The Relations of Brugada ECG Pattern and Fragmented QRS in Patient with Schizophrenia

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Abstract

Objective Schizophrenia is a psychiatric disease with high risk of fatal rhythm disorders and sudden cardiac death. A previous study reported that Brugada syndrome was highly prevalent in patients with schizophrenia. In this study we aimed to investigate the prevalence of Brugada syndrome and fragmented QRS in patients with schizophrenia.

Materials and Methods Two hundred and fifty patients with schizophrenia who were followed up in the psychiatry clinic, and 400 age- and sex-matched non schizophrenia controls were included. Standard ECGs and high intercostal ECGs with V1 and V2 derivation above two intercostal intervals were taken.

Results In schizophrenia patients, Type 1 Brugada syndrome was not observed, Type 2 Brugada was identified in one subject and Type 3 Brugada was observed in two patients. In the control group, Type 2 Brugada pattern was identified in one subject and again one control had Type 3 Brugada pattern (p=0.320). The fragmented QRS (fQRS) incidence, QRS duration and corrected QT were observed to be higher in the schizophrenia group compared to the control group (p=0.001, p=0.003, p<0.001, respectively).

Conclusion There is no increased prevalence of Brugada-ECG pattern in patients with schizophrenia. Importantly, the prevalence of fQRS was significantly higher in patients with schizophrenia compared to the control group. Fqrs can be used to estimate the frequency of cardiovascular events in patients with schizophrenia.

Keywords Schizophrenia; Brugada Syndrome; fragmented QRS
INTRODUCTION

Brugada syndrome is an autosomal dominant inherited genetic syndrome and known to have an increased risk of sudden death linked to rapid polymorphic ventricular tachycardia or ventricular fibrillation. Recent studies showed that fragmented QRS (fQRS) is a reliable electrocardiogram (ECG) finding with the importance of an indicator of myocardial fibrosis and scarring.

One of the common causes of sudden cardiac death in schizophrenia is thought to be cardiac arrhythmia. Although the cause of the increase in the incidence of cardiac arrhythmia is uncertain, medications used or genetic variations identified in schizophrenia patients are thought to affect the electrophysiology of the heart through sodium channels. A previous study reported that there was a very high rate (11.6%) of Brugada syndrome, which has a genetic inheritance and high risk of sudden cardiac death, in patients with schizophrenia.

In this study we aimed to investigate the frequency of Brugada syndrome and fQRS in patients with schizophrenia.

MATERIALS and METHODS

This study is a descriptive study. Our study included a total of 250 patients being monitored in the psychiatry clinic for the diagnosis of schizophrenia according to the Diagnostic Statistical Manual of Mental Disorders – IV classification. Patients who did not give permission for electrocardiography (ECG), patients with advanced heart failure, valve disease and bundle branch block were excluded from the study. The study was approved by Ordu University ethic committee(03.06.2016, no:2016/54) and all participants provided written informed consent. The study also included an age- and sex-matched control group of 400 individuals applying to the psychiatry clinic without diagnosis of schizophrenia.

ECG Analysis

Standard ECGs and high intercostal ECGs with V1 and V2 derivations above two intercostal intervals were obtained from all participants. All ECGs were screened for Type 1 (At the end of QRS, an ascending and quick slope with a high take-off ≥2mm followed by concave or rectilinear downsloping ST), Type 2 and Type 3 Brugada syndrome ECG characteristics by a cardiologist blind to the patients’ diagnoses. Fragmented QRS (fQRS) was defined as narrow QRS complex (duration <120 ms) with R wave notching, S wave notching, RSR’ pattern or more than one R’ in at least two consecutive derivations. The diagnosis of Brugada Syndrome requires typical ST-segment elevations in right precordial ECG leads and events suggestive of cardiac arrhythmia or a family history of Brugada.

Statistical analysis

SPSS (SPSS 20.0 software) packet program was used for statistical analysis. Continuous variables were given as mean standard deviation (SD) and categorical variables were given as percentages. Pearson chi-square analysis and Fisher’s Exact test were used to compare categorical variables. A p value <0.05 was considered statistically significant.

