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SHOULD SERUM FOLATE BE A ROUTINE TEST IN A CRITICALLY ILL PATIENTS?
SERUM FOLAT KRİTİK HASTALARDA RUTİN BİR TEST OLMALI MI?

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ABSTRACT

In intensive care patients, there is an increased consumption and need for folate due to sepsis, comorbid conditions, and malnutrition. The aim of our study was planned to investigate the frequency of folate deficiency in intensive care patients. The data of the 100 patients was collected between June 2019 and September 2019. Serum folate levels were defined as normal above 4 ng/mL, 2-4 ng/mL borderline and below 2 ng/mL deficiency. Serum folate deficiency (<2 ng/mL) was detected in 19 patients (31.6% (6 patients) was female and 68.4% (13 patients) was male. Hypertension was most frequently comorbidities together with folate deficiency. There was a significant negative correlation between folate levels and "Acute Physiology and Chronic Health Evaluation (APACHE)" II scores. A high APACHE II score may be an important predictive factor for folate deficiency. Current reference ranges may cause folate malnutrition. For intensive care patients, it may be necessary to set new threshold values for folate deficiency.

Keywords: APACHE II, folic acid deficiency, intensive care unit

ÖZ

Yoğun bakım hastalarında sepsis, komorbid durumlar, malnütrisyon gibi nedenlerle artan folat tüketimi ve ihtiyacı vardır. Çalışmamız yoğun bakım hastalarında folat eksikliğinin sıklığını araştırmak amacıyla planlandı. Yüz hastanın verileri Haziran 2019 ile Eylül 2019 arasında toplandı. Serum folat düzeyleri 4 ng/mL üzeri normal, 2-4 ng/mL sınırda ve 2 ng/mL altı eksiklik olarak tanımlandı. Serum folat eksikliği (<2 ng/mL) 19 hastada (%31.6 (6 hasta) kadın, %68.4 (13 hasta) erkek saptandı. Hipertansiyon folat eksikliğine en sık eşlik eden komorbid hastalıktı. Folat düzeyleri ile "Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi (APACHE)" II puanları arasında anlamlı negatif korelasyon vardı. Yüksek APACHE II skoru, folat eksikliği için önemli bir öngörücü faktör olabilir. Mevcut referans aralıkları folat malnütrisyonuna neden olabilir. Yoğun bakım hastaları için folat eksikliği için yeni eşik değerlerin belirlenmesi gerekebilir.

Anahtar kelimeler: APACHE II, folik asit eksikliği, yoğun bakım ünitesi

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INTRODUCTION

Vitamin B12 and Folate (B9) are vitamins which have a role to formation of erythrocytes, leukocytes and platelets. Megaloblastic anemia and hyperhomo cysteinemia occur in the deficiency of both vitamins.[1] Neuropsychiatric complications such as depression, irritability, insomnia, cognitive decline, fatigue, and mouth ulcers are expected in folate deficiency.[2,3] A serum folate level under 3 ng/mL is diagnosticfor folate deficiency.[2] Folate levels may be lower than normal levels in hospitalized patients.[4] Folate deficiency can be revealed due to increased need such as pregnancy, decreased intake with nutrition, alcohol use, hemodialysis, continue renal replacement therapy and some medications.[5] Although vitamin B12 deficiency develops over the years, folate deficiency can develop within weeks or months due to body stores are limited. Vitamin B12 and folate deficiency should be considered in patients with chronic diarrhea, unexplained anemia, in the presence of macrocytosis (MCV>100 fL), pancytopenia and hypersegmented neutrophils.[1] If folate deficiency is suspected in hospitalized patients, the blood sample taken for testing must be taken immediately after the patient's admission, before feeding and before blood transfusion.[6] Folate deficiency is known to cause hyperhomocysteinemia, and hyperhomocysteinemia leads to an increased risk of cardiovascular, cerebrovascular disease and venous thromboembolic events in some studies.[7,8] The goal of our study was to find out how common folate deficiency is in intensive care patients, how it relates to other comorbid conditions, particularly thromboembolic disease, how severe the disease is, and whether folate levels should be checked in all intensive care patients.

