department. The combined deficiency was more prevalent in the psychiatric inpatients than in patients from Internal Medicine department.

Keywords: Folic Acid Deficiency; Vitamin B12 Deficiency; Cobalamin Deficiency; Psychiatric Inpatients

Abbreviations

FA: Folic Acid; MCV: Mean Corpuscular Volume; BMI: Body Mass Index; Antipsych: Antipsychotics; Anticonv: Anticonvulsants; SSRIs: Selective Serotonin Reuptake Inhibitors; BZD: Benzodiazepines; PPI: Proton Pump Inhibitors; MTZ: Mirtazapine; TZD: Trazodone; APK: Antiparkinsonian Drugs; NSAID: Nonsteroidal Anti-inflammatory drugs; Sch: Schizophrenia; Dep: Depression; NS: Non-statistical Significance

Introduction

Diet is increasingly recognized as a potentially modifiable factor influencing the development and treatment of psychiatric disorders [1]. The deficiency of certain micronutrients with fundamental roles in the central nervous system metabolism, such as vitamin B12 and folic acid, may favor the onset and exacerbation of certain psychiatric disorders.

Vitamin B12 and folic acid are two essential water-soluble vitamins. Daily requirements are 2 µg and it is estimated reserves are sufficient to 3-4 years [5]. Folic acid is mainly acquired from diet: fruits, green leafy vegetables, legumes, and liver [2-4]. Minimum daily requirements are of 50-100 µg, and the deficit takes about 4 months to develop [5].

Both vitamins' metabolism is closely related, as they are essential in various metabolic pathways that take place in the central nervous system. Among other functions, they are necessary for purine and pyrimidine nucleotides synthesis and facilitate production of S- adenosyl methionine (SAM), a cosubstrate involved in methyl group transfers by promoting the conversion from homocysteine to methionine [6-8]. This metabolite is necessary to produce phosphatidylcholine and sphingomyelin, basic components of neuronal myelin sheaths [9].

Despite being proved the relationship between these vitamin deficiencies and neuropsychiatric symptoms, serum vitamin B12 and folic acid request is not yet an entirely implemented practice among psychiatric patients, both at outpatient level as in acute patients' units. Besides, there are not enough conclusions in actual literature about the kind of risk populations that may benefit from screening, the type of examination to be requested, how to cope with the treatment and the actual utility of vitamin replacement in the reversion of affective, cognitive, or psychotic symptoms [7].

Psychiatric patients often present poor nutrition, reduced self-care, frequent and long hospitalizations, high alcohol consumption rates, polymedication, and much of them show unstable and fragile economic status, social and family situation. All these factors contribute to consider them as a vulnerable population group most likely to suffer from malnutrition and specific nutrient deficiencies such as vitamin B12 and folic acid, especially those whose mental illnesses developed at early ages and that follow a chronic course.

Deficient dietary intake and malabsorption constitute the most common causes of cobalamin deficiency. Therefore, strict vegetarians and infants born to vitamin B12-deficient mothers are considered as high-risk groups. Malabsorption is more frequently observed in the elderly, mainly due to atrophic gastritis [10], being pernicious anemia an autoimmune disorder that produces an absolute loss of intrinsic factor [11] one of its most well-known causes. Other causes of malabsorption include ileal resection and gastrectomy, chronic pancreatitis, as well as the long-term use of some drugs [2,10,12,13].

Similarly, a poor diet, certain malabsorptive syndromes common to cobalamin deficiency and chronic diarrhea can produce folic acid deficiency, there are other situations that increase risk such as breastfeeding, pregnancy, alcoholism and the intake of certain drugs which interfere with the metabolism [2,10,13].

Hematological and neuropsychiatric alterations are the most frequent clinical manifestations related to cobalamin deficiency [14]. Nevertheless, these are often absent, since it expresses sub-clinical in most patients, and although low vitamin B12 prevalence is common, only 5-10% of patients show symptoms.

Signs and symptoms of both vitamin deficiencies are quite similar, being the main difference, the absence of neurological manifestations related to low folic acid levels. These include weakness, diarrhea, mouth ulcers, hair graying, glossitis, headache, irritability, and memory loss, among others. Within hematological alterations, megaloblastic anemia is the most persistent one, being common to both vitamin deficiencies [11,14,15].

