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Electrocardiographic Findings in First-Episode Schizophrenia Patients: QT, QTc, P-Wave Dispersion, and Tp-e/QTc Ratio

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Abstract

To investigate the electrocardiographic results of newly diagnosed first-episode schizophrenia patients compared with healthy controls. This study included 70 individuals (35 diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, criteria and 35 healthy controls). Resting supine electrocardiography (ECG) recordings were obtained for all of the participants and evaluated by the same cardiologist. The heart rate, P wave durations, QT interval, Tpeak-to-Tend (Tp-e) value, P wave dispersion (PWD), QT dispersion, and Tp-e dispersion were calculated. There were no statistically significant differences in the demographic data among the participants. The mean age of the patient group was 27.06 ± 7.53 years, while that of the control group was 26.77 ± 4.33 years ($p>0.05$). The QT interval dispersion, PWD, Tp-e dispersion, and corrected QT (QTc) dispersion durations were higher in the patient group compared to the control group ($p<0.05$). The minimum Tp-e value and Tp-e/QTc ratio were lower in the patient group. Considering the obtained data, it can be suggested that even at the time of initial diagnosis without prior treatment, patients with schizophrenia are at risk for cardiac arrhythmias and rhythm disorders. Therefore, it is recommended that physicians take potential cardiac conduction issues into account when evaluating these patients and initiating medical treatment.

Keywords: schizophrenia, first-episode, electrocardiography, heart rate, QTc dispersion, P wave dispersion, Tp-e dispersion

1. Introduction

Schizophrenia is a neuropsychiatric disorder that affects 1% of the world's population (1). The disease progresses chronically with impairments in thought processing, emotional response, reality evaluation, neurocognitive areas, and functional capacity (2, 3). Its etiopathogenesis has not been fully elucidated. Various mechanisms such as genetic factors, neurotransmitter systems, immune system abnormalities, cranial changes, and environmental factors have been considered (3, 4). Although its etiology has not yet been clarified, it is known that with the chronicity of the disease, patients experience significant adaptation problems in work, family, and social areas (5, 6). In addition, the life expectancy of these patients is significantly shortened compared to the general population. The most common cause of early mortality is cardiovascular diseases. Compared to the general population, the mortality rate due to cardiovascular diseases is doubled in these patients (7). Sedentary lifestyles, smoking, alcohol use, and eating high-calorie foods have been indicated as responsible for the increase in mortality rates due to cardiovascular diseases (8, 9). In addition to all of these, it has also been suggested that antipsychotic drug treatment, which is started after diagnosis and must be used an extended period of time, also plays a role (9).

Routine electrocardiography (ECG) recordings are a non-invasive and widely used assessment tool for evaluating the cardiovascular disease risks of patients. The P wave duration and P wave dispersion (PWD), which can be easily calculated via ECG, are simple indicators of atrial conduction. Prolongation of the PWD duration serves as a warning for many cardiac conduction disorders and atrial fibrillation (AF) (10). Similarly, the development of ventricular arrhythmias can also be predicted using ECG. Indicators of ventricular repolarization include the QT interval, corrected QT (QTc) interval, QT dispersion (QTD) duration, Tpeak-to-Tend (Tp-e), and Tp-e/QTc ratio (11). These measurements are associated with ventricular arrhythmia and disruptions in electrical conduction (12). Values such as the PWD, QTc dispersion (QTcD), Tp-e, and Tp-e/QTc ratio, which can be easily calculated with ECG, allow for easy prediction of both

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atrial and ventricular rhythm disorders (10-12). Consequently, studies using ECG in mental disorders have increased in recent years. Psychiatric conditions such as obsessive-compulsive disorder, panic disorder, bipolar disorder, schizophrenia, and substance use disorders have been studied using ECG (13-18). Based on this body of literature, it was aimed herein to investigate the electrocardiographic results of newly diagnosed schizophrenia patients who had never used psychiatric drugs by comparing them with healthy controls.

2. Materials and methods

2.1. Inclusion and Exclusion Criteria

The study included patients who met the diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), were newly diagnosed, had no prior or current medical treatment, and were admitted for treatment at the Gaziosmanpaşa Mental Health and Diseases Hospital Psychiatry Clinic. Only newly diagnosed schizophrenia patients were included; patients with a prior diagnosis or who had received psychiatric treatment were excluded. Patients with personality disorders, alcohol/substance use disorders, or chronic diseases that could affect ECG results (such as obesity, diabetes mellitus, hyperlipidemia, hypercholesterolemia, heart failure, and heart conduction disorders) were also excluded from the study. Additionally, individuals receiving antiarrhythmic treatment and those who did not wish to participate were not included.