MATERIALS AND METHODS

This was a cross-sectional study, and the data were collected retrospectively. The data analysis was performed on patients who were followed in the Internal Medicine Intensive Care Unit of Kayseri City Training and Research Hospital. All patients who did not match the exclusion criteria between June and September 2019 were enrolled in the research. A total of 100 patients were reached. Blood samples were taken from patients immediately after they were admitted to the hospital and before they were fed.Serum folate levels were defined as normal above 4 ng/mL, 2-4 ng/mL borderline and below 2 ng/mL deficiency. World Health Organization (WHO) criteria for anemia in men and women are <13 and <12 g/dL, respectively.[9] Patients with using folic acid or drugs that affect folic acid metabolism, pregnancy, inflammatory bowel disease, using chronic alcohol were excluded.

This study was approved by the ethics committee and the institutional review board of Kayseri Training and Research Hospital.

Statistical Analysis

In the statistical analysis of the data, the SPSS 20.0 program was used. To compare continuous measurements between two groups, Student t test or Mann-Whitney U test or was used. The Kruskal-Wallis test was used to compare paraæmeters with a non-normal distribution, while the one-way ANOVA test was used to compare parameters with a normal distribution for three and more groups. The correlation between categorical variables were tested bySpearman correlation. Continuous measures were presented as median (minimum-maximum) and categorical variables as numbers and percentages. Categorical variables were compared using chi-squared or Fisher's exact test. A p value <0.05 was considered to be statistically significant.

RESULTS

The study involved 100 patients (51 women, 49 men). They were followed-up in intensive care unit. Mean age was 70.3±19.0 (20-95) years old. Table 1 shows the demographic characteristics of the patients.

Anemia was detected in 74% of the all patients, including 72.5% of the women (37 patients) and 75.5%

Table 1. Demographic features and laboratory parameters of the patients

Number of the patients	100
Sex	
Female	51
Male	49
Age (years)	70.3±19.0
Comorbidities	
Diabetes mellitus	28 (18.1)
Hypertension	48 (31)
Chronic renal failure	20 (12.9)
Hearth failure	11 (7.1)
Chronic liver disease-cirrhosis	7 (4.5)
Chronic obstructive pulmonary disease	10 (6.5)
Hematological malignancy	5 (3.2)
Solid tumor	16 (10.3)
Cerebrovascular events	10 (6.5)
Laboratory parameters	
WBC (10^3/µL)	11(0.1-168.5)
Hemoglobin (g/dL)	10.8±2.7
MCV (fL)	89.1(63.2-125.3)
Platelet (10^3/µL)	187 (7-616)
Serum albumin (g/L)	30.1±7.1
Serum folate level (ng/mL)	3.69(0.6-20)
Vitamin B12 level (ng/L)	555.8(58-2000)

*Values are presented as number (%), mean±standard deviation or median (minimum-maximum).

of the men (37 patients). Serum folate deficiency was present in 68.4% (13 patients) of patients with anemia and in 23.1% (6 patients) of those without anemia. Serum folate deficiency (< 2 ng/mL) was detected in 19 patients (31.6% (6 patients) was female and 68.4% (13 patients) was male (Table 2). No statistically significant difference was found when patients with and without anemia were compared by gender (p=0.168). Vitamin B12 deficiency was detected in 5.3% (1 patient) of those with deficiency in serum folate level and in 18.8% (9 patients) of normal ones. The patients did not have a history of chronic alcohol use. Patients included in the study had 64% sepsis at the time of hospitalization.

The mean APACHE-II score of the patients was 29.1 ± 8.7. The median length of stay in the ICU was 5 (1-37) days. Hypertension was most frequently comorbidities together with folate deficiency (Table 2). There was a significant negative correlation between folate levels and APACHE II scores (p: 0.01 r: -0.26).