Finally, it is worth noting the psychiatric manifestations caused by both deficiencies, being in some cases the first and only clinical signs. Mild cognitive impairment, dementia, mood changes (dep-

ression, agitation, mania), psychotic symptoms (auditory and visual hallucinations, suspicion, persecutory delusions, incoherent speech, and disorganized thought process), delirium and other disorders have been found. The incidence of these symptoms varies between 4 and 50% [3,7,9,15].

Both serum vitamin levels are often low in various psychiatric disorders, especially schizophrenia and depression. In addition, vitamin deficiency appears to be associated with poorer treatment response, longer and more severe episodes, and a more unfavorable clinical course [16,17]. Studies of folate and cobalamin supplementation in patients with these disorders have shown a significant recovery, both clinically and socially, suggesting the potential role of these vitamins in the treatment of these disorders and thus strengthening this association [18,19].

Few studies about both vitamin deficiencies prevalence in psychiatric patients have been done in our environment. Several epidemiological studies at global level have revealed significant deficiencies of vitamin B12 and folic acid in this kind of patients, in fact, the reported prevalence of a low serum cobalamin level among them varies between 5% and 30% and that of a low serum folate level does between 10 and 33% [8]. However, determining prevalence in these groups of individuals is a difficult task, as there is little agreement in the current literature about the magnitude of these deficits in control groups, such as inpatients from other hospitalization units, the general population, or the elderly [6].

The aim of this study was to determine the prevalence of vitamin B12 and folic acid in a group of hospitalized psychiatric patients in acute mental units and to analyze if their deficiencies are more prevalent in this group compared to patients admitted to Internal Medicine department without any psychiatric history. We also wanted to evaluate if the presence of a severe mental disorder predisposes to the deficiency of these vitamins.

Methods

We conducted a cross-sectional descriptive study evaluating the prevalence of vitamin B12 and folic acid deficiency in newly admitted psychiatric patients in the acute hospitalization unit of our hospital. All newly admitted patients with aged ≥18 years were consecutively included.

Patients presenting a serum creatinine ≥2 mg/dL, advanced chronic liver disease, cognitive impairment, discharged or deceased within 48 hours after hospital admission were excluded.

The control group was matched to avoid confusing factors (patients with psychiatric comorbidity, history of mental disorder and/or aged over 65 years were excluded).

Sociodemographic, clinical, anthropometric and laboratory variables including serum vitamin B12 and folic acid levels and the values of hemoglobin, hematocrit and mean corpuscular volume were collected in all patients upon admission the psychiatric unit. Specific surveys, scales or tests were used as needed. Thus, to evaluate social and family situation we used the Gijon's social and family evaluation scale, whereas nutritional status was assessed through the Mini Nutritional Assessment questionnaire (MNA).

All psychiatric diagnoses assigned to the patients were determined according to the ICD-10 classification of mental and behavioural disorders. The same variables were collected in the control group at the Internal Medicine department.

Normal vitamin B12 levels were considered between 200-931 pg/mL and folic acid between 2.7-20 ng/mL as established by the kit manufacturer of our laboratory.

Prior to the data collection, all patients received an informed consent to participate in the study. Only individuals who were able to understand and to provided information, and therefore their informed consent for inclusion therein were included. The sample was finally represented by 140 patients, 70 psychiatric patients and 70 controls.

The relationship between qualitative variables was analyzed using the Chi-squared test, whilst the relationship between qualitative and quantitative variables was analyzed using the T-student test or the Mann-Whitney U test. Subsequently, a bivariate analysis was made with the patients admitted to Internal Medicine department. A statistical level of significance was set whenever $p \leq 0.05$. All analyses were done by using the software package SPSS 25.00.

Results

Descriptive analysis of the psychiatry

Seventy patients were included, 34 men (48.6%) and 36 women (51.4%). Mean age was 47.3 ± 13.8 years. Sociodemographic characteristics and blood parameters are described in table 1.

