The effect of Gilbert's syndrome on the dispersions of QT interval and P-wave: an observational study

QT ve P dalga dispersiyonu üzerine Gilbert sendromunun etkisi: Gözlemsel bir çalışma

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ABSTRACT

Objective: Gilbert's syndrome (GS) decreases the incidence of atherosclerotic heart disease. The aim of the study was to evaluate whether the arrhythmia risk markers such as P-wave dispersion (Pd), QT dispersion (QTd) are reduced in patients with GS compared with healthy subjects.
Methods: Sixty-one patients diagnosed with GS (31 females, 30 males) who had applied to the internal medicine outpatient clinic in the hospital were included in this cross-sectional, observational study. A control group of 61 healthy persons (31 females, 30 males), who were non-smokers and drinkers, were included. Both groups were between 16-45 years old. Results of anthropometric measurements, laboratory assays and electrocardiographic findings were recorded for each participant. Independent sample t-test and nested ANOVA were used for data analysis.
Results: In the GS group were Pd value 36±16.7 msec, QTd 48.7±10.7 msec and heart rate (HR) 74±8 beat/min. In the control group were Pd 51±28 msec, QTd 53±12 msec and HR 78±10 beat/min. The Pd of patients group ($p<0.001$), QTd ($p=0.038$) and HR ($p=0.021$) were significantly lower than the control group.
Conclusion: According to our study's results, in these patients, increased bilirubin levels are associated with decrease in HR, Pd and QTd, which consequently might decrease the incidence of cardiac arrhythmias and coronary artery disease. Further studies are needed to clarify the protective role of bilirubin in risk of arrhythmias in this category of patients. *(Anadolu Kardiyol Derg 2013; 13: 559-65)*
Key words: Gilbert's, bilirubin, P-wave dispersion, QT dispersion, heart rate

ÖZET

Amaç: Gilbert sendromu (GS) aterosklerotik kalphastalığı sıklığını azaltır. Bu çalışmanın amacı P dalga dispersiyonu (Pd), QT dispersiyonu (QTd) gibi aritmi risk belirteçlerinin sağlıklı bireylerle kıyaslandığında GS'li hastalarda azalmış olup olmadığını değerlendirmektir.
Yöntemler: Hastanemiz iç hastalıkları polikliniğine başvuran toplam 61 GS hastası (31 kadın, 30 erkek) kesitsel gözlemsel bu çalışmaya dahil edildi. Sigara içmeyen 61 sağlıklı (31 kadın, 30 erkek) kişi çalışmaya alındı. İki grup da 16-45 yaş grubu arasındaydı. Antropometrik ölçümler, laboratuvar ve elektrokardiyografik bulguların sonuçları her katılımcı için kaydedildi. Veri analizi için bağımsız örneklem t-testi ve kümelenmiş ANOVA kullanıldı.
Bulgular: GS grubunda Pd 36±16,7 msec, QTd 48,7±10,7 msec ve kalp hızı (KH) 74±8 atım/dk idi. Kontrol grubunda Pd 51±28 msec, QTd 53±12 msec ve KH 78±10 atım/dk idi. Hasta grubunda Pd ($p<0,001$), QTd ($p=0,038$) ve KH ($p=0,021$) kontrol grubundan anlamlı düşük bulundu.
Sonuç: Bizim çalışmamızın sonuçlarına göre, bu hastalarda artmış bilirubin düzeyi, KH, Pd ve QTd'de azalma ile ilişkilidir, bunun sonucu olarak kardiyak aritmi ve koroner arter hastalığı insidansı azalabilir. Bu kategorideki hastalarda aritmi riskinde bilirubinin koruyucu rolünü göstermek için daha kapsamlı çalışmalara ihtiyaç vardır. *(Anadolu Kardiyol Derg 2013; 13: 559-65)*
Anahtar kelimeler: Gilbert's, bilirubin, P dalga dispersiyonu, QT dispersiyonu, kalp hızı

Introduction

Gilbert's syndrome (GS) is an autosomal recessive disease, which is a benign condition that does not progress into chronic liver disease or fibrosis (1). GS occurs in 3%-17% of the population (12.4% males and 4.8% females) (2). Bilirubin glucuronidation is decreased due to a partial defect in the UDP-glucuronosyl transferase enzyme. It shows a fluctuation of increased indirect bilirubin (IB) levels. It may need no treatment. It is diagnosed incidentally without giving any clinical manifestation (3, 4).

