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Investigation of electrocardiogram and inflammation parameters in patients with first episode mania

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Abstract

Aim: This study examined inflammation markers and electrocardiogram data in patients with first-episode mania (FEM). It aimed to examine the inflammation processes in the early stages of the disease and the frontal QRS-T (fQRS-T) angle in bipolar disorder (BD).

Materials and Methods: After exclusion criteria, 53 FEM patients and 59 healthy controls (HC) were included in the study. Sociodemographic, electrocardiogram (ECG) and lab data of the participants were evaluated.

Results: Mean of age and gender distribution did not differ between the groups (p=.743, p=.294, respectively). The heart rate of the FEM group was significantly higher than the HC group (p<.001). fQRS-T was significantly wider in the FEM group than in healthy controls (p=.20). Albumin was significantly lower in the FEM group than in the HC group (p<.001). CRP and CAR values were significantly higher in the FEM group than in HC (p=.009 and p=.011, respectively). In the FEM group, HDL value was significantly lower than HC, while LDL value was significantly higher than HC (p=<.001 and p=.001, accordingly). MHR and AIP values were significantly greater in the FEM group than in HC (p=<.001 and p=.006, respectively). The fQRS-T angle in FEM patients was associated with MHR (r=.37).

Conclusion: This study is unique in evaluating inflammatory markers, fQRS-T angle, and heart rate in FEM patients. In this study, we found significantly higher inflammatory markers of MHR, CRP, and CAR in FEM patients in the control group. We found that these findings were consistent with the literature. Since the fQRS-T angle was wider in the FEM group, the cardiovascular risk may be increased in the early stages of BD disease.

Introduction

Bipolar disorder (BD) is common among around 1% of the general population, regardless of socioeconomic or ethnic background. BD is an important psychiatric illness that can cause disability among young people. BD is characterized by manic, hypomanic, and depressive episodes. A manic episode is a condition where symptoms such as irritability, risky behaviors, grandiose delusions, increased libido, increased amount of speech, flight of ideas, decreased need for sleep, increased energy, and irritability continue for at least one week. If hospitalization occurs, this period may be shorter. A diagnosis of BD type 1 is made in a patient who has had a manic episode [1].

Although genetic factors have been accused of the etiology of BD, sufficient evidence has not been obtained in this regard [2]. Inflammation is presumed to be a major role in the development of BD. It has been documented in previous investigations that activation of the immune system might be contributing to the emergence of BD symptoms [3].

In patients with BD, an increased systemic inflammatory response has been detected. Many investigations have detected abnormal levels of inflammatory biomarkers in patients with BD. For instance, C-reactive protein (CRP) is a protein manufactured by hepatic cells and plays a vital role in infections. In acute or chronic inflammatory processes, CRP rises in the blood [4]. It has been previously reported that the serum level of CRP increases during a manic episode [5]. Albumin is a negative acute phase reactant and is expected to decline in inflammatory states. CRP to albuminin ratio (CAR) is defined as one of the new indicators of inflammation. Although CAR has not been studied in BD patients, in one study, CAR was elevated in

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patients with schizophrenia relative to healthy people [6].

Meanwhile, there are evidences of autonomic dysfunction in BD patients, especially in manic episodes. Decreased heart rate variability and sympathetic activation have been reported in the manic phase. It is also well established that there is an elevated risk of cardiovascular disease in BD patients [7]. However, we could not find any study on cardiovascular disease risk in BD patients in the literature during the absence of drug use. On the other hand, some studies have indicated that increased inflammatory response can lead cardiac conduction abnormalities [8,9]. For instance, it is known that inflammatory response may trigger myocardial dysfunction, cardiac fibrosis, and increased coagulation, and these cardiovascular changes can cause cardiac arrhythmias [10].

Frontal QRS-T (fQRS-T) angle is defined as a new marker that can be easily measured on an electrocardiogram (ECG) and is measured higher in those with a high risk of cardiovascular disease [11]. It has been revealed that the fQRS-T angle may be predicted myocardial dysfunction [12].

