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Cardiac Repolarization Properties in Children with Inflammatory Bowel Disease

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BACKGROUND/AIMS
Inflammatory bowel disease (IBD) (Crohn's Disease-CD and Ulcerative Colitis-UC) is a chronic autoimmune inflammatory disease. Cardiac involvement and electrophysiologic abnormalities has an important place in terms of morbidity and mortality among extraintestinal involvement. In this study, we investigated p-wave and QTc dispersion which may cause ventricular and supraventricular rhythm disorders if prolonged.

MATERIAL and METHODS
Twenty five IBD patient in remission period and 20 control patient were enrolled to the study. Twelve lead electrocardiogram were evaluated in all patients and p wave dispersion, QT and QTc dispersion was calculated manually.

RESULTS
QTcmax value of IBD patients were higher than control patients (p=0.05). UC patients had higher QTc max value and QTc dispersion than control patients (p=0.042).

CONCLUSION
UC patients are under risk of ventricular arrhytmias. Follow up with regular ECG in these patients and QTc calculation will be useful in monitoring of IBD patients.

Keywords: Children, inflammatory bowel disease, p-wave dispersion, QTc dispersion

INTRODUCTION

Crohn's Disease (CD) and Ulcerative Colitis (UC) are chronic, autoimmune and inflammatory diseases that mainly affect the gastrointestinal tract and progress with acute exacerbations and remissions. Systems beyond the gastrointestinal tract can be affected in both UC and CD. Extraintestinal system involvement can be seen at any time in the course of the disease and even symptoms of extraintestinal involvement may appear as the first sign of the disease. Cardiovascular involvement like thrombotic events, valvulitis, myocarditis, pericarditis, electromechanical changes are common in IBD (1-5). Subclinic myocardial involvement was shown in IBD patients, even in remission periods (6). Arrhytmia and conduction disorders are seen in IBD especially in UC patients (7, 8). In the course of disease, cardiac conduction defects, like atrioventricular block, first degree AV block may be seen (8-10). Beyond these electromechanic changes supraventicular tachyardia, mesalamine induced sinus bradycardia are reported previously in patients with IBD (10, 11).

It has also been shown that in IBD patients, corrected QT (QTc) dispersion leading to ventricular tachyarrhythmia has increased p-wave dispersion, which can lead to atrial fibrillation (12-14). Similar to subclinical myocardial mechanical involvement demonstrated by strain echocardiographic studies, electromechanical changes may be observed in IBD patients without obvious conduction disturbances during remission periods (15). From this perpective, we aimed to evaluate QTc and p wave disperison in pediatric IBD patients in remission period.

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MATERIAL and METHODS

Thirty eight IBD patients in remission (at least 1 year or more) who were followed in the tertiary pediatric gastroenterology clinic were evaluated. Thirteen patients were excluded from the study (the family of 4 patients did not want to be included in the study, 4 patients were under the age of 5, 2 patients were using medication that affect Qtc duration and 3 patients had additional rheumotological disease). Twenty-five IBD patients (UC/CD: 15/10, male/female 13/12; 5-18 years of age, mean age 12.7±2.9;) and 20 control patients (male/female; 11/14, 6-18 years of age, mean age 12.1±3.7) were included to the study. All medical records of patients diagnosed with IBD based on clinical symptoms, laboratory, radiological, endoscopic and histopathological features were examined and current clinical and laboratory findings were evaluated. All of the patients were in remission, and none of the patients had active complaints. Thirteen of the patients were treated with Mesalamine and Azathiopurine, 6 of them were taking Mesalamine treatment, three patient were under Infliximab and Mesalamine therapy and three patients were taking Infliximab, Mesalamine and Azathiopurine medication.

Healthy children who referred to pediatric cardiology clinic with noncardiac chest pain or innocent murmur were the control patients. Written consents were taken from patients' family. Local ethics committie in Umraniye Research and Training Hospital approved the study.

Echocardiographic evaluation was performed in all patients. Blood pressure of patients was measured with sphygmomanometry. 12-lead electrocardiograms (ECG) were obtained at a velocity of 50mm/s and at an amplitude of 20mm/mV from all patients. Manual ECG analyses were performed by a pediatric cardiologist who was blinded to patient and control subjects. QT-intervals were measured manually in all leads. the interval from the beginning of the QRS complex to the end of downslope of the T wave that crossing the isoelectric line, which was defined as the QT-interval.

The QTc interval was calculated by using Bazett (17) formula QTc=QT / √RR. In all leads QT and RR intervals were measured in 3 consecutive cardiac cycles. QT-dispersion was defined as the difference between the maximum and minimum corrected QT-interval. The duration between the beginning of the P wave (first deflection of the p wave) and the end of the P wave was defined as the P wave. P wave dispersion was defined as the difference between maximum and minimum P-wave durations (6).

Statistical Analysis

Statistical Package for the Social Sciences 22 software package (IBM Corp., Armonk, NY, USA) was used for stastical analysis. Kolmogorov- Simirnov test was used to determine the distribution of normality. Data were expressed as mean ± standard deviation, categorical data were expressed as number and percentages (%). Mann Whitney U test was used for comparison of groups. $p<0.05$ was used for statistical significance.

