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Mean platelet volume level in patients with generalized anxiety disorder

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ABSTRACT

OBJECTIVE: Generalized anxiety disorder (GAD) is characterized by persistent and chronic anxiety state. Stressful life events and anxiety usually cause an increase in platelet volume and activity through various mechanisms. Mean platelet volume (MPV), which is indicative of platelet size, is accepted as an indication of platelet activity.

METHOD: In this first retrospective cohort study about MPV among GAD patients, we compared complete blood count especially in terms of platelet count (PLT), platelet distribution width (PDW), plateletcrit (PCT) and MPV values of 60 GAD patients with 60 healthy controls.

RESULTS: MPV was found to be significantly higher ($p = .008$) and platelet count was found to be significantly lower in the GAD group ($p = .001$). The area under the ROC curve (AUC) of MPV levels for GAD was 0.655 (95% CI: 0.557–0.754, $p < .001$).

DISCUSSION: Increased MPV levels in GAD patients in our study supports the hypothesis of increased platelet activation due to sympathetic system activation. Also platelet levels were found to be significantly lower in GAD patients in our study. This finding is consistent with the non-linear inverse relation between platelet volume and platelet count. According to ROC curve analysis for differentiation of GAD from those in the control group, MPV would be considered to be a "poor" biochemical marker. We believe that further controlled prospective studies about this issue will be valuable.

Introduction

Generalized anxiety disorder (GAD) is characterized by persistent and chronic anxiety state that lasts for at least 6 months which takes place in multiple areas of life. The lifetime prevalence is thought to be between 5.7% and 14.2% [1]. GAD patients are more likely to be encountered at primary health care facilities with non-specific complaints such as headache, muscle stiffness, gastrointestinal complaints, back pain and insomnia [2]. Major depressive disorder is a common companion to GAD beside increased rates of alcohol and substance abuse. It also aggravates physical diseases especially cardiovascular disorders [2,3].

Increased platelet activity has been detected in patients with major depression with a history of myocardial infarction and also in patients without any other risk factors effecting platelet activity [4,5]. On the other hand, anxiety symptoms in patients with coronary artery disease have been shown to be more effective in increased platelet activity than depression [6]. In a meta-analysis, Roest et al. [3] suggested that anxiety increased the risk of developing coronary artery disease by 26% when other medical conditions were controlled.

The exact mechanism of increased platelet activity after mental stress remains unclear. Anxiety disorders related "peripheral changes" are considered to be a cumulative sign of the total central nervous system activity. Stressful life events and anxiety usually elevate circulating levels of blood catecholamines. Increased catecholamine levels are thought to increase thrombosis by causing an increase in platelet activity and sympathoadrenal activation is thought to stimulate platelets through the α-2 receptors, resulting in an increase in platelet volume and activity [7,8]. It is accepted that serotonin which plays an important role in anxiety disorders is also an important factor in determining vascular tone and platelet aggregation [9]. Plasma platelets have the ability of synthesis, release and reuptake of serotonin similar to neurons in the central nervous system [10]. In addition, treatment with selective serotonin reuptake inhibitors may lead to a decrease in platelet activity [11].

Mean platelet volume (MPV), which is indicative of platelet size, is accepted as an indication of platelet activity [12]. Increased MPV levels are thought to be closely related to cardiovascular disorders [13]. MPV values were studied in also schizophrenia, bipolar disorder and panic disorder with contradictory and inconclusive results [14–18]. We could not find any study evaluating the MPV levels in GAD patients in the literature. In this study we aimed to evaluate MPV values in GAD patients and explore the diagnostic value of MPV in GAD.

Method

Study population

In this retrospective cohort study, complete blood count especially in terms of platelet count (PLT), platelet distribution width (PDW), plateletcrit (PCT) and MPV values of 60 patients without any psychiatric treatment history who admitted to the psychiatry outpatient clinic of Adiyaman University Training and Research Hospital and diagnosed with GAD were compared with the data of 60 healthy subjects who were similarly distributed in regard to age (18–60 years) and gender. The diagnosis of GAD was made according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) by an experienced psychiatrist.