MCV was greater than 100 fL in 26.3% of patients with low folate levels, but there was no statistically significant relationship between folate levels and the presence of macrocytosis (p=0.378). Leukopenia was most common in the borderline group, and thrombocytopenia was most common in the group without folate deficiency; however, there was no statistically significant difference between these groups (p=0.839 and p=0.804, respectively) (Table 3). Vitamin B12 deficiency was most common in the group without folate deficiency (18.8%), a statistically significant difference (p=0.03).

Considering the relationship between folate deficiency and 28-day mortality, the highest mortality was observed in the borderline group with 39.4%, followed by the lower group with 31.6%. There was no statistically significant difference between folate levels and 28-day mortality (p=0.068) When the relationship between serum folate level and cardiac complications, stroke and deep vein thrombosis was examined, no statistically significant difference was found among groups (Table 2).

DISCUSSION

Folate level is not a routine test in intensive care patients. There fore, there is not much study in the literature on its frequency of deficiency. Boles et al. found a 52% incidence of low serum folate in 138 severely ill patients.[10] In an other study, folate deficiency was found 16 % in hospitalized patients.[4] This presented study has shown that folate deficiency was found 19 % in patients in intensive care unit. Since advanced age is known to be a risk factor for folate

Table 2. Demographic, laboratory and clinical characteristics of patients according to serum folate level

	Serum folate levels			p value
	Low n=19	Borderline n=33	Normal n=48	
Sex				
Female	6 (31.6)	18 (54.5)	27 (56.3)	0.168
Male	13 (68.4)	15 (45.5)	21 (43.8)	
Age (years)	84 (32-93)	74 (40-95)	77 (20-93)	0.197
APACHE-II score	28.7±7.7	31.9±5.9	27.3±10.2	0.06
Comorbidities				
Diabetes mellitus	4(21.1)	9(27.3)	16(33.3)	0.568
Hypertension	8(42.1)	16(48.5)	24(50)	0.842
Chronic renal failure	4(21.1)	7(21.2)	9(18.8)	0.956
Hearth failure	2(10.5)	4(12.1)	5(10.4)	1.000
Chronic liver disease-cirrhosis	2(10.5)	4(12.1)	1(2.1)	0.175
Chronic obstructive pulmonary disease	2(10.5)	5(15.2)	3(6.3)	0.414
Hematological malignancy				
Solid tumor	-	2(6.1)	3(6.3)	0.706
Cerebrovascular events	2(10.5)	10(30.3)	4(8.3)	0.026
	2(10.5)	4(12.1)	4(8.3)	0.908
Cardiac complications, n (%)				
Yes		28 (84.8)	44 (91.7)	
No	19 (100)	5 (15.2)	4 (8.3)	0.196
Stroke, n (%)				
Yes		1 (3)	1 (2,1)	0.753
No	19 (100)	32 (97)	47 (97.9)	
Deep vein thrombosis, n (%)				
Yes	1 (5.3)	3 (9.1)	2 (4.2)	0.649
No	18 (94.7)	30 (90.9)	46 (95.8)	
Duration of stay in intensive care unit (days)	6(2-27)	7 (1-37)	5 (1-27)	0.431
28-day mortality, n (%)				
Yes	6 (31.6)	13 (39.4)	8 (16.7)	0.068
No	13 (68.4)	20 (60.6)	40 (83.3)	

*Values are presented as number (%), median (minimum-maximum) or mean±standard deviation.
**APACHE II scores: Acute Physiology and Chronic Health Evaluation II score