Main Points:

- QTc prolongation of QTc dispersion in systemic inflammatory diseases is a risk factor for life-threatening arrythmias
- In our study, QTc dispersion is higher in IBD group, especially in UC patients than control patients.
- We found p wave dispersion above 40 ms which is a risk factor atrial arrythmias.

RESULTS

There were no statistical significant difference in terms of age, sex, weight, height, BMI and systolic and diastolic blood pressure between IBD and control group. Demographic data is shown in Table I.

The study patients were all in remission period (PUCAI score was <10 for UC patients. PCDAI score was <12.5 for CD).

There were no significant difference statistically in terms of heart rate between IBD and control. Heart rate was 92.4±22.8 per minute in IBD group and 95.2±11.2 per minute in control group ($p=0.33$).

QTcmax value of IBD patients and control patients were 526.7±46.5 ms and 452±37.4 ms respectively ($p=0.05$) (Table 2). QTc dispersion (150.4±42.5) was higher in IBD group than control patients (79.1±37.6) but did not reach statistical significance.

TABLE I. Demographic and electrocardiographic features of study and control patients

	Demographic Features of Study Patients		
	IBD	**Control**	**p**
Gender (M/F)	13/17	14/11	0.56
Age (years)	11.8±4.72	10.4±3.87	0.24
Weight (kg)	40.5±23.9	37.1±20.4	0.25
Height (cm)	142.3±24.7	140.1±23.5	0.32
BMI	18.4±5.26	17.4±3.37	0.08
SBP (mmHg)	104.7±14	101±11.9	0.27
DBP (mmHg)	63.7±9.16	58±11	0.27
	Electrocardiographic Measurements		
HR	92.4±22.8	95.2±11.2	0.33
HR (min)	88.5±20.4	92.7±16	0.61
HR (max)	97.2±17.9	104.7±16	0.18
P (min)	75.7±16.7	4.34±0.86	0.23
P (max)	101.4±3.72	60±23	0.53
P dispersion	37.1±14.9	35.7±27.6	0.95
QT (min)	314.2±42.7	300±30.5	0.61
QT (max)	357.1±73.4	317.1±43.8	0.28
QT dispersion	43.8±16.8	37.4±29.5	0.86
QTc (min)	396.5±57	372±16	0.74
QTc (max)	526.7±46.5	452±37.4	0.05
QTc dispersion	150.4±42.5	79.1±37.6	0.095

IBD: Inflammatory bowel disease; BMI: Body mass index; SBP:Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; HRmin: Heart rate minimum; HRmax: Heart rate maximum; P(min): P wave duration minimum; P(max): P wave duration maximum; QTmin: QT minimum; QTmax: QT maximum; QTcmin: corrrected QT minimum; QTcmax: corrected QT maximum

TABLE 2. Electrocardiographic features of Crohn's Disease and Ulcerative Colitis and control patients

	CD	UC	Control	p*	p†	p°
HR	79.3±18.5	107.5±22.7	95.2±11.2	0.78	0.11	0.87
HRmin	75.6±21.3	98±26.3	92.7±16	0.57	0.51	0.87
HRmax	85±14.7	106.5±15.2	104.7±16	0.25	0.067	0.63
P wave (min)	63.3±25.1	85±25.1	160±23	0.39	0.83	0.10
P wave (max)	93.3±11.5	107.5±18.9	85.7±27.6	0.57	0.66	0.63
Pwave dispersion	30±17.3	42.5±12.5	37.1±17.8	0.57	0.66	0.63
QTmin	320±40	310±50.3	300±30.5	0.78	0.51	0.87
QTmax	360±69.2	355±86.9	317.1±43.8	0.78	0.6	0.53
QTdispersion	42.6±26.1	45±24.1	38.4±29.5	0.99	0.83	0.98
QTc min	373±61.9	414±54.5	372.8±16	0.41	0.93	0.62
QTc max	498±2.64	548±53.7	452±37.4	0.41	0.73	0.048
QTc dispersion	136±41.7	161.2±45.7	79.1±37.6	0.42	0.51	0.042

IBD: Inflammatory bowel disease; CD: Crohn's Disease; UC: Ulserative Colitis; HR: Heart rate; HRmin: Heart rate minimum; HRmax: Heart rate maximum; P(min): P wave duration minimum; P(max): P wave duration maximum; QTmin: QT minimum; QTmax: QT maximum; QTcmin: corrrected QT minimum; QTcmax: corrected QT maximum
P*: comparison between CH vs UC
p†: comparison between CH vs Control
p°: comparison between UC vs Control

Mean, minimum and maximum heart rate was higher in UC patients than control patients but did not reached statistical significance. Heart rate was 79.3±18.5 per minute in CD patients, 107.5±22.7 per minute in UC patients and 95.2±11.2 per minute in control group.

