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Research Article

Comparison of Platelet Parameters and Electrocardiogram Data in Patients with Generalized Anxiety Disorder with Healthy Control Group

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Abstract

Aim: Generalized anxiety disorder (GAD) refers to the intense stress and tension felt in the face of various life events. Various studies have shown that cardiovascular diseases are more common in patients with anxiety. Frontal QRS-T (fQRS-T) has been shown to be elevated in cardiovascular diseases. In this study, the fQRS-T, hemogram, and biochemistry values of patients with GAD were compared with healthy controls (HC) and the cardiovascular risk status of GAD patients was evaluated.

Material and Methods: Seventy patients with a diagnosis of GAD and no comorbidity followed in the district state hospital's psychiatry outpatient clinic were included in this study. Sociodemographic data, disease severity, hemogram, biochemistry values, electrocardiogram (ECG) data of these patients were recorded. Disease severity was evaluated with The Generalized Anxiety Disorder Test-7 (GAD-7). These values were compared with 80 HCs without any psychiatric or organic disease. The correlation of fQRS-T value with platelet parameters and age was investigated in GAD patients.

Results: According to the statistical analysis, fQRS-T was wider in patients with GAD than in HC (p<.001). Accordingly, basophil count was statistically lower in patients with GAD (p<.001). Eosinophil count and mean platelet volume (MPV) were significantly elevated in patients with GAD (p=.019 and p=.003 respectively). Accordingly, fQRS-T and MPV are highly correlated (p<.001). The GAD-7 score and fQRS-T were positively correlated (p=.001). According to the linear regression analysis for fQRS-T, MPV and GAD-7 scores positively and significantly predict fQRS-T (p<.001 and p=.036 respectively).

Conclusion: This study is the first in the literature to examine fQRS-T in patients with GAD. In this study, we discovered that MPV predicts fQRS-T in GAD. Future studies are essential in predicting cardiovascular risk using methods demonstrating platelet dysfunction in anxiety disorders.

Keywords: Generalized anxiety disorder, mean platelet volume, frontal QRS-T angle

INTRODUCTION

Generalized anxiety disorder (GAD) is marked by psychological and physical signs. Persistent anxious mood, irritability, difficulty concentrating, and feeling restless are psychological symptoms. Although most patients report memory problems, this often develops secondary to difficulty concentrating. Repetitive anxious thoughts consist of everyday events and physical complaints. For example, in the case of autonomic hypersensitivity, the patient begins to worry that he will have a heart attack if he notices the heartbeat. Physical complaints originate from muscle tension and autonomic hypersensitivity. Tension in the muscles can cause tension-type headaches, especially in the frontal or occipital regions, and tremors and pain in the back and shoulder region. Autonomic hypersensitivity can cause various somatic complaints by affecting all systems in the body. For example, the respiratory system is affected, causing a feeling of tightness in the rib cage and excessive breathing. Cardiovascular complaints are in the form of palpitations and chest pains (1).

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In general practice, patients with GAD refer to physicians because of physical rather than psychological symptoms. According to studies, these patients seek treatment from non-psychiatrists twice as often as they seek treatment from psychiatrists. Most patients with non-cardiac chest pain complaints have GAD (2). Patients with GAD apply to cardiology clinics at almost the same rate as panic disorder patients. However, panic disorder is recognized more than GAD due to the increasing media attention, especially in recent years. Other presenting complaints of GAD include chest pain, irritable bowel syndrome, hyperventilation syndrome, and fatigue. Therefore, examinations such as exercise electrocardiogram (ECG), echocardiogram, coronary angiogram, and endoscopy performed to evaluate most of these patients unnecessarily increase the cost on the healthcare system. There are limited data on the increased risk of cardiovascular disease in patients with GAD. In several studies, it has been reported that the risk of cardiovascular disease is elevated in patients with GAD (3).

Hypothalamic-pituitary-adrenal dysregulation, changes in platelet functions, impaired immune system and decreased heart rate variability are blamed in the pathophysiology of GAD. In addition, cardiac risk factors such as sedentary life, smoking, diabetes, dyslipidemia, alcoholism and hypertension are detected more frequently in GAD patients. These pathophysiological mechanisms and risk factors suggest that there may be a relationship between GAD and cardiovascular disease (3).

Frontal QRS-T angle (fQRS-T) is a non-invasive and simple ECG parameter that can be simply computed from ECG without requiring any special software. The fQRS-T is the definite angle diffraction between the QRS and T axes. This ECG parameter is quite recent and provides valuable insight into the process of myocardial repolarization (4). Researchers have documented that fQRS-T can forecast upcoming cardiovascular events in diverse populations, and this parameter has been linked to arrhythmias and sudden death (5).