Total (N = 70)		B12 deficiency (N = 8)	FA deficiency (N = 27)
Sex	N (%)	N (%)	N (%)
Male	34/70 (48.6%)	3/8 (37.5%)	18/27 (66.7%)
Female	36/70 (51.4%)	5/8 (62.5%)	9/27 (33.3%)
Age (years)			
Mean ± SD	47.3 ± 13.8	50.8 ± 12.3	44.2 ± 14.5
Range	23.0 - 76.0	38.0 - 76.0	23.0 - 76.0
Vitamin B12 (pg/mL)			
Mean ± SD	386.9 ± 205.2	164.3 ± 30.5	306.7 ± 198.9
Range	111.0 – 1168.0	111.0 - 194.0	155.0 - 1168.0
Folic acid (ng/mL)			
Mean ± SD	4.4 ± 3.7	2.8 ± 1.0	1.9 ± 0.5
Range	1.0 - 17.5	1.0 – 4.4	1.0 - 2.6
Hemoglobin (g/dL)			
Mean ± SD	13.5 ± 1.6	13.5 ± 1.7	13.7 ± 1.7
Range	8.9 - 18.7	11.6 - 16.3	8.9 - 17.0
Hematocrit (%)			
Mean ± SD	40.0 ± 5.0	39.5 ± 4.9	40.7 ± 5.5
Range	25.9 - 52.8	34.4 - 47.8	25.9 - 52.6
MCV (fL)			
Mean ± SD	90.5 ± 5.5	91.1 ± 4.8	90.4 ± 6.3
Range	66.3 - 101.0	81.9 - 96.5	66.3 - 98.4

Table 1: Distribution in relation to total sample and vitamin deficiency groups.

Abbreviations: FA: Folic Acid. MCV: Mean Corpuscular Volume.

The vitamin B12 deficiency was found in 8 cases (11.4%) and folic acid deficiency in 27 cases (38.6%). Fifty-eight patients presented B12 serum levels between 200-850 pg/mL and 4 (5.7%) had higher levels of 850 pg/mL. In the group of patients with folic acid deficiency, 21 (77.8%) had levels above 1.5 ng/mL and 6 patients (22.2%) had lower levels. The combined prevalence of both vitamin deficits was found in 4 cases (5.7%). Differences in cobalamin levels between the group of patients with and without folic acid deficit were statistically significant (p = 0.0003), being greater in the latter (Table 2).

N (%)		Vit. B12 levels (pg/mL) Mean ± SD	Folic acid levels (ng/mL) Mean ± SD
Sex			
Male	34 (48.6%)	342.4 ± 170.4	3.6 ± 3.0
Female	36 (51.4%)	429.0 ± 227.7	5.1 ± 4.2
Age			
20-39	19 (27.1%)	355.9 ± 114.9	3.1 ± 2.5
40-59	37 (52.9%)	397.1 ± 249.9	4.3 ± 3.6
≥ 60	14 (20.0%)	401.9 ± 173.8	6.3 ± 4.6
Educational Attainment			
Without studies	2 (2.9%)	285.5 ± 152.0	1.6 ± 0.8
Primary studies	27 (38.6%)	363.4 ± 209.6	3.9 ± 2.5
Secondary studies	30 (42.9%)	408.8 ± 196.4	4.8 ± 4.5
University studies	11 (15.7%)	403.3 ± 238.1	5.0 ± 3.9
Employment Status			
Employed	8 (11.4%)	333.6 ± 138.3	3.3 ± 1.3
Unemployed	35 (50.0%)	399.1 ± 202.6	4.5 ± 4.0
~~Pensioner~~ Retiree	20 (28.6%)	367.7 ± 214.1	4.2 ± 3.2
Incapacitated	7 (10.0%)	441.4 ± 273.4	5.7 ± 5.3
Previous hospital~~ization~~ admission			
No	22 (31.4%)	365.2 ± 243.5	4.0 ± 3.5
Yes (<3)	10 (14.3%)	418.5 ± 207.6	6.1 ± 5.5
Yes (≥3)	38 (54.3%)	391.2 ± 183.8	4.1 ± 3.2
Nutritional status*			
Normal	19 (27.1%)	343.1 ± 151.3	4.0 ± 3.1
Risk of malnutrition	39 (55.7%)	414.0 ± 231.4	4.1 ± 3.6
Malnourished	12 (17.1%)	368.2 ± 187.7	5.9 ± 4.7
BMI (Kg/m^2)			