QTc max and QTc dispersion were higher in UC patients than control patients. In UC patients QTc max was 548±53.7 and 452±37.4 in control patients (p=0.048). QTc dispersion was 161.2±45.7 in UC and 79.1±37.6 in control patients (p=0.042) (Table 2).

DISCUSSION

Cardiac involvement is not rare in IBD. Besides subclinic myocardial involvement in IBD, there are obvious conditions affecting cardiovascular system such as myocarditis, pericarditis, thromboembolic events and vasculitis (1-5). However, although electrophysiologic changes were shown in IBD, there is not enough emphasis on QTc prolongation and its the consequences. QTc prolongation is the prolongation of ventricular repolarization that can predispose to ventricular arrhythmias and cause sudden death. It may be acquired or congenital. The QTc interval can be affected by many factors. Drugs, toxins, electrolyte imbalance, heart failure, myocarditis, rheumatic heart disease, endocrinologic reasons such as hypothyroidism, diabetes mellitus, increase in intracranial pressure, end stage liver disease are some of the reasons for QTc prolongation (16). Besides QTc prolongation in systemic inflammatory diseases and autoimmune diseases is a prominent finding recently. Regardless of the cause, QTc prolongation can cause life-threatening arrythmias. Studies based on general population showed that increased QTc and QTc dispersion are serious risk factors for malignant ventricular tachyarrythmias and sudden death. Prolongation in QT interval which means prolongation in ventricular repolarization causes early after depolarizations and generate malignant ventricular arryhtmias such as Torsades de pointes which progress to ventricular fibrilation rapidly and it can lead to sudden death (17).

Recent studies showed that QTc prolongation is correlated to inflammation (18, 19). A correlation has been shown between inflammatory cytokines and Qtc prolongation (20). QTc shortening is obtained with anti-inflammatuar treatment in chronic inflammatory processes such as rheumatic arthritis and connective tissue diseases (16). Also in chronic autoimmune inflammatory diseases QTc prolongation is found to be correlated to disease severity and CRP (21).

Activation of central sympathetic system by inflammatory cytokines causes cathecolamine release leads to the release of proinflammatory cytokines from circulating monocytes and lenfocytes via B2 adrenergic receptors. With this vicuous cycle, electrophysiologic changes occur in the heart (18).

Increased sympathetic activity may be a direct cause of arrythmia or indirectly affects the heart through the Ca and K channels resulting in prolongation of the QT interval (16). In addition, proinflammatory cytokines, particularly TNF alfa, IL-1 and IL-6, act on spesific ion channels on cardiomyocites, thereby prolonging the action potential duration resulting in increased excitability.

P wave dispersion is defined as the difference between maximum and minimum duration of p wave. It is an ECG marker that expresses the inhomogeneous spread of sinus stimulation in the atrial myocardium. The increase in p wave dispersion means an increase in the irregularity of atrial refractory period. This is a risk factor for the development of atrial fibrillation by re-entry mechanism (22). As in the QTc dispersion, p wave dispersion has been shown to correlate with systemic inflammation and CRP elevation in different diseases (23-27).

Although the mechanism of QTc prolongation in autoimmune diseases is not fully understood, it is thought that autoantibodies interact with the ion channels of the cardiomyocites and

prolongs the action potential duration (18). This may affect the exitability of the myocardium and it can trigger the development of arrhythmia.

In spondyloarthirits and chronic arthirits new-onset ventricular tachyarrhythmias and QT prolongation were reported (27). In a study with adult patients diagnosed with ankylosing spondylitis, QTc was prolonged due to inflammation, and QTc duration was shortened by controlling inflammation with Infliximab treatment. (28). In our study, only 6 of our patients were receiving Infliximab therapy. The presence of prolongation of Qtc dispersion in these patients who are in the remission period may be interpreted subclinical inflammation. In one study a case of azothiopurine induced acute myocarditis was reported (29). We did not find any signs of myocarditis in any of our patients.

Altough we did not find a statistically significant difference in p wave dispersion between IBD patients and control patients, in our study UC patients had 42.5±12.5 ms p wave dispersion. P wave dispersion value for atrial arrhytmias is >40 ms (30). We have received close monitoring of these patients from atrial arrhythmias.

There is no certain cut off QT dispersion values but according to a few studies >40 ms QT dispersion is a risk factor for ventricular arryhtmias (31). In our study QT dispersion of IBD patients were above this limit.

In our study QTc dispersion in IBD was higher than control patients and this was attributed to UC patients. UC patients had higher both QTc maximum and QTc dispersion than control patients. There are a few studies investigating QT values in IBD. There is only one pediatric study found prolonged p wave dispersion and QT and QTc dispersion (13). Our study is the first study to reveal that UC patients are at risk for ventricular arrhythmias. Therefore, in addition to routine pediatric gastroenterology follow-up, these patients should be monitored regularly by pediatric cardiology. Our study also showed that these patients should be regularly monitored for ECG. With regular follow-up, control of inflammation should be ensured and possible gastrointestinal and extra-intestinal complications can be prevented or detected early.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Umraniye Research and Training Hospital (26.12.2019/54132726-000-272233).

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