Patients and controls whose data were missing or incomplete on record system were not included in the study. People with risk factors (drug use, hypertension, diabetes, coronary artery disease, cancer, hyperlipidemia, alcohol and substance use, pregnancy) that may have an impact on platelet counts were not included. Patients with other psychiatric comorbidities including unipolar depressive disorder were not included in the study even though their primary diagnosis were GAD.

This study was approved by the Adiyaman University Training and Research Hospital ethics committee (20.04.2017/3-10).

Biochemical analysis

Venous blood samples were obtained from antecubital vein of both patient and control group between 8 and 10 a.m. after at least 8 h of starving. Samples were centrifuged in 1 h and serum samples were studied at the same day in the biochemistry laboratory of Adiyaman University Training and Research Hospital with CELL-DYN 3700 SL analyzer (Abbott Diagnostics, Chicago, U.S.A.). The reference intervals were accepted as 142–424×10^3/uL for platelet count, 0–1000 fL for PDW, 0–1000% for PCT and 6.8–10.8 fL for MPV.

Statistical analysis

Statistical Package for Social Sciences (SPSS v20, Chicago, IL, U.S.A.) program for IOS were used. Descriptive parameters are expressed as mean, standard deviation or percentage. Kolmogorov–Smirnov test was applied to evaluate the normal distribution of the variables. Two-sided t-test and Pearson Chi-square test were used for comparison of normally distributed variables. Abnormal distributed variables were compared with Mann–Whitney U-test. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic value of MPV. A value of less than .05 was considered statistically significant.

Results

The mean age was 39.82 ± 18.97 in the GAD group and 34.92 ± 14.60 in the control group. The ratio of females was 63.3% in the GAD group and 71.6% in the control group, and there was no significant difference in terms of age and gender between the two groups (p = .229 and p = .330, respectively).

According to the comparison of complete blood count values, MPV was significantly higher (p = .008) and platelet count was significantly lower in the GAD group (p = .001). Other variables showed no significant differences. A comparison of socio-demographic variables and complete blood count values of the patient and control groups are given in Table 1.

When the groups were separated according to the gender; MPV was significantly higher (p = .010) and platelet count was significantly lower in the women GAD group (p = .001) whereas there was no significant difference between control and GAD groups among men. Comparison of MPV and platelet counts of men and women are given in Table 2.

Correlation between age and complete blood count values also are given in Table 3 separately.

ROC curve analysis performed to assess the diagnostic value of MPV is shown in Figure 1. The area

Table 1. Comparison of socio-demographic variables and complete blood count values of patient and control groups.

		GAD	Control	p
Age (years)		38.35 ± 18.97	34.90 ± 14.62	.229
Gender	Women (n:81)	38 (%63.3)	43 (%71.6)	.330
	Men (n:39)	22 (%36.7)	17 (%28.4)	
WBC (10^3/uL)		8.04 ± 1.70	7.88 ± 1.84	.623
HGB (g/dL)		14.01 ± 1.42	13.64 ± 1.54	.177
HTC (%)		42.12 ± 3.98	41.74 ± 5.02	.644
RBC (10^6/uL)		4.86 ± 0.46	4.80 ± 0.55	.478
MCV (fL)		85.92 ± 4.93	85.84 ± 5.22	.936
PLT (10^3/uL)		258.83 ± 52.41	297.93 ± 57.85	.001*
PDW (fL)		19.44 ± 2.10	19.33 ± 1.25	.721
PCT (%)		0.21 ± 0.05	0.20 ± 0.04	.112
MPV (fL)		8.15 ± 1.41	7.50 ± 1.24	.008*

Notes: GAD: generalized anxiety disorder; WBC: white blood cell; HGB: haemoglobin; HTC: haematocrit; RBC: red blood cell; MCV: mean corpuscular volume; PLT: platelet; PDW: platelet distribution width; PCT: platelectrit; MPV: mean platelet volume.
*p < .05.