Underweight (<18.5)	8 (11.4%)	458.6 ± 269.3	8.3 ± 6.5
Normal (18.5-24.9)	34 (48.6%)	373.8 ± 200.0	4.0 ± 3.5
Overweight (25-29.9)	16 (22.9%)	380.2 ± 190.9	3.4 ± 1.5
Obesity (>30)	12 (17.1%)	385.0 ± 209.4	4.2 ± 2.2
Vitamin B12 deficiency			
No	62 (88.6%)	415.6 ± 200.4	4.6 ± 3.9
Yes	8 (11.4%)	164.2 ± 30.5	2.8 ± 1.0
Folic Acid deficiency			
No	43 (61.4%)	437.2 ± 194.7	5.9 ± 4.0
Yes	27 (38.6%)	306.7 ± 198.9	1.9 ± 0.5

Table 2: Vitamin B12, folic acid levels and sociodemographic/clinical variables in the psychiatric cohort.

Abbreviations: BMI: Body mass index. *Evaluated with Mini Nutritional Assessment questionnaire.

The average cobalamin level in the sample was 386.9±205.2 pg/mL, and folic acid was 4.4±3.7 ng/mL (Table 3). Anemia was detected in 15 patients (21.4%), 11 men and 4 women. Anemia was normocytic in 13 patients, microcytic in 2, and macrocytosis; lack of anaemia was found in 2 cases. In the groups ofpatients with low levels of cobalamin and folate, anemia was observed in 1 out of 4 subjects.

The most frequent comorbid conditions were dyslipidemia (25.7%), arterial hypertension (21.4%), diabetes mellitus (12.9%) and infectious diseases (12.9%). Besides, two patients had a history of chronic gastritis and 1 coeliac disease. Twenty-eight patients (40%) were active smokers, 21 were former smokers and 21 had never smoked. Most subjects (41.4%) had never consumed alcohol, 28.6% were former drinkers and 30% were active drinkers.

Alcohol consumption was associated with a decrease in serum folic acid levels (p = 0.0493). In addition, 25 of the 70 patients (35.7%) were regular users of other drugs, being cannabis and cocaine the most frequent ones. More than half of the patients (55.7%) were at risk of malnutrition and 17.1% were malnourished (according to the MNA form), and only 27.1% had a normal nutritional status. In addition, 48.6% of patients had a normal weight and the rest were either overweight or obese. The mean BMI was within the normal weight range (24.5 ± 5.5). No significant association was found between nutritional variable and vitamin levels (Table 2).

According to the Gijon's social and family evaluation scale, 47.1% were considered at social risk and 25.7% presented any social problem. The most frequently situations were low or no income, poor family support and loneliness. However, the social and family status was not significantly associated with vitamin levels. In our study the most frequently drugs used were antipsychotics (62.9%), benzodiazepines (57.1%), followed by anticonvulsants (31.4%), selective serotonin reuptake inhibitors, SSRIs (24.3%) and proton-pump inhibitors, PPIs (18.6%). No significant differences were observed in the bivariate analyses between patients with and without vitamin deficiencies (Table 3 and 4).

The most common psychiatric disorders were bipolar disorder in 17 patients (24.3%), schizophrenia in 13 patients (18.6%), and

Drugs	Total (N = 70)	%	No B12 deficit (N = 62)	%	B12 deficit (N = 8)	%
Antipsych.	44	62.9	39	62.9	5	62.5
Anticonv.	22	31.4	21	33.9	1	12.5
SSRI	17	24.3	16	25.8	1	12.5
BZD	40	57.1	37	59.7	3	37.5
PPI	13	18.6	13	21	0	0
MTZ/TZD	12	17.1	11	17.7	1	12.5
APK	9	12.9	8	12.9	1	12.5
NSAID	9	12.9	9	14.5	0	0

Table 3: Medication prior to admission and its distribution in patients with and without vitamin B12 deficiency.