All in all, it can be said there are inflammation-related underlying mechanisms in BD and cardiovascular abnormalities. Although there are studies in the literature reporting an increased risk of inflammation and cardiovascular disease in BD patients, these studies were conducted in the chronic phase of the disease. However, we could not find a study evaluating the risk of cardiovascular disease in the early stages of BD. In addition, we evaluated the parameters of inflammation in the early stages of the disease, based on the hypothesis that BD may occur with neuroinflammatory processes.

This study examined inflammation markers and electrocardiogram data in patients with first-episode mania (FEM). It aimed to examine the inflammation processes in the early stages of the disease and the fQRS-T angle in BD.

Materials and Methods

Study design and participants

This study had a retrospective and comparative nature. A permit was secured from the regional ethics committee for the present study (Adiyaman University Non-Interventional Clinical Researches Ethical Committee, IRB number: 2021/08-01). The investigation was executed under the Helsinki Declaration. The study sample comprised 53 out of 68 patients who sought treatment Psychiatry Inpatient Unit of Adıyaman Training and Research Hospital between January 1, 2016, and July 31, 2021, and were diagnosed with first-episode mania. The sample size was calculated as 53 using G*Power (3.1 Version, Dusseldorf, Germany) (The power of test: 0.8, alpha significance level: 0.05, Cohen's d effect size: 0.58). These FEM patients were hospitalized and treated. These patients were diagnosed with mania by experienced psychiatrists using the the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [13]. As a result of the hospital records of these patients, their history and interviews with their relatives, it was understood that they had not received psychiatric treatment before and that they had their first mania attack. Those with known arrhythmia, hypertension, valvular disease, diabetes mellitus, hypothyroidism, hyperthyroidism, and epilepsy were not included in the study because there may be changes in inflammation scores and ECG parameters. From patients of FEM, one patient with arrhythmia, two patients with hypertension, two patients with diabetes mellitus, and ten patients with insufficient ECG recording were not included in the study. For the control group of this study, data were collected from 59 healthy volunteers who applied to the psychiatry outpatient clinic for various reasons and did not have any comorbidities or psychiatric diseases.

Laboratory analysis

An electronic hematology testing device CELL-DYN Ruby (Abbott Diagnostics, Abbott Park, IL, USA) was used for complete blood count analysis. An Architect c8000 Chemistry System (Abbott Diagnostics, USA) measured albumin, CRP, and lipid panel. Routine complete blood count (white blood cell, platelet, neutrophil, lymphocyte, monocyte, basophile, eosinophile, hemoglobin) and biochemical parameters (hemoglobin, albumin, CRP, total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), fasting triglyceride levels of all participants were evaluated. Neutrophil lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), and platelet lymphocyte ratio (PLR) were assessed. The atherogenic index of plasma (AIP) is determined according to a logarithmic equation (fasting triglycerides/HDL-C).

Electrocardiogram analysis

ECG recordings were performed using a 12-lead ECG (Nihon Kohden, Tokyo, Japan). These ECGs are stored in patient files and hospital archives. ECGs were taken during the patient's admission to the psychiatry inpatient unit. These ECGs were collected from the hospital file archive system. Two specialist cardiologists evaluated these EKGs, one with nine years of experience and the other with 12 years of experience. Heart rate, QT, QRS, corrected QT (QTc), and fQRS-T angle were measured on ECG. The fQRS-T angle was calculated using the difference in angle between the direction of ventricular depolarization (QRS wave) and the direction of ventricular repolarization (T wave).

Statistical analysis

IBM SPSS Statistics for Macintosh version 26.0 (Armonk, NY: IBM Corp.) package program was implemented for the interpretation of the collected information. The normality distribution of the continuous variables was verified using the Kolmogorov-Smirnov test. Pearson Chi-Square test was performed to compare categorical variables between FEM and healthy controls (HC) groups. Continuous numerical variables of the groups with normal distribution were tested with the independent sample t-test, and those that did not fit the normal distribution were examined with the Mann-Whitney U test. The significance threshold was rated as $p<.05$ in statistical analyzes.