Although the risk of cardiovascular disease in GAD patients has been evaluated in longitudinal studies in the literature, there is no similar study evaluating fQRS-T like this study. In this study, it is aimed to evaluate the risk of cardiovascular disease in GAD patients through the evaluation of fQRS-T and hemogram parameters and to provide treatments to prevent cardiovascular disease development in these patients.

MATERIAL AND METHOD

Study Design

The current research is a comparative and interpretive study. The Local Ethics Committee accepted the research protocol (Approval date: 2021-12-14; IRB Number: 2021/10-10). Permission was secured from all subjects before the project, and the examination was implemented following the Declaration of Helsinki.

Sample Size

The sample size was calculated as a result of the evaluation of the study by Almis et al. (6) 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 was applied according to the study of Almis et al. (6) (group 1: mean 7.50, standard deviation 1.24; group 2: mean 8.15, standard deviation 1.41; mean difference between groups: $p<0.05$). As a result, it was determined that at least 57 people must be in each group.

Study Group

The patients included in this study were followed by the same psychiatry specialist in the district state hospital psychiatry clinic. Cardiovascular examination of all patients was performed by a specialist cardiologist. Eighty-three patients with GAD, determined through The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), were involved in the examination (7). The Structured Clinical Interview for DSM-5-Clinician Version (SCID-5/CV) was used to diagnose patients in the study. Those with hypertension (n=2), coronary artery disease (n=1), valve disease (n=1), and arrhythmia (n=2), and those not within the age range of 18 to 65, were not included in the study. The symptom checklist 90 (SCL-90) was used to evaluate additional psychiatric disorders of GAD patients. Seven patients with depression were not included in the study. A total of 70 GAD patients were included as eligible for the study. Eighty healthy controls (HC) without any psychiatric or organic disease, who applied to the cardiology outpatient clinic to obtain a driver's license, employment report, and health report, were included in the study. Those with known coronary artery disease, valve disease, diabetes, hypertension, arrhythmia, thyroid gland disease, kidney disease, iron deficiency anemia were not included in the study. Age, gender, smoking status, hemogram, biochemistry, blood pressure measurements, and ECG parameters of the participants were used. Hemogram, biochemistry and ECG examinations of GAD patients were performed at the time of their first application to the psychiatry outpatient clinic.

The Generalized Anxiety Disorder Test-7 (GAD-7)

GAD-7 is a quick self-report instrument in line with DSM-IV-TR guidelines for assessing GAD (8). This is a scoring scale (0=none, 1=several days, 2=over half the days, 3=nearly every day) composed of seven questions that evaluate the feelings associated with the items on the scale over the last two weeks. The aggregate scores of 5, 10, and 15 on the scale are cut-off scores for mild, moderate, and severe anxiety, correspondingly. The Turkish validity and reliability study of the GAD-7 scale was performed by Konkan et al. (9). Konkan et al reported that the most acceptable value of sensitive and specificity for the diagnosis of GAD was 8 in GAD-7 scale. The GAD-

7 scale was administered to the patients during their first application to the psychiatry outpatient clinic.

Electrocardiogram Examination

The 12-lead ECG (Nihon Kohden, Tokyo, Japan) was monitored for each subject. QRS and QT interval parameters were generated systematically. QRS duration was measured between Q wave onset and S wave finish. QT interval was described as the duration between QRS onset to T wave end. QT interval differs with the heart rate (with a rise in heart rate, QT interval reduces, while with a drop in heart rate, QT interval lengthens). Thus, it needs to be adjusted accordingly to the heart rate. The corrected QT interval (QTc) represents the QT interval at a constant heart rate of 60. QRS and T axes were readily accessible in the documentation of the ECG machine. The report checked them, and the fQRS-T was determined by the actual difference between the QRS and T axes. ECG examination was performed by an 8-year-experienced cardiologist.

Laboratory Analyses

A venous blood sample was collected on admittance to the hospital. An electronic hematology testing device CELL-DYN Ruby (Abbott Diagnostics, Abbott Park, IL, USA), was utilized to measure white blood cells (WBC), including neutrophils and lymphocytes. We also measured hemoglobin, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), and platelet counts.

