Research Article / Araştırma Makalesi

The Importance of Electrocardiographic Evaluation in Patients with Celiac Disease

Çölyak Hastalarında Elektrokardiyografik Değerlendirmenin Önemi

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Abstract

At the present study, study we aimed to analyze the risk factors for cardiac arrhythmias related disease factors by evaluating some ventricular repolarization parameters in the electrocardiographic (ECG) evaluation of CD. The study was conducted retrospectively from the files of the patients. The ECG evaluation of 63 patients aged 5-18 years diagnosis with CD and 63 healthy control group in Adana City Training and Research Hospital, between 01.2018-11.2022. Patients who were taking any drugs, who had a chronic disease and/or abnormal tests (vitamin B12, folate, tissue transglutaminase, anti-endomysium antibody titers) were excluded from the study. The ventricular repolarization parameters (QT interval, QTc interval, QT dispersion, QTc dispersion, Tp-e interval, Tp-e/QT, Tp-e/QTc) analyzed on ECG and compared both groups. The measured ventricular repolarization parameters of the patients and control groups were not statistically different. From the ECG data, it was found that the QTc min value was higher in patients diagnosed before 5 years old than the patients diagnosed after 8 years old. While the QTc dispersion was higher in patients diagnosed after 8 years old than the patients with an age at diagnosed before 5 years old. It was found that the values of QT min, QT max, and QT in the ECG were influenced by the duration of the disease and significantly high related with the disease duration (more than 5 years). We found that QTc dispersion was higher in patients with a later diagnosis. This suggests that cardiac involvement is also increased in patients with a late diagnosis.

Keywords: Pediatric, Electrocardiograph, Celiac Disease, Cardiac arrhythmias

Özet

Bu çalışmada Çölyak Hastalığı (ÇH)'ında elektrokardiografik (EKG) değerlendirmede bazı ventriküler repolarizasyon parametrelerini değerlendirerek aritmi risk faktörleri ve bununla ilişkili hastalık faktörlerini değerlendirmek amaçlanmıştır. Çalışma Adana Şehir Eğitim ve Araştırma Hastanesi Çocuk Gastroenteroloji Polikliniği'nde Ocak 2018 ve Kasım 2022 yılları arasında ÇH tanısı ile takip edilen, 5-18 yaş arası, 63 hastanın, retrospektif olarak dosyalarında var olan EKG verilerinin değerlendirmesi ile yapılmıştır. Çalışmaya 63 sağlıklı çocuk kontrol grubu olarak dahil edildi. Kardiyak fonksiyon üzerine etkisi olan ilaç kullanan, kronik hastalığı olan (diabet, tiroidit, Kistik Fibroz gibi) ve kan parametrelerinde bozukluk (B12 vitamin düzeyi, folat, doku transglutaminaz antikoru, anti endomisyum antikoru titre düzeyi) olan hastalar çalışma dışı bırakıldı. EKG'de ventriküler repolarizasyon parametreleri (QT aralığı, QTc aralığı, QT dispersiyonu, QTc dispersion, Tp-e aralığı, Tp-e / QT, Tp-e / QTc) bakılarak hasta ve kontrol grupları arasında karşılaştırıldı. Hasta ve kontrol grubunun ölçülen ventriküler repolarizasyon parametre arasında istatistiksel olarak anlamlı fark yoktu. QTc dispersiyonun tanı yaşından etkilendiği görüldü. Buna göre QTc min değeri ilk tanı anındaki yaşı <5 olan hastalarda ilk tanı aldığı yaşı >8 olan hastalara göre daha yüksek bulunurken, QTc dispersiyonu ilk tanı anındaki yaşı >8 olanlarda ilk tanı anındaki yaşı <5 olanlara göre daha yüksek bulunmuştur. EKG'deki QT min, QT max ve QT değerlerinin hastalık süresinden etkilendiği görüldü. Hastalık süresi >5 yıl olan hastalarda diğerlerinden daha yüksek bulundu.Biz çalışmamızda tanı yaşı büyük olan hastalarda QTc dispersiyonunun artmış olduğunu bulduk. Bu bize geç tanı alan hastalarda kardiyolojik etkilenmenin de artmış olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Çocuk, Çölyak Hastalığı, Elektrokardiyografi, Kardiyak aritmi