For the healthy control group, individuals who visited the mental health outpatient clinic for a military health board or single physician report, matched with the patient group in terms of demographic data, and who had no prior or current psychiatric diagnosis or alcohol/substance use disorder were included.

2.2. Data Collection Tools

All of the participants were informed about the study, and verbal and written consent were obtained from those who agreed to participate. After filling out the demographic data forms, resting ECG recordings were taken with the participants in the supine position.

2.3. Demographic Data Form

This form was created by the researchers in line with the aims of the study. It included demographic data such as age, marital status, education level, and employment status. In addition to demographic data, clinical assessment questions, such as whether there was prior psychiatric treatment or alcohol-substance use, were also included in the same form.

2.4. ECG Evaluation

For all participants who agreed to participate in the study, ECG recordings were taken in the supine position at a speed of 25 mm/s and a calibration of 10 mm/mV. Participants were not allowed to cough or talk during the recording. All measurements were evaluated by the same cardiologist. The heart rate and P wave durations in all of the leads were calculated, with the difference between the maximum and minimum values considered as the PWD. The distance from the start of the Q wave to the end of the T wave was measured as the QT interval, while the difference between the maximum and minimum durations was calculated as the QT wave dispersion.

2.5. Statistical Analysis

All of the calculated data were evaluated using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). The normality distributions of the data were analyzed using the Kolmogorov–Smirnov test. Descriptive analyses were performed to provide information about the general characteristics of the participants. Continuous variables were presented as the mean ± standard deviation, and categorical variables were presented as the number (n) and percentage (%). Demographic data were examined using cross-tabulation and chi-square tests. Since the ECG measurements did not follow normal distribution, they were evaluated using the Mann–Whitney U test. $p<0.05$ was considered statistically significant.

3. Results

3.1. Demographic and Clinical Characteristics of the Participants

For this study, 50 patients diagnosed with schizophrenia according to DSM-5 criteria and who had no prior psychiatric treatment were interviewed. Of these patients, 8 declined to participate and were excluded from the study. Among the remaining 42 patients, 2 had a diagnosis of diabetes mellitus, 1 had a permanent pacemaker, 2 had been diagnosed with schizoaffective disorder, 1 had a history of psychiatric treatment, and 1 had an alcohol/substance use disorder, resulting in their exclusion from the study.

Seventy participants who met the inclusion criteria were measured using the same ECG device. Measurements were taken before treatment initiation for the 35 patients diagnosed with schizophrenia and the 35 healthy controls. The calculated mean ages were 27.06 ± 7.53 years for the patient group and 26.77 ± 4.33 years for the healthy controls ($p > 0.05$). In the patient group, there were 7 women (20%) compared to 6 women (17.14%) in the healthy control group. There were no statistically significant differences in the marital status and education levels between the participants ($p > 0.05$). None of the participants used alcohol/substances. Since all of the patients in the patient group smoked, the control group was also selected from among smokers. The participants had an average cigarette consumption of 1 pack per day.

3.2. ECG Findings in the Patient Group

In the patient group, the heart rate was calculated as a minimum of 59, a maximum of 118, and an average of 82.06 ± 13.20 beats per minute. The electrocardiographic PWD was 27.52 ± 5.18 ms, Q wave dispersion was 38.19 ± 6.58 ms, and Tp-e dispersion was 21.97 ± 4.81 (Table 1).

3.3. Comparison of ECG Data Between Patient and Control Groups

The Mann–Whitney U test results for the groups are provided

in Table 2. In the comparison of the groups, the heart rate, QT minimum (QTmin), and QT maximum (QTmax) values were not statistically different ($p > 0.05$). The PWD, QTD, Tp-e dispersion, and QTcD durations were higher in the patient group, while the Tp-e/QTc ratio was lower (Table 2).