Drugs	Total (N = 70)	%	No FA deficit (N = 43)	%	FA deficit (N = 27)	%
Antipsych.	44	62.9	29	67.4	15	55.6
Anticonv.	22	31.4	16	37.2	6	22.2
SSRI	17	24.3	12	27.9	5	18.5
BZD	40	57.1	26	60.5	14	51.9
PPI	13	18.6	7	16.3	6	22.2
MTZ/TZD	12	17.1	9	20.9	3	11.1
APK	9	12.9	6	14	3	11.1
NSAID	9	12.9	6	14	3	11.1

Table 4: Medication prior to admission and its distribution in patients with and without folic acid deficiency.

Abbreviations: FA: Folic Acid. Antipsych: Antipsychotics. Anticonv: Anticonvulsants. SSRIs: Selective Serotonin Reuptake Inhibitors. BZD: Benzodiazepines. PPI: Proton Pump Inhibitors. MTZ: Mirtazapine. TZD: Trazodone. APK: Antiparkinsonian Drugs. NSAID: Nonsteroidal anti-inflammatory Drugs.

12 patients (17.1%) were classified as an unspecified psychotic episode. In the group of patients with low cobalamin levels, the predominant disorders were schizophrenia and delusional disorder (25% in each case), while in patients with low folic acid levels, the bipolar disorder (25.9%) was the most frequent. 57.1% of patients had a family psychiatric history. Folic acid levels in patients with food disorder (2/70) were significantly higher than those without this diagnosis (16.1 ± 2.0 versus 4.0 ± 3.1 ng/mL, p = 0.0190) (Table 7). Twenty-two patients (31.4%) were admitted for the first time, while of the remaining 48, 38 (79.2%) had been admitted more than 3 times and 10 (20.8%) between 1 and 3 times. There was no significant association between vitamin levels and the number of previous admissions (Table 5).

Comparative analysis

Seventy patients admitted to the Internal Medicine department were studied. Forty one patients were males (58.6%) and 29 (41.4%), females. Mean age was 51.4 ± 10.1 years, vs 47.3 ± 13.8 in the psychiatric cohort (Table 6).

The most frequent causes of hospital admission were acute infections (32.9%), weight loss (11.4%), fever and anemia in 8.6% of cases, respectively.

The average serum cobalamin levels were significantly lower in psychiatric patients compared to the other group (386.9 ± 205.2

Psychiatric disorder	N (%)	Vitamin B12 level (pg/mL) Mean ± SD	Folic acid levels (ng/mL) Mean ± SD
Bipolar disorder	17 (24.3%)	410.6 ± 192.3	3.5 ± 1.8
Schizophrenia	13 (18.6%)	318.3 ± 123.2	3.4 ± 1.3
Psychotic episode	12 (17.1%)	375.1 ± 275.0	3.0 ± 1.4
Depressive episode	7 (10.0%)	373.0 ± 237.6	4.8 ± 5.2
Manic episode	6 (8.6%)	465.0 ± 202.5	6.5 ± 4.7
Delusional disorder	6 (8.6%)	352.3 ± 251.7	4.3 ± 2.9
Substance use disorder	1 (1.4%)	223.0	3.0
Schizoaffective disorder	4 (5.7%)	316.8 ± 109.3	2.6 ± 1.1
Food disorder			
Yes	2 (2.9%)	631.5 ± 345.8	16.1 ± 2.0*
No	68 (97.1%)	379.7 ± 199.3	4.0 ± 3.1*
Major depressive disorder	2 (2.9%)	465.0 ± 52.3	11.0 ± 8.3
Anxiety disorder	1 (1.4%)	489.0	4.0
*Comparison of folic acid levels between patients with and without food disorder. p = 0.0190.			

Table 5: Mean serum levels of vitamin B12 and folic acid with respect to psychiatric disorders.