Results

The comparison of sociodemographic and ECG data of the FEM and HC groups is shown in Table 1. FEM patients consisted of 27 females and 26 males, and HCs consisted of 31 females and 28 males. The mean age of the FEM group was 24.15±6.62, and the mean age of the HC group was 24.98±7.38. There was no difference between the groups regarding mean age and gender distribution (p=.743, p=.294, accordingly). The heart rate of the FEM group was significantly higher than the HC group (p<.001). fQRS-T angle was significantly wider in the FEM group than in healthy controls (p=.20).

The comparison of the laboratory data of the FEM and HC groups is shown in Table 2. The Basophil count of the FEM group was significantly lower (p<.001). Albumin was significantly lower in the FEM group than in the HC group (p<.001). CRP and CAR values were significantly higher in the FEM group than in HC (p=.009 and p=.011, respectively).

In the FEM group, HDL value was significantly lower than HC, while LDL value was significantly higher than HC (p=<.001 and p=.001, respectively). MHR and AIP values were significantly higher in the FEM group than in HC (p=<.001 and p=.006, respectively).

According to Pearson correlation analysis, it was found a significant relationship between fQRS-T angle and MHR in FEM patients (r=.37). QTc interval in FEM patients was significantly associated with PLR and AIP (r=.29 and r=.28, respectively) (Table 3).

Discussion

There is growing proof that inflammation and the immune system are involved in psychiatric disorders. This is the first study in the literature in which ECG and critical markers of inflammation were evaluated together in the early stages of BD. The main results of our study were that the inflammatory markers CRP and CAR values were elevated in the FEM group versus the HCs. Moreover, MHR and AIP were significantly greater in the FEM group than in the HCs. We found the relationship of fQRS-T angle and MHR, and QTc interval and PLR and AIP in FEM patients.

MHR is a novel, easily calculated marker of inflammation. The relationship of inflammatory markers such as NLR, PLR, and CAR with mood disorders has been recently investigated in the literature. MHR is a prognostic factor indicating inflammatory status in cardiovascular diseases. Stimulation of monocytes triggers inflammation and causes cytokine release by migrating macrophages to tissues. However, monocyte activation is a trigger for the formation of atherosclerosis. HDL-C has immune-modulating actions that reduce monocyte and macrophage activity [14].

Açıkgöz et al. stated that MHR might imply deteriorated endothelial dysfunction [15]. Thus, the MHR may be part of the inflammatory mechanism. Here, we also detected increased MHR in manic episodes. These findings also sup-

Table 1. Comparison of Sociodemografic and ECG Parameters of Patients with FEM and HC.

	FEM Patients (n=53)	HC (n=59)	p
Age	24.15±6.62	24.98±7.38	.743[1]
Gender			.394[3]
Female (n/%)	27 (50.9)	31 (52.5)	
Male (n/%)	26 (49.1)	28 (47.5)	
Heart rate, bpm	89 [50-130]	79 [50-115]	<.001[2]
QRS, msec	78.47±6.79	79.15±7.32	.562[1]
QT, msec	361.26±24.56	362.53±25.11	.676[1]
QTc, msec	403.15±29.34	404.77±29.02	.885[1]
fQRS-T angle (°)	26 [12-38]	23 [0-82]	.020[2]

[1]Independent samples t test was used. [2]Mann-Whitney U test was used. [3]Pearson Chi square test was used. p<.05 was accepted as statically significance. FEM: First-episode mania, HC: Healthy controls, QTc: Corrected QT interval, fQRS-T: Frontal QRS-T.

Table 2. Comparison of Laboratory Parameters of Patients with FEM and HC.