Table 2. Comparison of MPV and platelet counts of men and women.

		GAD	Control	p
MPV (fL)	Women (n:81)	8.15 ± 1.43	7.38 ± 1.20	.010*
	Men (n:39)	8.15 ± 1.41	7.80 ± 1.33	.439
PLT (10³/uL)	Women (n:81)	260.98 ± 53.52	308.13 ± 55.68	.001*
	Men (n:39)	255.11 ± 51.47	272.14 ± 56.72	.334

Notes: GAD: generalized anxiety disorder; PLT: platelet; MPV: mean platelet volume.
*P < .05.

Table 3. The correlation between age and platelet parameters.

| Platelet parameters	r	p
Red blood cell count	−0.075	.417
Haemoglobin	−0.091	.323
White blood cell count	−0.085	.358
Haematocrit	0.031	.735
Mean corpuscular volume	0.083	.367
Platelet count	−0.189	.039*
Platelet distribution Width	−0.104	.258
Plateletcrit	−0.311	.001**
Mean platelet volume	−0.228	.012*

*p < .05.
**p < .01.

under the ROC curve (AUC) of MPV levels for GAD was 0.655 (95% CI: 0.557–0.754, $p < .001$). The optimal cut-off value for MPV level was 7.45 fL, and its sensitivity and specificity for diagnosis of GAD were 65% and 56.7%, respectively.

Discussion

In recent years, studies have increasingly been made on platelets to understand some psychiatric disorders and to evaluate the pharmacological properties of psychiatric drugs. Platelets contain many clotting and growth factors, as well as serotonin (5-HT), ADP, ATP and calcium at high concentrations. They have α-2, β-2 adrenoceptors, benzodiazepine and 5-HT (1, 2, 6, 3) receptors on their membranes [19]. Markovitz et al. [20] found that emotional stress increases platelet activity and suggested that stressors may play an important role in vascular events such as myocardial infarction. In the case of increased stress and anxiety, serotonin binds to 5-HT-2 receptors on platelets and mediates the release of factors that promote platelet aggregation [21]. Pecknold et al. [22] found that platelet 5-HT reuptake was increased in patients with major depression accompanying panic disorder. With the guidance of psychopharmacological studies on platelet receptors, researchers have suggested that human platelet 5-HT-2A receptor is a valid peripheral indicator of brain 5-HT-2A receptors [23]. Moreover Garcia-Sevilla et al. [24] have found an increase in the number of platelet α-2 adrenergic receptors in mood disorders and suggested that platelet α-2 receptors may also be an indicator of brain α-2 receptors. In another study, subchronic psychological stress has
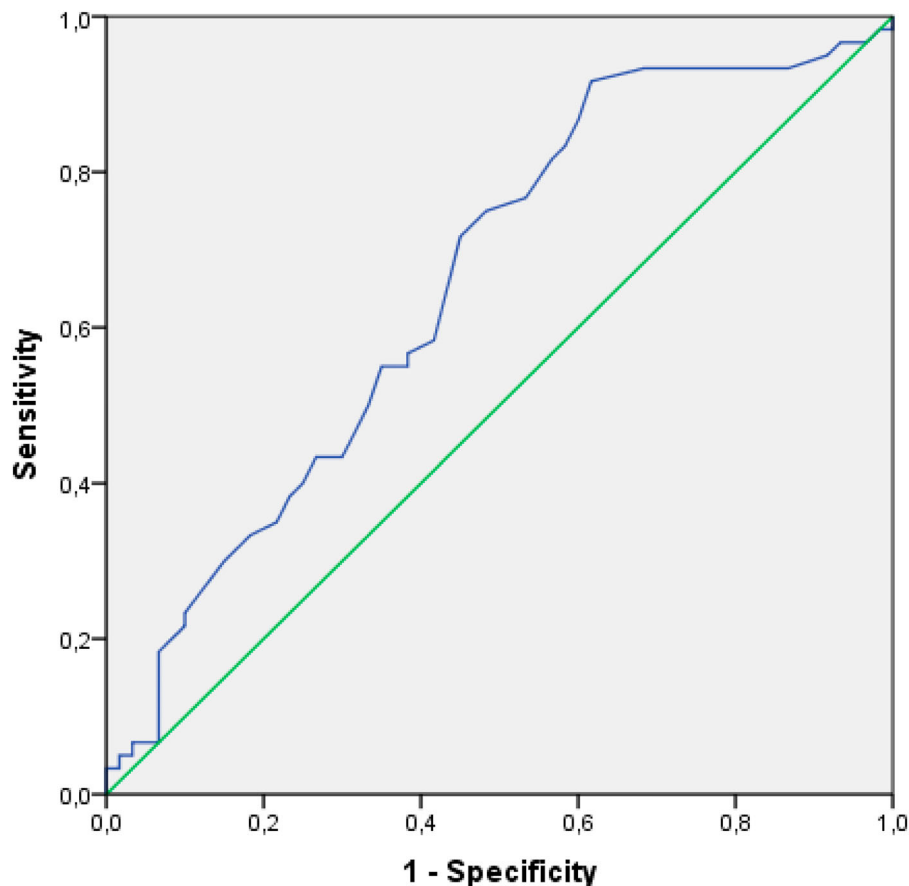
Figure 1. ROC curve analysis performed to assess the diagnostic value of MPV.