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1. Introduction

Celiac Disease (CD) is an autoimmune gastrointestinal tract disease caused by an autoimmune reaction to the protein gluten. Although CD was previously known as affecting only the gastrointestinal tract, it is now considered a disease with multisystemic involvement. (1) The patterns of presentation in CD are changing over time, shifting from classical symptoms to non-classical symptoms, which now take the form of extraintestinal symptoms rather than intestinal symptoms. (2) Although classical symptoms include abdominal pain and diarrhea, the neurologic and cardiac systems are also known to be affected. Clinical findings of the gastrointestinal tract in CD are primarily due to the destruction of intestinal villi secondary to autoimmune activation, while cardiac involvement is thought to be secondary to myocarditis. It is found that CD affect the autonomic nervous system and may cause dysautonomia. (3) In animal studies, serum IgA antibodies have been shown to bind to monkey cardiac tissue cells in CDs. (4,5) Also CD has an estimated prevalence between 1.8 – 5.7 % in patients with myocarditis. (6) The literature reports that cardiac involvement and an increased risk of arrhythmias occur in CD, as in many autoimmune diseases. The arrhythmia rate is 2.1%-3.3%, and the most common arrhythmia is atrial fibrillation. (7)

At the present study, we aim to determine the factors related to arrhythmias by evaluating the ventricular repolarization parameters in patients with CD. We also aimed to find out the influence of the age at diagnosis and duration of disease on these parameters.

2. Materials and Methods

Study population

Sixty-three patients aged between 5 and 18 years old diagnosed with CD and 63 healthy control group in X Hospital, Pediatric Gastroenterology Clinic, between January 2018 and November 2022, were included. CD patients diagnosed with ESPGHAN 2012 guideline were included. All the patients in the study were diet-compliant. The duration of the diasease was defined as the time from diagnoses to the time of study. The CD patients were classified according to the age of diagnoses (before 5 years, 5-8 years, after 8 years). And the other subgroup was the classified as the duration of the disease (duration is less than 2 years, 2-5 years, more than 5 years). Patients with chronic drug use, neurological diseases, additional cardiac diseases in echocardiographic evaluation, left ventricular systolic dysfunction, history of cardiac arrhythmias, electrolyte disorders, and vitamin and mineral deficiencies were excluded from the study. Ethics Committee approval of X Hospital on 15/12/2022 with decision no./meeting number 2325/118. The study was performed in accordance with the Declaration of Helsinki.

Electrocardiogram

A standard 12-lead electrocardiogram (ECG) (GE healthcare MAC 2000, 8200W. Tower Avenue, Milwaukee, WI, USA) was performed at 25 mm/s and 10 mm/mV, measured manually and interpreted by a single pediatric cardiologist. On ECG, the QT interval was measured between the onset of the QRS complex and the end of the T wave. The QT dispersion was defined by calculating the distance between the longest QT interval (QTmax) and the shortest QT interval (QTmin) on the ECG. The corrected QT interval as a function of heart rate was calculated using Bazett's formula, and the corrected QT (QTc) was defined. QTc dispersion was defined by calculating the difference between the longest QTc (QTc max) and the shortest QTc (QTc min). The Tp-e interval was determined as the distance between the peak and end of the T wave. The ratios Tp-e/QT and Tp-e/QTc were calculated. The QT interval, QTc interval, QT dispersion, QTc dispersion, Tp-e interval, Tp-e/QT, and Tp-e/QTc parameters were compared between CD and control groups. Additionally, these parameters were compared between CD patients by grouping them according to age at diagnosis and disease duration.

Statistical analyses were performed using the SPSS version 20.0 software package (SPSS, Inc., Chicago, IL, USA). The Pearson chi-square or Fisher's exact test was used to compare the categorical variables. The

Shapiro–Wilk test used to confirm the normal distribution of the continuous variables. The Student's t test or the Mann–Whitney U test was used for the comparison of continuous variables between groups. For comparison of continuous variables between groups in age at diagnosis, one-way ANOVA was used. Tukey tests were used for multiple comparisons of the groups. The statistical significance level was 0.05.

3. Results

A total of 63 patients with CD were evaluated. Twenty-two (34%) patients were male and 41 (65%) patients were female. The mean current ages of the patients and the control groups were 10.9±3.4 and as 11.7±2.5 years, respectively. The mean age at diagnosis was 6.9±3.74 years, and the mean duration of the disease was 3.8±3.1 years in CD patients.