	FEM Patients (n=53)	HC (n=59)	p
Hemoglobin, mg/dL	14.03±1.90	14.04±2.06	.961[1]
WBC, 10^3/μL	8.09 [1.12-16.77]	8.17 [4.43-14.34]	.618[2]
Neutrophil, 10^6/μL	4.87 [.5-12.02]	4.98 [2.09-9.89]	.531[2]
Lymphocyte, 10^3/μL	2.41 [.91-9.38]	2.60 [.93-8.87]	.229[2]
Monocyte, 10^3/μL	.75±.1.09	.53±.20	.125[1]
Eosinophil, 10^3/μL	.15 [.00-.53]	.18 [.00-1.00]	.947[2]
Basophil, 10^3/μL	.06 [.00-.46]	.10 [.00-.95]	<.001[2]
Platelet, 10^3/μL	255 [150-422]	249 [146-402]	.624[2]
Albumin, mg/dL	4.00 [2.80-7.40]	4.2 [3.00-5.30]	<.001[2]
CRP, mg/dL	.60 [.1-3.60]	.20 [.2-.7]	.009[2]
Total-C	167.20±47.58	172.51±40.86	.526[1]
Fasting Triglyceride	133 [44-861]	128 [34-737]	.610[2]
LDL-C	98.62±32.09	77.27±30.40	.001[1]
HDL-C	48.62±12.88	68.97±17.38	<.001[1]
NLR	2.34±1.68	2.26±1.24	.777[1]
PLR	118.65±48.53	112.42±54.59	.527[1]
MLR	.34 [.10-4.26]	.23 [.01-.93]	.064[2]
CAR	.15 [.02-1.03]	.05 [.04-.17]	.011[2]
MHR	.02 [.00-.16]	.01 [.00-.02]	<.001[2]
AIP	.35±.32	.17±.35	.006

[1]Independent samples t test was used. [2]Mann-Whitney U test was used. p<.05 was accepted as statically significance.
FEM: First-episode mania, HC: Healthy controls, WBC: White blood cells, Total-C: Total Cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, CRP:C-reactive protein, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MLR: Monocyte lymphocyte ratio, CAR: CRP albumin ratio, MHR: Monocyte high density lipoprotein cholesterol ratio, AIP: Atherogenic index of plasma.

Table 3. Correlations between fQRS-T and QTc interval, and inflammatory parameters in FEM patients.

Variable	fQRS-T angle	QTc
NLR	.05	.08
PLR	.11	.29*
MLR	.09	.03
CAR	.12	.19
MHR	.37*	.05
AIP	.23	.28*
CRP	.17	.20

FEM: First-episode mania, fQRS-T: Frontal QRS-T, QTc: Corrected QT interval, NLR: Neutrophil lymphocyte ratio, PLR: Platelet lymphocyte ratio, MLR: Monocyte lymphocyte ratio, CAR: CRP albumin ratio, MHR: Monocyte high density lipoprotein cholesterol ratio, AIP: Atherogenic index of plasma, CRP:C-reactive protein.
*p<.05.

port the inflammation that occurs in depressive and manic episodes in previous studies. In previous studies, MHR was found to be higher in patients with schizophrenia and BD than in the Hcs [16]. Therefore, MHR may help demonstrate inflammation in neuropsychiatric diseases. In a research undertaken by Caliskan et al., it was established that the MHR was significantly elevated in newly diagnosed BD patients and BD patients with long-term follow-up than in the HCs. They associated this situation with increased systemic inflammation and toxicity with the cumulative effect of mental and physical burden and prolonged progression in advanced stages of bipolar disorder [17].

Our study found heart rate and fQRS-T angle from ECG findings to be wider in patients with FEM than in the HCs. QRS-T angles on ECG have been discussed and researched over the years, however, until the last decade, there have not been extensive papers published on the risk assessment implications of QRS-T angles. The spatial QRS-T angle was indicated sooner than the fQRS-T angle. The spatial and fQRS-T angle depicts both ventricular repolarization and depolarization vectors. It is a critical ECG variable with prognostic value for outcome because various variables on both repolarization and depolarization have been documented to identify cardiac morbidity and mortality [11,18]. Increased heart rate is more strongly associated with mortality [19]. Heart rate is mainly an indicator of the autonomic effect on the sinus node, and increased adrenergic activity is pro-arrhythmic, while the heightened vagal tone is cardiac protective [20]. Furthermore, a higher heart rate can result in increased myocardial oxygen usage, and this increases the risk of ischemia in patients with coronary artery disease [19]. Additionally, the results of the present study have shown that wider fQRS-T angle may be related to higher MHR in FEM patients. It has been thought fQRS-T angle is affected by higher inflammatory response in FEM patients. What is more, QTc intervals in FEM patients have been associated with PLR and AIP. Indeed, many studies have indicated the association between systemic inflammation and cardiac conduction abnormalities [21,22].