Table 3. Laboratory parameters of the patients according to serum folate level

	Serum folate levels			p value
	Low n=19	**Borderline n=33**	**Normal n=48**	
WBC (10^3/µL)	12.9(0.7-36.7)	11.4(0.07-168.5)	10.1(0.8-30.1)	0.364
Leukopenia				
Yes	1(5.3)	3(9.1)	3(6.3)	0.839
No	18(94.7)	30(90.9)	45(93.8)	
Hemoglobin (g/dL)	11.6±2.6	10.4±2.9	10.9±2.7	0.295
Anemia				
Yes	13(68.4)	25(75.8)	36(75)	0.825
No	6(31.6)	8(24.2)	12(25)	
MCV (fL)	95.3(76.1-118.1)	88.8(72.3-125.3)	88.4(63.2-118)	0.076
Macrocytosis				
Yes	5(26.3)	4(12.7)	7(14.6)	0.378
No	14(73.7)	29(87.9)	41(85.4)	
Platelet (10^3/µL)	203(12-435)	167(7-532)	189(22-616)	0.768
Thrombocytopenia				
Yes	6(31.9)	13(39.4)	16(33.3)	0.804
No	13(68.4)	20(60.6)	32(66.7)	
Serum albumin (g/L)	27.4±6.9	27.7±7.4	32.8±5.9	0.001
Serum folate level (ng/mL)	1.38(0.6-1.97)	2.85(2.02-3.81)	8.98(4.08-20)	<0.001
Vitamin B12 level (ng/L)	472.9(179.7-2000)	613.9(234.3-2000)	487.6(58-2000)	0.098

*Values are presented as median (minimum-maximum), number (%) or mean±standard deviation.
**WBC: White blood cell, MCV: Mean corpuscular volume.

deficiency,[5] the higher average age in this study may be the reason why more folate deficiency was detected.

Serum folate levels less than 2.7 ng/ml are considered deficient, and levels between 2.7-5.3 ng/ml are considered indeterminate.[5] The need for folate may vary depending on the situation. Folate deficiency related with elevated homocysteine levels which is a risk factor for thromboembolic events.[11,12] Epidemiological evidence has shown that adequate folate intake during pregnancy decreases neural tube defects in newborns. The optimum folate level should be between 7 ng/mL and 13 ng/mL to prevent neural tube defects.[13] According to Singh G et al, a serum folate level of less than 7.0 ng/mL in intensive care patients may be an indication of malnutrition.[11] In this study, the median folate levels was found 3.69(0.6-20) ng/ml in intensive care patients. For this reason, folate replacement should be done as above level 7 ng/ml. Oral daily folic acid replacement is recommended as 1 to 5mg for the correction of folic deficiency. According to a study, the level of folic acid in physiological doses in enteral or parenteral nutrition products is insufficient for intensive care patients.[14] This study has shown that folate deficiency is observed more frequently in intensive care patients.

Deficiency of folate in intensive care is associated with more severe disease.[15] In this study, a very low correlation level was found between high APACHE II score and folac deficiency. No relationship was found between comorbidities and folate deficiency in intensive care patients. Therefore, the need for intensive care may not be considered as an important risk factor for folate deficiency.

Symptoms of folate deficiency often occur slowly. Anemia is a late finding in folate deficiency. It is characterized by large-sized and abnormal red blood cells (megaloblasts). In laboratory, megaloblast cells have increased MCV levels.In patients with elevated MCV levels, vitamin B12 and folate deficiencies are routinely screened, however, these tests are limited due to low sensitivity and specificity.[16] The patients had low folate levels together with increased MCV values were only 26.3 % of the all patients in this study. Therefore, MCV levels have low sensitivity and specificity in terms of reflecting of folate deficiency in intensive care patients.[1]

CONCLUSION

In conclusion, being in intensive care is a significant risk factor for folate deficiency. A high APACHE II score may be a significant predictor of folate insufficiency.For intensive care patients, it may be necessary to set new threshold values for folate deficiency. Current reference ranges may cause folate malnutrition. The limitations of our study were as follows: First of all, our number of patients was relatively small, and secondly, since advanced age is known to be a risk factor for folate deficiency, the higher average age in this study may be the reason why more folate deficiency was detected. Prospective studies with a greater number of patients are needed to determine new reference values for intensive care unit.

Ethics Committee Approval: Ethics committee approval was received for this study from the Kayseri Training and Research Hospital Ethics Committee (Date:26.02.2020, Number: 2020136).

Informed Consent: Written consent was obtained from all participating in the study.

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