Table 1. Analysis of quantitative variables in the schizophrenia patient group

	Minimum value	Maximum value	Mean Value	Standard deviation
Heart rate	59	118	82.06	13.20
QTmin	306	398	325.19	16.26
QTmaks	338	369	354.94	10.64
QTd	24	49	38.19	6.56
Pmin	69	77	73.39	2.06
Pmaks	95	111	100.65	5.04
Pd	19	37	27.52	5.18
Tp-e min	58	75	66.87	5.79
Tp-e maks	74	103	88.84	8.97
Tp-e d	13	29	21.97	4.83
QTc min	374	398	388.61	7.32
QTc maks	410	451	435.35	10.47
QTc d	36	60	46.61	5.66
Tp-e/QTc	.16	.23	.20	.023

Abbreviations in the table: QT: Electrocardiography QT interval, P: Electrocardiography P wave, Tp-e: Electrocardiography Tp-e value

Table 2. Analysis of Quantitative Variables of Participants

	Healthy Control Group (N=35)	Schizophrenia Patient Group (n=35)	U value	p
Kalp hızı	29.67	32.29	425.000	0.564
QTmin	33.83	28.26	380.000	0.220
QTmaks	29.03	32.90	406.000	0.394
QTd	16.78	44.76	38.500	**0.000***
Pmin	31.52	30.50	449.500	0.821
Pmaks	*18.13*	43.45	79.000	**0.000***
Pd	17.52	44.05	60.500	**0.000***
Tp-e min	38.53	23.71	239.000	**0.001***
Tp-e maks	26.98	34.89	344.500	0.081
Tp-e d	18.55	43.05	91.500	**0.000***
QTc min	18.47	43.13	89.000	**0.000***
QTc maks	15.80	43.71	9.000	**0.000***
QTc d	15.50	46.00	.000	**0.000***
Tp-e/QTc	36.62	25.56	296.500	**0.014***

Abbreviations in the table: QT: Electrocardiography QT interval, P: Electrocardiography P wave, Tp-e: Electrocardiography Tp-e value
The Mann-Whitney U test was used for the calculations. *p<0.05

4. Discussion

Herein, the electrocardiographic results of newly diagnosed schizophrenia patients with no psychiatric drug use were investigated by comparing them with those of healthy controls. In the results, the heart rate, QTmin, QTmax, p wave minimum (PWmin), and Tp-e maximum values of the patients were not different than those of the controls. However, the QTD, P wave maximum (PWmax), PWD, Tp-e dispersion, and QTc minimum/maximum and dispersion times were prolonged in the patient group. The Tp-e minimum and Tp-e/QTc ratio were shortened in the patient group compared to the healthy controls.

The heart rates of the patients were not different than the healthy controls. The heart rate varies physiologically during the day and is reported to increase at night and decrease during the day. Changes in the heart rate can be expressed in 2 ways, as time-dependent and frequency-dependent. In time-dependent analysis, ECG records the time between 2 R waves, while frequency-dependent analysis shows the change in the vagal tone. High frequency reflects parasympathetic activity and low frequency reflects sympathetic activity (19). With this complex nature, it has been suggested that heart rate changes may be a biomarker in mental diseases including schizophrenia (20). In a meta-analysis study conducted to calculate the heart rate changes in patients with schizophrenia, it was found that the heart rates of the patients changed due to vagal tonus changes. It was also reported that different results could be obtained in different periods of the disease (first attack period, agitated-acute disease period, while in remission, and depending on the drugs used) (21). Similarly, in another review study, it was shown that vagal tones may change in patients with schizophrenia and the heart rate may change accordingly. It was shown that the time-dependent or frequency-dependent heart rate may change depending on different periods of the disease and different characteristics of the patients included in the study (19). In a study conducted on a limited number of first-episode schizophrenia patients (n=8), there was no difference in the low or high frequency heart rate. It was reported that the vagal stimuli in the patient and control groups were not different (22). In 2 separate studies conducted in Türkiye on patients with chronic schizophrenia, the heart rates were not different in the patient and control groups (13, 23). Similarly, in the results of the current study, the heart rates of the newly diagnosed schizophrenia patients who had not received drug treatment before or in their current state were not different than those of the healthy controls.

AF is one of the most common cardiovascular diseases and affects approximately one-third of people worldwide (24, 25). Diabetes mellitus, hypertension, thromboembolic events, and vascular diseases increase the risk of AF (26). In addition to these, an increased risk of AF has been reported in chronic psychiatric diseases including schizophrenia and bipolar disorder. In line with this, a significant increase in the risk for AF was described in 10–20-year follow-up studies in chronic mental diseases (27). Severe heart failure, stroke, and sudden death are among the most important outcomes feared for AF. It has been reported that any anticoagulant treatment should be used to prevent these complications (28). There are even publications recommending the use of oral anticoagulants from the moment of the first diagnosis against the increased risk of AF in patients with mental illnesses such as schizophrenia and bipolar disorder (27, 29). The P wave durations and PWD time, which can be easily calculated via ECG, are predictive for AF (10). In studies conducted in Türkiye on chronic mental

diseases, increased PWD has been shown. In one of these studies, it was found that the PWD durations of 44 patients with bipolar disorder were prolonged compared to the controls (18). In 2 separate studies conducted on chronic schizophrenia patients, the PWD was prolonged when compared with the healthy controls (13, 23). The cardiac effects of antipsychotics, mood stabilizers, antidepressants, or other psychiatric treatments cannot be calculated even if there is no medication use for a month. In the results herein, unlike these other studies, newly diagnosed schizophrenia patients with no prior treatment use were evaluated. The results obtained were similar to those in the literature. The PWD times of the patients were approximately 2 times longer than the healthy controls. It is noteworthy that while the PWmin value did not change, the PWmax value and PWD time were prolonged by up to 2 times.