Psychiatric group (N = 70)		Internal Medicine group (N = 70)	Comparison
Sex			
Male	34/70 (48.6%)	41/70 (58.6%)	χ^2 = **1.03,** df = 1, P = NS
Female	36/70 (51.4%)	29/70 (41.4%)	
Age (years)			
Mean ± SD	47.3 ± 13.8	51.4 ± 10.1	t = 2.02, df = 127, P = 0.0460
Range	23.0 - 76.0	20.0 - 64.0	
Vitamin B12 (pg/mL)			
Mean ± SD	386.9 ± 205.2	596.8 ± 515.4	W = 2948.00, P = 0.0381
Range	111.0 - 1168.0	80.0 - 2001.0	
Folic acid (ng/mL)			
Mean ± SD	4.4 ± 3.7	4.5 ± 3.5	W = 2354.50, P NS
Range	1.0 - 17.5	0.8 - 17.5	
Hemoglobin (g/dL)			
Mean ± SD	13.5 ± 1.6	11.3 ± 2.1	t = -7.11, df = 129, P < 0.0001
Range	8.9 - 18.7	6.5 - 14.8	
Hematocrit (%)			
Mean ± SD	40.0 ± 5.0	33.9 ± 6.4	t = -6.27, df = 130, P < 0.0001
Range	25.9 - 52.8	18.8 - 47.6	
MCV (fL)			
Mean ± SD	90.5 ± 5.5	90.3 ± 9.2	W = 2229.50, P = NS
Range	66.3 - 101.0	62.6 - 120.0	
B12 deficit	8/70 (11.4%)	8/70 (11.4%)	χ^2 = **0.00,** df = 1, P = NS
Folic acid deficit	27/70 (38.6%)	26/67* (38.8%)	χ^2 = **0.00,** df = 1, P = NS

Table 6: Demographic characteristics and analytical parameters (N = 140).

Abbreviations: MCV: Mean Corpuscular Volume. NS: Non Stadistical Significance.

In 3 patients the serum folate levels were not determined (haemolyzed blood).

versus 596.8 ± 515.4 pg/mL, p = 0.0381). Serum folic acid levels were similar in both groups, with no significant differences (4.4 ± 3.7 versus 4.5 ± 3.5 ng/mL). In the control group, mean hemoglobin and hematocrit levels were found 11.3 ± 2.1 g/dL and 33.9 ± 6.4%, respectively), being significantly lower than the values obtained in psychiatric patients (p < 0.0001). In addition, 46 cases of anemia were reported, 6 of which were macrocytic. In both groups the same number of patients with cobalamin deficiency was observed

(11.4%), while the folic acid deficit was obtained in 38.8% of the Internal Medicine patients, practically identical to that collected in the study sample (38.6%), so there were no significant differences (Table 6). Finally, the combined deficiency of both vitamins in psychiatric patients (5.7%) was more prevalent than in the other cohort (1.5%).

Discussion

Several studies show similar results to those obtained by our group, Silver., *et al*. study conducted in Israel [20] and other one in Iran [21], demonstrated cobalamin deficiency in 18.9 and 13.1% of subjects, respectively, while other authors have found much higher values.

For example, two studies carried out in Turkey [30,31] reported a very high prevalence (45.5% and 66.1%, respectively), which could be attributed to the high percentage of the vegetarian population or eating habits. Other authors have reported a much lower prevalence of folic acid deficiency compared to ours [25,30,31]. However, other researchers such as Lerner., *et al*. obtained results closer to ours [8].

There is notable variability in the prevalence values described in the different published studies [8,22-32]. This circumstance could be partly justified by the different cut-off points used to define the deficit of both vitamins, as well as the age differences of the analyzed cohorts. In addition, other factors such as genetic differences, different eating habits, socioeconomic and cultural conditions should be considered to understand this variability of results (Table 7).

