

Assessment of the Association Between Complete Blood Cell Parameters, Levels of Vitamin B₁₂ and Folate, Decreased Iron Storage and Recurrent Vasovagal Syncope Episodes

Tekrarlayan Vazovagal Senkop Epizotları ile Vitamin B₁₂ ve Folat Seviyeleri, Azalmış Demir Depoları ve Tam Kan Sayımı Parametreleri Arasındaki İlişkinin Değerlendirilmesi

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Keywords

Vasovagal syncope, fainting, serum ferritin, complete blood count, mean platelet volume, mean corpuscular hemoglobin concentration

Anahtar Kelimeler

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Abstract

Objective: To evaluate the relationship between recurrent vasovagal syncope (VVS) and complete blood cell parameters, serum levels of ferritin, vitamin B₁₂, and folate.

Materials and Methods: This retrospective study included patients with recurrent VVS and healthy controls. Children and adolescents presenting with at least two VVS episodes were included. Exclusion criteria were as follows; having an electrocardiogram abnormality, patients without an evident trigger before fainting, having an infection, having a history of chronic disease, and taking any medications or vitamin supplements, including folate, vitamin B₁₂, and iron.

Results: A total of 44 patients and 66 healthy controls were included. There were no significant differences between the groups in terms of age and gender. Mean corpuscular hemoglobin concentration (MCHC) (p=0.014), mean platelet volume (MPV) (p=0.020), and levels of ferritin (p<0.0001) were significantly lower in the patient group. No significant differences were found between the groups with respect to other laboratory parameters. Binary logistic regression analysis showed that every 1-unit decrease in serum ferritin constitutes a 0.972 [95% confidence interval (CI)= 0.954–0.990] fold risk. Also, every 1-unit decrease in MPV constitutes a 0.453 (95% CI=0.275–0.745) fold risk of VVS.

Conclusion: This study showed lower levels of serum ferritin, smaller platelet sizes, and lower levels of MCHC. Additionally, smaller platelet sizes and lower levels of ferritin were independent risk factors.

Öz

Amaç: Tekrarlayan vazovagal senkop (VVS) ile tam kan sayımı, serum ferritin, vitamin B₁₂ ve folat düzeyleri arasındaki ilişkinin incelenmesi amaçlanmıştır.

Gereç ve Yöntemler: Çalışmamız tekrarlayan VVS ve sağlıklı çocuk ve adolesanları içermiştir. Hasta grubuna en az iki tipik VVS atağı geçirmiş olgular dahil edildi. Elektrokardiogramında anormallik varlığı, bayılma öncesi VVS için belirgin bir tetikleyicinin yokluğu, enfeksiyon ya da kronik bir hastalık öyküsünün varlığı, vitamin B₁₂, folat ya da demir replasmanı alıyor olmak dışlama kriterleri olarak

belirlendi. Yaş, cinsiyet, senkop sonrası bakılmış olan tam kan sayımı, serum ferritin, vitamin B₁₂ ve folat düzeyleri retrospektif olarak kaydedildi.

Bulgular: Bu çalışmaya 44 tekrarlayan VVS olgusu, 66 sağlıklı kontrol dahil edildi. Ortalama korpüsküler hemoglobin konsantrasyonu ($p=0,014$), ortalama platelet volümü (MPV) ($p=0,020$), ve serum ferritin düzeyleri ($p<0,0001$) VVS grubunda anlamlı olarak daha düşüktü. Gruplar arasında diğer laboratuvar parametreleri açısından anlamlı farklılık saptanmadı. Binary lojistik regresyon analizi serum ferritin düzeylerindeki her 1 birim düşüklüğün tekrarlayan VVS riskinde 0,972 kat [%95 güven aralığı (GA)= 0,954–0,990], MPV değerindeki her 1 birim düşüklüğün ise tekrarlayan VVS riskinde 0,453 kat (%95 GA=0,275–0,745) artışa neden olduğunu gösterdi.

Sonuç: Çalışmamız sonucunda serum ferritin, MPV ve ortalama hücresel hacim değerleri hasta grubunda anlamlı olarak düşük saptanmıştır. Bununla birlikte düşük MPV ve düşük ferritin düzeylerinin tekrarlayan VVS için bağımsız birer risk faktörü olduğu sonucuna varılmıştır.

Introduction

Syncope is a common disorder that is described as an abrupt and impermanent loss of consciousness. The cumulative frequency of occurrence is 35% during the lifetime and the incidence increases around the age of 15 years. Syncope have been sorted out into three categories; i) cardiogenic, ii) non-cardiogenic, iii) undetermined causes (1). The major causes of the cardiac syncope are arrhythmias, and abnormalities of the left and right sides heart. The causes of noncardiac syncope are reflex syncope, also known as neurally mediated syncope, hypothermia, cerebrovascular conditions, seizures, and metabolic conditions (hypoglycemia, hypoxia). Vasovagal syncope (VVS) is the most prevalent type of reflex syncope. It is a consequence of abnormal interactions of complex neurocardiovascular mechanisms (2). Emotional stress, pain, fever, prolonged standing, cough, sneezing, micturition, and defecation may trigger VVS. The diagnosis is of VVS based on symptoms, physical examination, and electrocardiogram (ECG) findings (3).