The measured values of ventricular repolarization parameters (QT interval, QTc interval, QT dispersion, QTc dispersion, Tp-e interval, Tp-e/QT, Tp-e/QTc) of the patient and control groups are shown in Table 1. We did not find a statistically significant difference between groups for these parameters.

We found that QTc dispersion was affected by age at diagnosis. Accordingly, QTc min was higher in patients diagnosed before 5 years old than the patients diagnosed after 8 years old. While the QTc dispersion was higher in patients diagnosed after 8 years old than the patients with an age at diagnosed before 5 years old. (Table 2).

When the values of the QT min, QT max, and QT were analysed in ECG parameters we found that the duration of the disease was affected the values. Accordingly, all 3 parameters were higher according the disease duration (more than 5 years). However, no significant difference was found in QTc min, QTc max, QT dispersion, and QTc values (Table 3).

The sex and age parameters were similar in both groups. As expected, the body weight, and the height values were lower in CD.,

Table 1. Electrocardiographic characteristics in Celiac patients and control group

	Groups		
	Patient (n:63) (mean±SD)	Control (n:63) (mean±SD)	p
QT min(ms)	324.9±26.2	322.9±21.5	0.646
QT max (ms)	345.3±26.4	341.5±21.0	0.376
QT dispersion(ms)	20.4±10.8	18.5±12.0	0.375
QTc min(ms)	374.2±15.6	376.5±17.7	0.447
QTc max(ms)	400.0±14.5	400,3±19,4	0,934
QTc dispersion(ms)	25.8±12	23.8±13.5	0.377
QT (ms)	335.1±25.7	332.2±20.4	0.489
QTc (ms)	387.1±13.8	388.4±17.3	0.652
Tp-e (ms)	75.2±6.8	73.2±9.2	0.170
Tp-e/QT	0.22±0.02	0.22±0.03	0.329
Tp-e/QTc	0.19±0.02	0.19±0.02	0.136

Table 2: Electrocardiographic features according to age at diagnosis in celiac patients

	Age at Diagnosis (years)			
	<5 (n:21) (mean ±SD)	5-8 (n:21) (mean ±SD)	>8 (n:21) (mean ±SD)	p
QT min(ms)	325.3±21.5	317.8±23.7	331.6±31.7	0.235
QT max (ms)	344.4±23.1	336.6±24.3	354.9±29.2	0.077
QT dispersion(ms)	19±11.4	18.8±10.4	23.2±10.6	0.328
QTc min(ms)	379.8±12.8	376.3±16.9	366.4±14.5	**0.014**[a]
QTc max(ms)	399.5±9.3	404.2±16.6	396.3±16.2	0.210

QTc dispersion(ms)	19.7±9.7	27.9±11.2	29.9±12.9	**0.011**[a]
QT (ms)	334.9±21.6	327.2±23.5	343.2±30	0.129
QTc (ms)	389.6±10.1	390.3±15.7	381.4±13.9	0.065
Tp-e (ms)	74±6.8	75.9±6.5	75.6±7.5	0.631
Tp-e/QT	0.22±0.02	0.23±0.02	0.22±0.02	0.148
Tp-e/QTc	0.19±0.02	0.19±0.02	0.20±0.02	0.343

a: Between age at diagnosis <5 and age at diagnosis >8 p<0.05

Table 3: Electrocardiographic features according to duration of disease in celiac patients

	Duration of disease (years)			
	<2 (n:20) (mean ±SD)	**2-5 (n:23)** (mean ±SD)	**>5 (n:20)** (mean ±SD)	**p**
QT min(ms)	316.3±26.7	319.1±23.3	340.2±23.3	**0.005**[a,b]
QT max (ms)	339.2±30.5	337.6±20.4	360.2±22.6	**0.007**[a,b]
QT dispersion(ms)	22.9±9.1	18.4±11.4	20±11.7	0.401
QTc min(ms)	373.2±17.4	377.7±13.4	371.1±16.2	0.365
QTc max(ms)	400.4±17.5	404.6±13	394.3±11.3	0.065
QTc dispersion(ms)	27.2±12.5	26.9±12.6	23.2±10.9	0.501
QT (ms)	327.8±28.3	328.3±21.1	350.2±22.2	**0.005**[a,b]
QTc (ms)	386.8±16.2	391.2±11.6	382.7±12.9	0.134
Tp-e (ms)	75.9±6.6	74.1±6.9	75.7±7.3	0.638
Tp-e/QT	0.23±0.02	0.23±0.02	0.22±0.02	0.079
Tp-e/QTc	0.20±0.02	0.19±0.02	0.20±0.02	0.271