Statistical Analysis

Data were evaluated through SPSS software 26.0 (SPSS Inc., Chicago, IL, USA). Means and standard deviations were computed to represent numerical parameters, and percentages were computed to represent qualitative parameters. An elucidation of data patterns was done via the Kolmogorov-Smirnov test. Independent sample t-tests were applied when comparing continuous measures, while Mann-Whitney U tests were employed for non-continuous numerical measures. Chi-square tests were conducted to compare qualitative variables within the study group. Spearman correlation test was run to examine the relationship between fQRS-T, platelet parameters, disease severity score, and age. Linear regression analysis was performed to assess the impact of platelet parameters, disease severity score, and age on the fQRS-T.

RESULTS

According to the statistical analysis, fQRS-T was wider in patients with GAD than in HC (p<.001) (table 1). The comparison of laboratory parameters is presented in table 2. Accordingly, basophil count was statistically lower in patients with GAD (p<.001). Eosinophil count and MPV were significantly elevated in patients with GAD (p=.019 and p=.003 respectively). The correlation between fQRS-T with age, laboratory parameters, and GAD-7 score in patients with GAD is shown in Table 3. Accordingly, fQRS-T and MPV are highly correlated (p<.001). GAD-7 and fQRS-T were significantly and positively correlated (p=.001). Linear regression analysis was applied to evaluate the effect of age, GAD-7 score, MPV, PCT, and PDW on fQRS-T. Accordingly, the regression model was significant since p<.001 for ANOVA test. According to the linear regression analysis for fQRS-T, MPV and GAD-7 scores positively and significantly predict fQRS-T (p<.001 and p=.036 respectively) [F(5.58)=11.894, p=<.001, adjusted R square: .464].

Table 1. Comparison of sociodemografic and ECG parameters of patients with GAD and HC

	GAD Patients (n=70)	HC (n=80)	p
Age	32.34±6.87	32.53±6.29	.866[1]
Gender			
Female (n/%)	39 (55.7)	41 (51.2)	.585[3]
Male (n/%)	31 (44.3)	39 (48.8)	
Smoking (n/%)	23 (32.9)	22 (27.5)	.475[3]
Heart rate, bpm	79.79±13.90	78.71±12.93	.587[2]
QRS, msec	87.17±8.69	87.90±8.41	.603[1]
QT, msec	362.11±31.86	363.43±29.02	.792[1]
QTc, msec	404.49±28.84	404.51±27.15	.995[1]
fQRS-T (o)	40.84±26.82	23.85±19.44	**<.001[2]**

[1]Independent t test was used. [2]Mann-Whitney U test was used. [3]Chi square test was used. p<.05 was accepted as statically significance.
GAD: Generalized anxiety disorder, HC: Healthy controls, QTc: Corrected QT interval, fQRS-T: Frontal QRS-T angle

Table 2. Comparison of laboratory parameters of patients with GAD and HC

	GAD Patients (n=70)	HC (n=80)	p
Hemoglobin, mg/dL	14.78±1.84	14.29±1.98	.119[1]
WBC, 10^3/µL	7.65±1.81	7.90±1.62	.374[1]
Neutrophil, 10^6/µL	4.41±1.34	4.63±1.26	.325[1]
Lymphocyte, 10^3/µL	2.42±.76	2.54±.79	.377[1]
Monocyte, 10^3/µL	.53±.17	.50±.23	.829[2]
Eosinophil, 10^3/µL	.21±.17	.15±.12	**.019[2]**
Basophil, 10^3/µL	.04±.04	.08±.05	**<.001[2]**
Platelet, 10^3/µL	247.29±78.96	253.25±75.66	.540[2]
PDW, fL	19.93±1.25	20.14±2.01	.810[1]
MPV, fL•	8.34±1.21	7.73±1.47	**.003[2]**
PCT, %	.21±.05	.19±.05	.097[1]

[1]Independent t test was used. [2]Mann-Whitney U test was used. p<.05 was accepted as statically significance
GAD: Generalized anxiety disorder, HC: Healthy controls, WBC: White blood cells, PDW: Platelet distribution width, MPV: Mean platelet volume, PCT: Plateletcrit

Table 3. Correlation analyses of frontal QRS-T angle with age and inflammatory parameters in patients with GAD

	fQRS-T Angle
Age	r=.211
	p=.698
MPV	r=.666
	p=<.001
PCT	r=.119
	p=.328
PDW	r=.013
	p=.917
Platelet	r=.047
	p=.698
GAD-7	r=.420
	p=.001