There are various studies regarding the relationship between VVS and routine laboratory results such as complete blood count (CBC), levels of serum vitamin B₁₂, folate, and ferritin (4). Reduced monoamine oxidase activity was demonstrated in rats with iron deficiency. Also, since higher plasma norepinephrine levels were demonstrated in pediatric patients with postural orthostatic tachycardia syndrome (POTS), it was proposed that there may be an association between iron deficiency and catecholamine metabolism (5). Vitamin B₁₂ participates in the synthesis of catecholamines. Additionally, it is an important cofactor in myelin degradation. The levels of vitamin B₁₂ and folate are important in some neurological disorders even without a proven insufficiency (6).

Maybe, due to the connected functions of vitamin B₁₂ and folate in myelination and/or synthesis of methionine from homocysteine, deficiency in one vitamin alters the other's functions (7). The linkage between VVS and levels of folate, and vitamin B₁₂ may be result from hyperhomocysteinemia-related autonomic dysfunction (8).

Herein, we aimed to evaluate the association between VVS and CBC, levels of serum vitamin B₁₂, folate, and ferritin.

Materials and Methods

Study Design and Subject

We have obtained the approval of the Ethics Committee from Aydın Adnan Menderes University in line with the principles outlined in the second Declaration of Helsinki (protocol number: 2022/91, date: 12.05.2022). No informed consent was taken due to the retrospective design. This study was conducted from April 2021 to April 2022 in the departments of pediatrics, pediatric neurology, and pediatric cardiology of two universities. Forty-four pediatric patients who were admitted with a history of at least 2 episodes of VVS, and 66 healthy controls were included. Data were consist of 11 patients and 28 healthy controls from Sivas Cumhuriyet University (diagnosed by a pediatrician) and 33 patients and 38 healthy controls from Aydın Adnan Menderes University (diagnosed by a pediatrician, two pediatric neurologist, and a pediatric cardiologist). Only patients with an evident trigger were included. The control group consisted of 66 healthy children, who were admitted to the general pediatrics for examination before sportive activities and underwent CBC, vitamin B12, ferritin, and folate. Exclusion criteria were as follows; having an abnormality in the ECG, patients without an evident trigger before the fainting, having

a history of an infection in the last 4 weeks, having a history of chronic disease. Also, children who were on medication with any medications or vitamin supplements including folate, vitamin B₁₂, and iron were excluded. The results were extracted from the electronic database. Having hemoglobin levels <12 mg/dL and <13 mg/dL were accepted as anemia for females and males, respectively. Having ferritin levels <15 ng/mL and, folate levels <4 ng/mL were considered as deficiency. A level of <400 pg/mL is accepted as a low level for vitamin B₁₂. Normal values of mean corpuscular volume (MCV), red distribution width (RDW), mean platelet volume (MPV), and mean corpuscular hemoglobin concentration (MCHC) were accepted as 80-94 fL, 11.5-14.5%, 8-12 fL, and 34-36 g/dL (9,10).

Statistical Analysis

Statistical analyses were performed using the SPSS-22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). Kolmogorov-Smirnov test was applied to specify the normal distribution of numerical variables. Categorical data were presented with n and %. Normally distributed numerical data presented with mean \pm standard deviation, non-normally distributed data presented with median interquartile range. Student t-test was applied for comparison of normally distributed data and the Mann-Whitney U test was used for comparison of non-normally distributed data. The chi-square test was used for the comparison of categorical data. After the prior analysis binary logistic regression analysis was used to determine the risk factors. A p-value <0.05 was accepted as statistically significant.

Results

The study group consisted of 44 patients and 66 healthy controls. Three patients had iron deficiency anemia. Among the patients with VVS and iron deficiency, 4 of them had both high RDW and low MCV. Of the 110 children, none of them had a lower MPV and only 4 children had higher MPV. Precisely, 34 of the 44 patients had a lower MCHC level than 34 g/dL and 14 of them had a lower level of ferritin. Folate, vitamin B₁₂, and iron deficiencies were also seen in the healthy controls. The numbers of children with vitamin B₁₂ deficiency (<400 pg/mL), folate deficiency, iron deficiency, and iron deficiency anemia were 46, 10, 8, and 2, respectively. MCHC (p=0.014),

MPV (p=0.020), and levels of ferritin (p<0.0001) were significantly lower in VVS group (Table 1). Binary logistic regression analysis showed that every 1-unit decrease in serum ferritin constitutes a 0.972 [95% confidence interval (CI) =0.954-0.990] fold risk. Also, every 1-unit decrease in MPV constitutes a 0.453 (95% CI=0.275-0.745) fold risk for VVS (Table 2).