In a study by Kulacogulları et al., NLR, MLR, PLR, and MHR were investigated in patients with all three stages of bipolar disorder. Moreover, NLR and MHR were considerably greater in manic and depressive episodes in comparison to euthymic episodes [23]. In a retrospective report by Wei et al., in which 13329 patients were recruited, multiple inflammation markers were investigated in schizophrenia and BD patients, and neutrophils, monocytes, and fasting triglycerides were greater than in healthy controls. In the same study, platelet, total-C, HDL-C, and LDL-C were lower in both patient groups than in the HCs. Higher MHR, neutrophils, monocytes, platelets, lower total-C, fasting triglycerides, and LDL-C were found in manic patients. In the same study, systemic inflammation in schizophrenia and BD was particularly emphasized. These findings are also compatible with our study [24]. In a study by Huang et al., CRP levels were demonstrated to be markedly elevated in manic patients in comparison to the HCs, which is consistent with our study [25].

In our study, HDL-C was low, and LDL-C was high in FEM patients. When we look at the literature, it is seen that fasting triglycerides, fasting triglycerides to HDL-C ratio, and several atherogenic lipids are seen to decrease in mania and increase in depression [26-29]. Contrary to other studies, Shapiro et al. found triglyceride, high triglyceride HDL-C ratio, and low HDL-C in mania patients. As a result of pharmacological drugs used in BD, sedentary lifestyles, high body mass indices, tobacco use, and excessive alcohol intake, atherogenic lipid levels may be high. Hyperlipidemia is possible even in bipolar disorder patients who do not receive psychotropic treatment [30].

Ekinci et al. evaluated inflammation and lipid parameters in different attack periods in BD patients. They stated that high CRP could be a predictor of bipolar depressive and mixed episodes, and MLR value could be a predictor of a manic episode. The same authors stated lipid metabolism is more impaired in remission and mixed periods. They stated that there are high LDL-C, triglyceride levels, and low HDL-C levels especially in the mixed period. They should be evaluated regarding coronary risk when evaluating patients in this mixed period [31].

Huang et al. found significantly lower total-C in patients with mania compared to patients with bipolar depression. They reported the lowest lipid ratios (low triglyceride and low HDL-C) in acute mania. The underlying mechanism of this decrease in lipid profile is unclear. Serum cholesterol can affect the neural activities of serotonin, the number, and functions of its presynaptic and postsynaptic receptors, and may explain the effects in the acute phase. It may have broad impacts on neurotransmission with consequences not limited to cholesterol depletion, excitatory amino acid transport, gamma-aminobutyric acid reuptake and transduction, N-methyl-d-aspartate receptor signaling, and serotoninergic functions. Increasing exertion may not justify the decline in triglyceride and cholesterol quantities in mania [29].

In the aforementioned above, in the present study, FEM patients had increased inflammation parameters. This suggests that there might be neuroinflammation even in the early stages of BD. Furthermore, FEM patients had

raised heart rates and wider fQRS-T. Knowing that the fQRS-T increased when there was cardiovascular disease, these findings considered that FEM patients had heightened cardiovascular disease risk or that there may be a developing cardiovascular disease. Moreover, FEM patients had lower HDL-C and higher LDL-C serum levels. This presentation of lab values also increases the cardiovascular disease risk.

Our analysis has some shortcomings. To begin with, this investigation is retrospective and non-longitudinal. Therefore, we cannot infer causality or directionality. Second, some markers of inflammation, cytokines, etc., have not been studied. Third, smoking and body mass index, which may affect inflammation and cardiovascular disease risk, have yet to be evaluated. Therefore, further studies regarding inflammation and cardiovascular risk are required with more detailed and extensive populations of BD patients.

Conclusion

In conclusion, this study is unique in evaluating inflammatory markers, fQRS-T angle, and heart rate in FEM patients. In this study, we found significantly higher inflammatory markers of MHR, CRP, and CAR in FEM patients in the control group. We found that these findings were consistent with the literature. Since the fQRS-T angle was wider in the FEM group, the cardiovascular risk may be increased in the early stages of BD disease.

Ethical approval

A permit was secured from the regional ethics committee for the present study (Adiyaman University Non-Interventional Clinical Researches Ethical Committee, IRB number: 2021/08-01).

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