All studies used vitamin B12 and folic acid serum levels. The diagnostic criteria used to determine the vitamin B12 deficiency

Author (*et al.*)	Country	Age (range and/or mean)	N	Vitamin deficiencies	Diagnostic Criteria*	Environment
Carney M [22] (1967)	England	54 ± 9.6	423	B12:? Folate:	B12 < 150 Folate<2	Inpatients
Murphy P. (1969) [23]	England	>50	1004	B12: 3.4% Folate: 28.9%	B12 < 150 Folate < 3	Inpatients
Carney MW. (1978) [24]	England	52 ± 18.4	272	B12: 26.1% Folate: 21.3%	B12 < 150 Folate < 2	Inpatient
Elsborg L. (1979) [25]	Denmark	17-98	835	B12: 9.7%	B12 < 200	Inpatients
Bell I R. (1990) [26]	USA	60-100 74.5 ± 7.8	102	B12: 3.7% Folate: 1.3%	B12 < 150 Folate < 2	Inpatient
Brett AS. (1994) [27]	USA	17-90 59	162	B12: 4.3%	B12 < 200	Inpatient
Silver H. (2000) [20]	Israel	¿?	644	B12: 18.9% Folate: 5.6%	B12 < 200 Folate < 2.5	Inpatients
Lerner V (2006) [8]	Israel	18-76 39.4 ± 13.3	224	B12: 26.3% Folate: 29.9%	B12 < 223 Folate < 3.1	Inpatients
Saedisomeolia A. (2011) [21]	Iran	15-55	60	B12: 13.3% Folate: 8.3%	B12 < 120 Folate < 3	Inpatients (Sch.)

Ssonko M. (2014) [28]	Uganda	¿?	280	B12: 28.6%	B12 < 240	Inpatients
Lachner C. (2014) [29]	USA	>50	374	B12: 4.8-7.8%	B12 <180	Inpatients
Keklik M. (2016) [30]	Turkey	43.5 ± 15.4	425	B12: 21.9%	B12 < 150	Inpatients (Dep.)
Hamdi M. (2017) [31]	Turkey	15-76 35.4 ± 12.9	286	B12: 66.1% Folate: 0.7%	B12 < 200 Folate < 2.5	Inpatients
Yacizi AB (2019) [32]	Turkey	41.4 ± 12.3	189	B12: 45.5% Folate: 8.5%	B12 < 200 Folate < 3	Inpatients (Sch.)

Table 7: Prevalence studies of vitamin B12 and folic acid deficiencies carried out in psychiatric inpatients (n = 14).

Abbreviations: (Sch.): Patients with schizophrenia. (Dep.): Patients with depression.

*Units used are pg/ml (Vitamin B12), and ng/ml (Folate).

varied between 120 and 240 pg/ml, being 200 pg/ml the most commonly cut-off point used, which is the one we used. Regarding folic acid deficiency, the cut-off point varied between 2 and 3.1 ng/ml, although for 4 of them (57%) it was set between 2.5 and 3 ng/ml, as in our study.

In contrast to what is reported in the literature, we found no significant differences in the prevalence of vitamin B12 and folic acid deficiencies between the two cohorts. Unlike our results, Lerner., *et al*. (2006) [8], in a psychiatric group and a control group found non stadistical significance in the prevalence of cobalamin deficiency (26.3% vs 25.2%). However, in folate deficit prevalence they did find statistical significant differences in favor of psychiatric patients (29.9% vs 2.4%, $p < 0.0001$).

The relationship of these deficiencies and psychiatric illnesses has been studied and debated since these vitamins were first discovered in the 1940s [7] and more incisively in patients with schizophrenia or depressive disorders. In our study we obtained a prevalence of cobalamin and folate deficiency of 15% and 38%, respectively, in the group of patients diagnosed with schizophrenia. Saedisomeolia., *et al*. in a series of Iranian patients showed a cobalamin deficiency in 13.3% of cases [21]. However, the incidence of low folate levels in patients with this disorder varied between 12 and 36% [33]. In our cohort we did not observe a relationship between schizophrenia and levels of these vitamins, although the number of patients was low. However, some authors have demonstrated statistically significant associations with cobalamin [28,30] and folic acid deficiencies [21,30].

A previous study suggested that folate levels play an important role in the etiology and course of depression [34]. However, the literature has been inconsistent regarding differences in folate level between individuals with and without depression.