Spearman corelation analyses was used. p<.05 was accepted as statically significance.
GAD: Generalized anxiety disorder, MPV: Mean platelet volume, PCT: Plateletcrit, PDW: Platelet distribution width, PLR: Platelet to lymphocyte ratio, GAD-7: Generalized anxiety disorder-7 score

Table 4. Lineer regression analyses of frontal QRS-T angle in GAD patients

	B	Std. Error	Beta	t	p	95 % CI	
						Lower	Upper
Constant	-122.116	51.292		-2.381	.021	-224.789	-19.444
GAD-7	1.723	.803	.214	2.145	.036	.115	3.330
MPV	13.344	2.203	.604	6.056	<.001	8.934	17.754
Age	.187	.405	-.044	-.462	.797	-.998	.623
PCT	13.994	43.796	.030	.320	.750	-73.672	101.660
PDW	1.548	2.062	.071	.751	.456	-2.580	5.676

Lineer regression analyses was used. p<.05 was accepted as statically significance.
GAD: Generalized anxiety disorder, GAD-7: Generalized anxiety disorder-7 score, MPV: Mean platelet volüme, PCT: Plateletcrit, PDW: Platelet distribution width

DISCUSSION

According to the results of our study, fQRS-T were wider among patients with GAD. In addition, MPV, positively correlated with fQRS-T, was higher in the group with generalized anxiety disorder.

fQRS-T shows the difference in the frontal plane projections of the QRS and T wave vectors showing ventricular repolarization and can be easily measured electrocardiographically. Aro et al., the first to analyze the connection between fQRS-T angle and cardiac mortality, stated that a wide fQRS-T angle was predictive of arrhythmic deaths (10).

Numerous studies have examined the increased cardiovascular risk associated with GAD. It is typical for patients with cardiovascular disease to suffer from anxiety disorders and related diseases, which can adversely affect cardiac mortality at the beginning and progression of their illness. The links between anxiety disorders and cardiovascular disease can be explained both physiologically (autonomic dysfunction, inflammation, endothelial dysfunction, alterations in platelet aggregation) and behaviorally. Because anxiety disorders and poor heart health are associated, it is crucial that these conditions are identified and treated promptly and accurately. The good news is that pharmacological and psychotherapeutic interventions are generally safe and effective for managing anxiety disorders (11,12).

There is a high incidence of GAD in people with heart disease. Meta-analysis found that cardiac patients were more likely to experience GAD at a point frequency of 11% and over a lifetime frequency of 26%. GAD frequency was reported at 14% in a meta-analysis of patients with coronary artery disease and heart failure. Comparatively, the general US population has a lifetime GAD frequency of 3 - 7% (13,14).

The cardiovascular risk of anxiety disorders is increased by a number of mechanisms. Inflammatory mechanisms have a significant contribution in the emergence and progress of heart disease (15). The development of heart diseases has been linked to inflammation pathways such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP). CRP levels have been linked to increased mortality in unstable angina patients. As a result, in patients with heart failure, inflammation is related to worsening of function, higher hospitalization rates, and poorer survival rates. It has been demonstrated that anxiety disorders are characterized by elevated inflammatory biomarkers (16,17). Research on healthy adults revealed high levels of anxiety to be correlated with increased levels of CRP, TNF-α, IL-6, homocysteine, and fibrinogen. Anxiety disorders, such as GAD, posttraumatic stress disorder (PTSD), and panic disorder (PD), have been implicated in inflammation, specifically CRP (18-20). It has been found that PTSD can also increase levels of TNF-α, IL-1, IL-6, interleukin-1β, and interferon-γ. There may be a link between anxiety disorders and inflammation that might be involved in the initiation to cardiovascular disease in anxiety disorders (21,22).

Regulating platelet activity, thrombosis, vascular tone, and leukocyte adhesion is important for maintaining vascular endothelial health (23). In patients with heart failure, endothelial dysfunction increases the likelihood of hospitalization, heart transplantation, and death (24,25). It has been found that anxiety disorders alter the endothelium of the vessels. Anxiety impairs the flow-mediated dilatation of the vasculature, suggesting more significant endothelial dysfunction (26-28). Patients with GAD, PD, and obsessive-compulsive disorder have lower levels of circulating endothelial progenitor cells,

which are essential for proper endothelial function and for preventing coronary artery disease progression (29). Further, in patients with PTSD, soluble tissue factor and von Willebrand factor levels are raised, which is related to thrombosis and atherosclerosis. Activation of platelets has been shown to play a major role in thrombosis and myocardial ischemia (30). There is evidence that serotonin increases platelet aggregation. There is proof that anxiety disorders are linked to disorders of the serotonin system, and this leads to increased cardiovascular disease risk (31,32).