RESULTS

The demographic characteristics of the groups included in our study are shown in Table 1. The ECG parameters of the groups are shown in Table 2. The fQRS frequency, QRS duration and QTc were observed to be higher in the schizophrenia group compared to the control group (p=0.001, p=0.003, p<0.001, respectively). Both mild and severe QTc prolongation were observed more often in the schizophrenia group (p<0.001, p<0.001, respectively). In subgroup analysis, fQRS (Fig.1) was found to be more common in male sex (p<0.011) and in those with fQRS, QTc was observed to be higher (425.7±42.4 vs. 397.6±25.4; p<0.001).
Table 1: Clinical and demographic characteristics of the study population

|                         | Schizophrenia Group (n: 250) | Control Group (n: 400) | p   |
|-------------------------|-------------------------------|------------------------|-----|
| Age, mean±SD (years)    | 44.33 ± 14.7                 | 45.6 ± 9.8             | 0.164 |
| Male, n(%)              | 130(52)                      | 230(57.5)              | 0.169 |
| Diabetes Mellitus, n(%) | 10(4)                        | 30 (7.5)               | 0.070 |
| Hypertension, n(%)      | 25(10)                       | 45 (11.2)              | 0.616 |
| Hyperlipidemia, n(%)    | 20(8)                        | 41(10.1)               | 0.338 |
| Heart Rate, mean±SD(beat/min.) | 78.4± 14.1                  | 77.6± 16.1             | 0.509 |
| Sodium channel blockers, n(%) | 85 (34)                     | -                      | -    |
| QT-interval–prolonging drugs, n(%) | 190 (76)                    | -                      | -    |
| Selective serotonin reuptake inhibitors, n(%) | 38 (15.2)              | 30 (7.5)               | 0.002 |
| Tricyclic antidepressants, n(%) | 40 (16)                     | 25 (6.2)               | <0.001 |
| Antipsychotics          |                               |                        |      |
| Clozapine, n(%)         | 150 (60)                     | -                      | -    |
| Olanzapine, n(%)        | 50 (20)                      |                        |      |
| Aripiprazol, n(%)       | 15 (6)                       |                        |      |
| Risperidon, n(%)        | 15 (6)                       |                        |      |
| Quetiapine, n(%)        | 5 (2)                        |                        |      |

DISCUSSION

According to the results of our study; The Brugada ECG frequency was similar to schizophrenia patients and non-schizophrenia control group. Importantly, the prevalence of fQRS was significantly higher in patients with schizophrenia compared to the control group.

Previous studies have shown that schizophrenia patients have higher mortality secondary to sudden cardiac death and cardiac arrhythmia compared to the normal population.\(^5\)\(^6\) The most important cause of this is considered to be the arrhythmogenic potential of the medications used and the possibility of genetic ion defects shown in this patient population that may affect cardiac electrophysiology.\(^3\) Brugada syndrome is a rare clinical entity with high risk of sudden cardiac death\(^1\) and a study by Bloom et al. found high rates of Brugada syndrome among schizophrenia patients in their population (north Holland). They suggested that the higher prevalence of Brugada syndrome may be responsible for the increased mortality rate in schizophrenia patients.\(^4\) Bloom et al. identified a higher incidence of sudden cardiac death in their study population. However, the association between higher prevalence of Brugada syndrome and increased rate of sudden cardiac death was only an observation far from being just an established clinical cause-effect relationship.\(^4\) Again, Bloom et al. proposed that the antipsychotics especially Na channel blockers used by schizophrenia patients may provoke Brugada syndrome.\(^4\) Contrary to the results of the study of Bloom et al, schizophrenia patients using antipsychotics and Na channel blockers were not found to have a higher prevalence of Brugada syndrome in our study. However, in line with the previous studies the QTc prolongation was identified to be higher in our patient population.\(^7\)\(^8\)

In the European countries such as Germany and Denmark, the prevalence of Brugada Pattern on ECG was low with the rates of <0.05% (<1 in 2000), while in Turkey it was reported to be ≥0.05% (≥1 in 2000) (Type 1 Brugada pattern 0.08%, Type 2-3 Brugada pattern 0.40%).\(^9\) The study by