More than half of the patients with depressive disorders in our study (56%) presented folic acid deficiency, although the number of patients with these disorders was small (9), and we did not find significant associations. In the literature this deficiency varies between 15 and 38% in these patients [16,23,32]. In addition, a meta-analysis comparing folate levels between people with and without depression ($k = 43$) concluded these levels were significantly lower in patients with this disorder [34]. It is interesting to note that we found a statistically significant association between serum folate levels and food disorders, although the validity of the contrast is doubtful since there were only 2 subjects affected (2.9%) so, as with other disorders, a bigger sample would be necessary to obtain more valid results. To our knowledge, there are no studies analyzing this association.

In our study, serum folate levels were significantly lower in men than in women in accordance with previous studies [8]. Regarding cobalamin, we also observed higher mean levels in women (429.0 ± 227.7 pg/ml) than in men (342.4 ± 170.4 pg/ml), although dif-

ferences were not significant. These results are consistent in the literature. Thus, Ssonko., *et al*. showed female participants were associated with protection from low serum levels [28]. However, they did not provide any explanation regarding these findings.

In a previous research [31], serum folic acid levels were significantly associated with age. This association was not demonstrated with vitamin B12, however, the older the patients, the lower the serum levels were.

The relationship between cobalamin deficiency and age has been widely described in the literature. These findings are justified by a lower absorption of cobalamin, due to a higher incidence of gastrointestinal pathology (mainly atrophic gastritis, hypochlorhydria and intrinsic factor deficit) as well as the use of drugs that alter the pharmacokinetics of cobalamin, such as PPIs [3,35].

Despite obtaining identical cobalamin deficiency prevalence (11%) in both cohorts, we found statistically significant differences when comparing average levels, being higher in the Internal Medicine cohort (596.8 ± 515.4 pg/mL vs 386.9 ± 205.2 pg/mL), coinciding with that described in a case-control study conducted by Yacizi., *et al*. in a cohort of 189 schizophrenic patients [32]. It is important to note that cobalamin deficiency in the Internal Medicine cohort could be greater than the 11% we obtained, since 1 out of 3 patients were admitted for infectious causes, and these conditions could be associated with falsely high values. A study with a similar design and patient profile to ours [7] did not document significant differences in average cobalamin levels between a cohort of psychiatric patients and a mentally healthy control group, however, differences were observed with respect to folate, which was 1.5 times greater in the control group. The average serum vitamin B12 documented in our study was like that obtained in other series [8,20]. In the present study a statistically significant association between alcohol consumption and low levels of folic acid was found ($p = 0.0493$). This relationship is extensively described in the literature. These lower levels are the result of reduced dietary folate intake, intestinal malabsorption, reduced liver uptake and storage and increased urinary folate excretion [36].

We found statistically significant differences between mean hemoglobin and hematocrit levels in both studied cohorts. While in the group of psychiatric patients these parameters were not related to anemia, in the Internal Medicine group they did. When interpreting this difference, it is necessary to consider the high incidence of anemia in patients admitted to the Internal Medicine Service, resulting from a wide range of conditions such as inflammatory processes, infectious and chronic diseases.

The present study has some methodological limitations: 1) it is a transversal study, and therefore we cannot confirm whether vitamin deficiencies would be justified solely by suffering from serious acute psychiatric disorders, 2) in psychiatric patients, in addition to mental illness history, other clinical situations were documented that could justify vitamin deficits, such as taking PPIs, anticonvulsants and/or medical history such as ceoliac disease and gastritis, 3) the analytical parameters used to diagnose vitamin deficiencies were only serum cobalamin and folic acid levels, without considering other more sensitive confirmatory tests (such as serum quantification of methylmalonic acid, homocysteine, and red blood cell folate), especially useful in those patients with borderline levels, 4) clinical situations such as pregnancy or active liver disease may cause a false decrease or elevation of serum cobalamin although the number of patients in our series was small. On the other hand, serum folate figures may not reliably reflect the state of tissue reserves as they are very sensitive to the short-term effects of diet [37]. Lastly, the number of patients with individual psychiatric diagnoses was very low, which prevents us from extrapolating results.

Conclusions

The vitamin B12 and folic acid deficiencies are prevalent among psychiatric inpatients, and there were no differences with respect to patients admitted to Internal Medicine department. The combined deficiency was more prevalent in the psychiatric patients than in patients from Internal Medicine department.

Conflict of Interest

The authors declare no conflicts of interest.

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