Discussion

The current study showed that MCHC, MPV, and levels of serum ferritin were significantly lower in patients with VVS. Also, binary logistic regression analysis indicated that lower levels of serum ferritin and MPV were independent risk factors.

Table 1. The comparison of demographical features and laboratory findings between the groups

	Syncope (n=44)	Control (n=66)	p-value
Age**	14.12 (3.79)	15.00 (3.00)	0.272
Gender			
Female	24 (54.5%)	38 (57.6%)	0.754
Male	20 (45.5%)	28 (42.4%)	
WBC**	6.59 (2.42)	6.55 (2.28)	0.698
ANC**	3.29 (1.76)	3.59 (1.53)	0.514
ALC**	2.53 (0.48)	2.62 (0.92)	0.840
RBC*	5.03 \pm 0.49	4.89 \pm 0.59	0.193
Hb**	14.05 (1.08)	13.8 (2.35)	0.963
Htc**	42.10 (3.28)	41.45 (6.48)	0.548
MCV**	83.40 (6.45)	82.50 (4.53)	0.786
MCHC**	33.40 (1.68)	33.85 (1.80)	0.014
RDW**	13.05 (1.28)	13.10 (1.25)	0.447
PLT*	30.09 \pm 62.64	294.73 \pm 99.42	0.682
MPV**	9.60 (0.80)	10.00 (1.73)	0.020
PCT**	0.28 (0.09)	0.31 (0.08)	0.893
PDW**	10.70 (1.80)	11.70 (3.58)	0.088
NLR**	1.35 (0.83)	1.47 (0.99)	0.181
Ferritin**	17.9 (18.5)	38.5 (42.18)	<0.0001
Folate*	14.94 \pm 51.45	7.46 \pm 3.94	0.341
Vitamin B ₁₂ **	296 (248.75)	303.00 (184.75)	0.905

*Non-normally distributed data were given as median (IQR). **Normally distributed data were given as mean (\pm SD). WBC: White blood cell, ANC: Absolute neutrophil cell, ALC: Absolute lymphocyte cell, RBC: Red blood cell, Hb: Hemoglobin, Htc: Hemotocrite, MCV: Mean corpuscular volume, MCHC: Mean corpuscular hemoglobin concentration, RDW: Red distribution width, PLT: Platelets, MPV: Mean platelet volume, PCT: Plateletcrit, NLR: Neutrophile lymphocyte ratio

Table 2. Binary logistic regression analysis for prediction of independent risk factors of vasovagal syncope

	OR	95% CI for OR lower limit	Upper limit	p-value
MPV**	0.453	0.275	0.745	0.002
Ferritin**	0.972	0.954	0.990	0.002
Constant	4806.80	-	-	0.001

**Normally distributed data. OR: Odds ratio, CI: Confidence interval, MCHC: Mean corpuscular hemoglobin concentration, MPV: Mean platelet volume

The pathophysiological mechanism of VVS is sophisticated and not well-understood. Usually, after a trigger, especially in combination with dehydration and/or a sudden upright posture, relative hypovolemia takes place. Afterward, cardiac contractility increases, the mechanoreceptors are triggered in the ventricle and then the vagal nerve transmits the signal to the central nervous system. The increased activity in vagal tone results in a decrease in heart rate. Additionally, the decrease in sympathetic activity causes a decrease in vascular tone in both arterioles and venules occurs. The decreases in preload, venous return, and ventricular volume leads to a drop in mean arterial pressure (11,12). Therefore, sympathetic system activation occurs due to reduced venous return during the early phase, and a suppression occurs in the sympathetic system in the terminal vasodilation phase. However, Vaddadi et al. (13) have proposed that in the terminal vasodilation phase, the parasympathetic system becomes active and suppression does not occur in the sympathetic system. Therefore, regardless of the controversy in the mechanism, the parasympathetic system becomes dominant over the sympathetic system in the terminal vasodilator phase. Head-upright-tilt test can be used to evaluate the syncope etiology and verify the diagnosis of VVS. According to the head-upright-tilt-table test, positive results in VVS can be categorized into cardioinhibitory type, vasodepressor type, and mixt type.