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**Table 2: Comparison of ECG parameters between Schizophrenia and Control Group**

|                        | Schizophrenia Group (n:250) | Control Group (n:400) | p   |
|------------------------|-----------------------------|-----------------------|-----|
| Brugada                |                             |                       |     |
| Type 1, n(%)           | 1(0.40)                     | 1(0.25)               | 0.320 |
| Type 2, n(%)           | 1(0.40)                     | 1(0.25)               |     |
| Type 3, n(%)           | 2(0.80)                     | 1(0.25)               |     |
| Mild Prolongation of QTc-interval, n(%) | 31(12.4)                 | 1(0.25)               | <0.001 |
| Severe Prolongation of QTc-interval, n(%) | 21(8.4)                   | -                     | <0.001 |
| QTc duration, mean±SD (ms) | 413.0 ± 31.4               | 390.4 ± 23.1          | <0.001 |
| QRS duration, mean±SD (ms) | 102.1 ± 24.1               | 92.3 ± 14.1           | 0.003 |
| fQRS, n(%)             | 50(20)                      | 39 (9.8)              | 0.001 |
| Heart Rate, mean±S-D(beat/min.) | 78.4 ± 14.1                | 77.6 ± 16.1           | 0.509 |
| QTc: Corrected QT, fQRS: Fragmented QRS |                       |                       |     |
Bloom et al. revealed that the prevalence of Brugada syndrome among patients monitored for schizophrenia was higher than the control group (11.6% vs. 1.1% and 2.4%). Although the prevalence of Brugada syndrome in Turkey is known to be higher compared to European countries, the present study demonstrated that the prevalence of Brugada syndrome was not higher among schizophrenia patients when compared to controls in Turkey (p:0.320) contrary to the results of the study of Bloom et al. which was conducted in north Holland. Although Brugada syndrome is an autosomal inherited disease, it is known to occur 8-10 times more often in men compared to women. In our study 52% of the patients were male, while in the study by Bloom et al. this rate was 70.9%. Consequently the Brugada prevalence found in the study by Bloom et al. was very high and we believe that larger prospective studies are required to explain this difference.

Yap et al. found a weak correlation between the manifestation of Brugada syndrome and increase in sudden cardiac death risk with the use of sodium channel blockers. In our study the prevalence of Brugada was not increased among schizophrenia patients, leading to the consideration that there was no effect of the medications used. Previous studies of schizophrenia patients have focused on the fact that genetic variations in ion channels may affect cardiac electrophysiology and may trigger arrhythmic deaths. Unfortunately we did not perform any genetic study in our research.

Many studies have shown that the presence of fQRS on ECG is related to myocardial fibrosis and and increases the risk of sudden cardiac death. Many causes including cardiac ischemia, myocarditis or increased sympathetic activity may cause development of myocardial fibrosis. Myocardial fibrosis disrupts the electrical activity of the heart and increases the risk of arrhythmic death. The antipsychotic medications used in the treatment of schizophrenia are known to cause myocarditis and increase sympathetic activity. In our study we found that the frequency of fQRS, which is a strong predictor of cardiac fibrosis was significantly higher in patients with schizophrenia. We suggest that this may be due to the cardiac effects of medications used or the neurohormonal changes in schizophrenia. fQRS, which is easy to assess with surface ECG, shows electrical heterogeneity secondary to myocardial fibrosis and may be beneficial to predict sudden cardiac arrhythmias. We believe that it will be valuable to determine whether there is a correlation between presence of fQRS on ECG and mortality in patients with schizophrenia with prospective studies.

**Study Limitations**

Our study had a cross-sectional design with no prospective monitoring of patients. Patients were not monitored to show the correlation between presence of fQRS and mortality. Lack of echocardiographic evaluation, magnetic resonance imaging or histological assessment in order to demonstrate myocardial fibrosis can also be considered as a limitation. Drug use of the patient group can also be considered as study limitations. However, the obligation of patients with schizophrenia to receive treatment is a part of their lives.

**CONCLUSION**

We found that the prevalence of Brugada ECG pattern was not higher in patients with schizophrenia. Many factors such as the low prevalence of Brugada syndrome in the general population, geography, genetics and sex may have affected the results of our study. The higher prevalence of fQRS in schizophrenia patients in our study leads to the consideration that myocardial involvement than the genetic transmission may be more frequent in these subjects. For the use of fQRS as a marker of cardiac risk in schizophrenia patients, there is a need for large scale studies in different geographical regions.
Disclosure statement
The authors declare that they have no competing interests.

Conflict of interest
The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Ordu University ethic committee (03.06.2016, no:2016/54)
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