4. Discussion

Cardiac electrical changes that can occur during ventricular repolarization can lead to fatal arrhythmias. As with autoimmune diseases, cardiac involvement and increased risk of arrhythmias have been reported in CD.(8)

It has been shown in the literature that QT, QTc interval, and QT dispersion, which are the parameters of ventricular repolarization, can predict ventricular arrhythmia and death. A long QTc is a sign of delayed cardiac repolarization on ECG. A QTc interval > 440 ms has been associated with the development of cardiac arrhythmias. In our study when we evaluated the QT and QTc intervals according to the age at the time of diagnosis, we did not find any difference. Whereas QTc dispersion was higher in CD patients diagnosed after 8 years compared to patients diagnosed before 5 years of age. This suggests that patients diagnosed at later ages are exposed to more inflammation that affects ventricular repolarization. In a study investigating the etiological causes of patients with myocarditis, 9 of 187 patients were diagnosed with CD, and an association between CD, myocarditis and ventricular arrhythmia was

demonstrated. (7) Presentation patterns with atrioventricular block and syncope, suggesting that the myocardium is affected in CDs, have also been demonstrated in isolated cases. (9, 10) In the literature, QTc interval prolongation was observed in one-third of untreated adult CDs, whereas this rate was 3% in patients on a gluten free diet. (11) In the literature there are a lot of studies investigating the relationship of the diet and the ventricular repolarization parameters. We investigated the normal distribution of the repolarization parameters with full dietary compliance in CD. We didn't have the ECG examinations of the patients with CD before the gluten free diet so this is the limitation of the study.

In our study, we did not find difference between CD and control groups according to ventricular repolarization parameters. We want to demonstrate the normalization of the repolarization parameters of the ECG by the full compliance of the diet in CD. We didn't have the ECG examinations of the patients with CD before the gluten free diet so we compared the CD patients with the control

groups. All the CD patients following up in the study were diet compliant patients.

In our study, QT min, QT max, and QT were correlated with disease duration. Accordingly, all 3 parameters were higher in disease duration more than 5 years than in patients with a disease duration less than 2 years. We examined no significant difference between QTc, QT dispersion, and QTc dispersion according to these groups. According to the age of diagnosis the QTc dispersion is statistically different in patients diagnosed before 5 years of age. In CDs, in particular, some studies have associated CD severity, disease duration, and genetic predisposition with cardiac involvement. (12)

Several studies have shown that even in patients with a normal QTc interval, Tp-e interval, which is a precursor of ventricular arrhythmias and sudden death. The increase of the ratio of Tp-e/QTc is an ECG marker of life-threatening ventricular arrhythmias. (13, 14) In a study Tp-e distribution and Tp-e/QT ratio were prolonged in CD compared with the control group, but they found no relationship between Tp-e distribution and IgA tissue transglutaminase levels in patients with CD. (15) Some studies in the literature found that the Tp-e range, Tp-e/QT, and Tp-e/QTc were significantly higher in CD patients than controls, which was associated with tissue transglutaminase IgA positivity. (16, 17)We found no significant difference in the Tp-e interval, Tp-e/QT, and Tp-e/QTc ratio between the CD and control groups or between the duration of CD and age at diagnosis. Many different cardiac findings may occur in CD, and ECG findings should be considered in the follow-up of these patients. . (18)

The main limitation of the study is the small number of the patients and controls in the study. Additionally, although all the patients left ventricular systolic function were normal in the study, we did not evaluated the left ventricular diastolic function. And also we didn't measure heart rate variability with 24-hour Holter monitoring. Repeated measurements after long-term follow-up could not be performed.

5. Conclusion

All the ECG parameters such as QT, QTc, QT dispersion, QTc dispersion, Tp-e, Tp-e/QT, and Tp-e/QTc, which are considered preliminary indicators of ventricular arrhythmia were not different between the groups. However, with respect to age at diagnosis, we found that QTc dispersion was prolonged in patients with a later diagnosis. This suggests that cardiac involvement is also increased in patients with a late diagnosis.

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