Finally, the QT interval duration, QTc duration, QT and QTcD durations, Tp-e and Tp-e/QTc ratios, which are easily evaluated by ECG and are predictors of ventricular arrhythmia (11), were examined in the current study. A change in the duration of the QT interval, indicates a change in the duration of ventricular repolarization. This is an indicator of recurrent arrhythmias and rhythm disturbances in patients (30). Studies have shown that QT intervals change in chronic mental diseases such as schizophrenia. In a study conducted on schizophrenia patients who were still receiving antipsychotic treatment, it was shown that their QTcD values were prolonged. However, the minimum and maximum values were not included (23). In a study conducted on schizophrenia patients who had not been on medication for at least 1 month, the QTD and all QTc values (minimum, maximum, and dispersion) were prolonged compared to the healthy controls, whereas the QTmin value was shortened compared to the healthy controls. This result was interpreted as the QTc values being more specific for the ventricular rhythm (13). In a study conducted on a limited number of first-episode schizophrenia patients, it was found that QTc values were prolonged (30). Similarly, in the present study, schizophrenia patients who were first diagnosed and had never used any medication were evaluated. In the results, the QTD duration was prolonged in the patient group, while the QTmin and QTmax values were not different than controls. For the QTc values, all of the results (minimum, maximum, and dispersion times) were prolonged. With this result, it was concluded that patients are at risk for cardiac conduction disturbances even when they are newly diagnosed, just as in patients with chronic schizophrenia.

Finally, although the Tp-e and Tp-e/QTc ratios are less common in studies conducted on patients with mental disorders, it was reported that the Tp-e dispersion value is more reliable than other parameters in demonstrating ventricular arrhythmia (31). In a study conducted on patients with chronic schizophrenia, the Tp-e dispersion was never examined (23). Similarly, Tp-e measurements were not included in a study conducted on patients with first-episode schizophrenia (30). In another study conducted on patients with chronic schizophrenia, the Tp-e minimum duration was shortened, the Tp-e maximum duration was prolonged, and naturally, the Tp-e dispersion duration was also prolonged (13). Tp-e values and Tp-e/QTc ratio values, which are very important parameters in demonstrating cardiac arrhythmias, were different than those of the controls in the current study. In the results herein, while the Tp-e maximum duration was not different than the controls, the Tp-e minimum duration was shortened and the Tp-e dispersion duration was prolonged compared to the controls, as expected. The Tp-e/QTc ratio was shortened, as the QTc duration of the patient group was almost doubled.

The present study should be evaluated by considering some limitations. The first of these is the relatively insufficient number of the sample. The other limitation is that the majority of the patients were male and the control group was also selected among males and no gender distribution was achieved. These limitations limited the generalization and interpretation of the results. Thus, the results should be supported by further studies with larger sample groups that have equal gender distribution.

In conclusion, in the current study, it was found that the values shown as predictors for atrial and ventricular arrhythmias in newly diagnosed schizophrenia patients with no prior drug use were different than the healthy controls. Among these values, the PWD, QTD, Tp-e dispersion and QTc values, which are particularly important, were prolonged. With these results, it was concluded that patients with schizophrenia are at risk for cardiac conduction and rhythm disturbances even without prior drug use. It is recommended that physicians should take these results into consideration when starting medical treatment and be alert for cardiac problems.

Ethical Statement

Approval was obtained from the Non-Interventional Local Ethics Committee of Gaziosmanpaşa University on April 30th, 2020, with project number 20-KAEK/077 and reference number 83116987-189

Conflict of interest

All of the authors declare that there are no conflicts of interest in connection with this paper.

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Authors' contributions

Concept: F.Ü.D., F.Ö., Design: F.Ü.D., Data Collection or Processing: F.Ü.D., E.Ç., Analysis or Interpretation: B.D., Literature Search: F.Ö., F.Ü.D., Writing: F.Ü.D, F.Ö., B.D., E.Ç.

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