In the presence of sympathetic activation, the release of platelets with larger volume from the spleen to the systemic circulation and thrombopoiesis in bone marrow increase (14). Kabul et al. (15) demonstrated that platelet sizes were significantly larger in vasodepressor type VVS than in the other VVS groups and the control group. However, platelet sizes were

significantly lower in patients with cardioinhibitory and mixt-type response groups than in the other groups. Therefore, it was proposed that MPV values may have a role in predicting increased vagal response in patients with cardioinhibitory and mixed-type VVS (16). In the present study, platelet sizes were significantly smaller in VVS group. Furthermore, lower MPV was an independent risk factor. However, since the head-upright-tilt-test could not be performed VVS subtypes could not be categorized. On the other hand, Yalçın et al. (17) proposed that mixt-type VVS is the most common type of VVS in younger patients (<25 years). Thus, in the current study, significantly lower platelet sizes in VVS group may be related to the higher frequency of mixt-type of VVS at younger ages.

Research showed that there may be an association between iron storage and syncope (5). Jarjour and Jarjour (18) suggested that patients with neurally mediated syncope had significantly lower iron storage. Guven et al. (19) demonstrated that lower ferritin levels were more prevalent in children with syncope. A clinical trial showed that fluctuations of epinephrine activated the syncope episodes (20). Therefore, some researchers proposed that lower iron storage may be related to alterations in catecholamine metabolism. This suggestion was also supported by the evidence that monoamine oxidase, which plays a key role in the metabolism of epinephrine and norepinephrine, activity reduced in rats with iron deficiency (5). Similarly, serum ferritin levels were significantly lower in the VVS group and lower levels of ferritin were an independent risk factor, in the current study.

MCHC is a measure of the concentration of hemoglobin in a given volume of the erythrocyte and a low MCHC is related to reduced iron storage (21). Moreover, it was demonstrated that low MCHC and increased reticulocyte counts are the first findings indicating iron deficiency, even without anemia (22). In the present study, the most frequent abnormal laboratory parameter is low MCHC. This is the first study that demonstrated that MCHC was significantly lower in patients with VVS. This association may be due to the fact that iron deficiency may lead to a lower MCHC. Moreover, it should be kept in mind that the suggested levels of ferritin higher than 15 ng/mL are for iron deficiency anemia. The suggested levels for ferritin regarding other disorders related to iron

deficiency may be different. Therefore, numerical data of laboratory results were compared between the groups in the present study. There were no significant differences between the groups in terms of other CBC parameters. The absence of a relationship maybe associated with the fact that abnormality of these parameters are not the first findings of iron deficiency and maybe normal in children with mild iron deficiency without anemia.

The relationship between VVS and serum levels of folate and vitamin B₁₂ has been explained by the key role in the carbon transfer metabolism that is important for the production of serotonin, the other monoamine neurotransmitters, and catecholamines (4,5). Also, both vitamins have important roles in myelination and the synthesis of methionine from homocysteine and lower levels lead to hyperhomocysteinemia. Hyperhomocysteinemia has negative impacts on autonomic nerve functions, oxidative stress, inflammation, the proliferation of smooth muscle cells, and vascular endothelium (9). Aminorroaya et al. (4) found no significant differences in terms of folate and vitamin B₁₂ deficiency between VVS group and healthy controls. However, serum vitamin B₁₂ levels were significantly lower in patients with frequent VVS episodes (≥ 3 episodes) than in those with infrequent (< 3 episodes) episodes (4). Kovalchuk et al. (23) found that serum levels of pyridoxine and vitamin B₁₂ were significantly lower in the VVS group. Although no significant differences were found between the groups, lower levels of serum folate were associated with longer durations of VVS (23). Öner et al. (24) demonstrated that vitamin B₁₂ levels were significantly lower in children with POTS, also known as presyncope, than in the healthy controls. In the current study, there were no significant differences between the groups in terms of serum levels of vitamin B₁₂ and folate. The absence of the relationship may be related to the small number of patients and the complexity of the VVS pathogenesis.

This is one of the few studies evaluating extensive laboratory result in VSS. However, its retrospective design with a small number of patients, and the absence of the results of total iron-binding capacity and serum levels of iron were the limitations. However, having an infection was an exclusion criterion to specify the serum ferritin results for the evaluation

of iron storage of the patients. Although the head-upright-tilt-table test is not a certain requirement for the diagnosis, since the subtypes of VVS could be determined, the absence of the test was another limitation.

Conclusion

In conclusion, the current study showed that lower levels of MCHC, smaller platelet sizes and lower levels of serum ferritin were related to VVS. Furthermore, smaller platelet sizes and lower levels of ferritin were independent risk factors.

Ethics

Ethics Committee Approval: We have obtained the approval of the Ethics Committee from Aydın Adnan Menderes University in line with the principles outlined in the second Declaration of Helsinki (protocol number: 2022/91, date: 12.05.2022).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.A., Concept: M.A., Design: M.A., A.K.T., E.Ç., A.T., Data Collection or Processing: M.A., A.K.T., E.Ç., S.F.Ç., A.T., Analysis or Interpretation: M.A., S.F.Ç., Literature Search: M.A., S.F.Ç., Writing: M.A., S.F.Ç., A.T.

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