been shown to increase platelet α-2 receptor concentration, especially in women [25].

MPV has long been considered as an indicator of platelet activity [12]. The number of studies about MPV values in the field of psychiatry is scarce. In their large scale study, Canan et al. [26] showed that MPV values were increased in major depression patients, and these values were decreased after 8 weeks of escitalopram treatment. Results of the studies about MPV values in panic disorder patients were contradictory. Some reported that MPV values were higher in panic disorder patients [15,16] whereas others reported otherwise [14,17]. Increased MPV was attributed to activation of platelets via α-2 receptors and decreased MPV was attributed to 5-HT transporter rate and its metabolism. Serotonin imbalance, increased catecholamine levels and sympathetic system activation also play an important role in the pathogenesis of GAD and recent studies showed that these factors have important effects on platelet activation. Therefore increased MPV levels in GAD patients in our study supports the hypothesis of increased platelet activation due to sympathetic system activation. Also platelet levels were found to be significantly lower in GAD patients in our study. This finding is consistent with the non-linear inverse relation between platelet volume and platelet count [27].

Larger platelets inhabits more granules therefore have more vasoactive and prothrombic factors [28]. In a 10-year follow-up study published recently, GAD was found to be associated with cardiovascular mortality independent of metabolic syndrome and other cardiovascular risk factors. However, this relationship was detected only in female patients and not in male patients [29]. Supporting this result, when men and women were separately compared between patient and control groups in our study, only women GAD patients were found to have increased MPV levels. Even so, one should kept in mind that this finding may be due to small number of men patients and controls ($n = 39$). Nevertheless, it can be suggested that higher MPV levels especially in females may have a predictive diagnostic value for GAD. However, ROC curve analysis for differentiation of GAD from those in the control group demonstrated that MPV, at a cut-off value of 7.45 fL yielded a sensitivity and specificity of 56.44% and 87.72% respectively ($p < .001$). Unfortunately there is no established diagnostic marker for any psychiatric disorder yet and MPV too would be considered to be "poor" at separating GAD from healthy subjects.

Relationship between disease severity and MPV could not be determined since the study was performed retrospectively and there were no measurements of any severity scale was available in the records. The participants' body mass index and smoking status could not

be reached since the study was performed retrospectively. This is one of the important limitations. Another limitation of this study is the lack of data about specific inflammatory mediators which may have important effects on MPV values. The other limitation of this study is that power analysis was not used in the calculation of sample size. Despite all the limitations, this is the first study to evaluate MPV values in patients with GAD. We believe that further controlled prospective studies about this issue will be valuable.

Disclosure statement

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