By binding to 5-hydroxytryptamine-2 (5HT-2) receptors on platelets, serotonin increases the secretion of factors that boost platelet aggregation. Vasodilation is achieved by the production of nitrous oxide by endothelial cells in healthy vessels in order to prevent thrombus formation. Atherosclerosis damages the endothelial cells, causing the vessels to dilate improperly, and exposure to serotonin causes vasoconstriction (33). There is an underlying mechanism linking increased blood serotonin levels to cardiac events in coronary artery disease (34). Platelet aggregation is generally higher in patients suffering from anxiety and acute stress (35,36). The function of platelets may also be affected in anxiety disorders, such as PTSD and PD. Platelet activation may increase in PTSD patients due to fluctuations in circulating catecholamines and hyperactive sympathoadrenal system (37). Earlier studies have shown that patients with PD have abnormal nitrous oxide and homocysteine levels in their blood. Patients with PD showed increased MPV, indicating increased platelet activity (38).

Psychiatric conditions can cause biochemical changes in platelets. MPV, a indicator of platelet sizing, is viewed as a marker of platelet functioning (39). A higher MPV is strongly related to cardiovascular diseases, such as acute myocardial infarction, ischemic heart disease, and congestive heart failure (40). In hospitalized congestive heart failure patients, MPV is a predictive factor for hospital admission and 6-month mortality. Research has indicated that MPV is an independent determinant of atherosclerosis (41,42).

Ozdemir et al. found high MPV levels in patients with acute myocardial infarction and found a positive correlation between sympathetic activity and MPV. They explained this with the activation of alpha 2 receptors of the adrenergic system, activation of peripheral platelets and increased thrombocytopoiesis in the bone marrow (43). In a study comparing MPV values before and after cardioversion in patients with atrial fibrillation, Makowski et al. showed that there was a significant decrease in MPV levels and platelet levels indicated by fluorescent antibodies 4 weeks after sinus rhythm restoration with sinus rhythm restoration. They pointed out that MPV is inexpensive and easy to study as a predictor of thromboembolism in patients with atrial fibrillation (44). Chu et al. (2010) found that high MPV was a cardiovascular risk factor in a meta-analysis that included more than 6000 people and collected from 24 studies. They stated that this was due to the higher MPV levels in patients with acute myocardial infarction compared to the group without myocardial infarction, the higher mortality rates in patients with myocardial infarction with high MPV, and the higher incidence of restenosis in patients with high MPV in patients who underwent coronary angioplasty (45).

Uysal et al. investigated the relationship between anxiety levels and the dose of MPV and propofol in preoperative patients and found that MPV levels were higher in the group with high anxiety levels, and they found that the need for propofol dose was higher in the group with high anxiety levels (46). Almış et al found MPV higher and platelet count lower in GAD patients compared to the control group. According to the ROC analysis, they showed that those with MPV cut-off value above 7.5 fl had 56% sensitivity and 87.72% specificity for GAD (6). In a study by Mukta et al. with 144 patients, they found MPV levels to be higher in GAD patients compared to the control group (47). Gul et al found MPV levels lower in panic disorder patients compared to the control group. They thought that this might be due to abnormalities in 5-HT receptor functions (48).

In the present study, the high MPV in patients with GAD and the positive correlation of MPV with fQRS-T may explain the platelet dysfunction and excessive platelet aggregation that increase the risk of cardiovascular disease in GAD.

The present study has drawbacks. To validate these results, there could be a larger number of participants and multicenter studies. Laboratory reserches at the molecular level and microscopic examinations (peripheral smear), which can show platelet functions more clearly, may show better results. Since coronary angiography or myocardial scintigraphy was not performed in GAD patients or healthy controls, the presence of cardiovascular disease cannot be completely ruled out. Evaluation of the lipid panel could be used to assess participants' cardiovascular disease risk.

CONCLUSION

In this study, fQRS-T was found to be elevated in GAD patients. Evaluation of fQRS-T in GAD patients may identify GAD patients at high risk of cardiovascular disease. It may be recommended that these patients be evaluated by a cardiologist. Providing these patients with more effective psychiatric treatment and avoidance of tricyclic antidepressants or antipsychotics with high cardiac side effects may be helpful.

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Ethical approval: *The current research is a comparative and interpretive study. The Adıyaman University Local Ethics*

Committee accepted the research protocol (Approval date: 2021-12-14; IRB Number: 2021 / 10-10).

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