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Coronary atherosclerosis has been associated with the development of atrial fibrillation (AF). The sinus node and the atrial tissues may develop fibrosis and scar tissue suddenly or gradually due to the decrease in blood flow related to atherosclerosis. Regions in the atria with diminished conduction velocity have been shown to favor reentry mechanisms, which can ensue in the progress of AF (5, 6). GS decreases the incidence of atherosclerotic heart disease (7-9). Decreased atherosclerosis in GS patients may lower the risk of AF and ventricular arrhythmia.

P-wave dispersion (Pd) is related to discontinuous inhomogeneous intraatrial and interatrial sinusoidal stimulations and is defined as a difference between maximum P-wave duration (Pmax) and minimum P-wave duration (P min) (10). Many studies have shown that Pd is a noninvasive electrocardiography (ECG) marker that can be used to determine the risk of AF (11, 12). QT dispersion (QTd) is known as the difference between maximum QT interval (QT max) and minimum QT interval (QT min) (13). Several studies have shown that increased QTd can be seen in many patients suffering from cardiac diseases such as post-myocardial infarction (MI) patients, patients with left ventricular hypertrophy, patients with heart failure, including idiopathic dilated cardiomyopathy, patients with acute MI, patients with long QT syndrome, hypertensive patients and patients with aortic stenosis (14, 15).

QTd was an independent predictor of the advancement of coronary atherosclerosis. In regional ischemia, inhomogeneity in extracellular potassium concentration develops within minutes, not only within the border area between normal and ischemic myocardium but also in the central ischemic area. Inhomogeneity in extracellular potassium results in homogeneity in conduction and refractoriness (16, 17).

However, arrhythmia markers have not been studied before in GS patients.

The aim of this pilot study was to evaluate whether the arrhythmia risk markers such as P-wave dispersion (Pd), QT dispersion (QTd) are reduced in patients with GS compared with healthy subjects.

Methods

Study design

This study was designed as an observational cross-sectional study that was carried out in Internal Medicine Department of Faculty of Medicine of Recep Tayyip Erdoğan University between March and July 2012.

Study population

Sixty-one patients diagnosed with GS (31 females, 30 males) who had applied to the clinic in the Recep Tayyip Erdoğan University Medical School Hospital were included in this study. A control group of 61 healthy persons (31 females, 30 males), who were non-smokers and drinkers, were included. Both groups were between 16-45 years old. Both the patients and the control groups were evaluated clinically with ECG by cardiologist and routine biochemical tests. Inclusion criteria were as follows: Increased levels of IB (0.8 mg/dL) with normal levels of lactate dehydrogenase (LDH) were not considered as hemolysis and corrected reticulocyte counts were done with a reticulocyte smear to the patients with lower 2% included from the study. Healthy subjects with IB <0.7 mg/dL who had not any known disease were included in the control group.

Exclusion criteria for both groups were as follows: Having heart disease, chronic renal failure, diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, hyperthyroidism, hypothyroidism, acute or chronic liver disease, cancer or any other chronic disease, acute or chronic infection, chronic drug user, smoking, drinking alcohol, hipoalbuminemia, hematologic diseases such as myelodysplastic syndrome, leukemia, lymphoma and vitamin B12 deficiency. Increased levels of IB with elevated levels of LDH were considered as hemolysis and excluded from the study (18). Corrected reticulocyte counts were done with a reticulocyte smear to the patients with normal levels of LDH, and the levels of more than 2% were excluded (19). The study was approved by the local ethics committees, and informed consent from each participant was obtained (Approval No: 2012/114).

Study variables

The baseline characteristics of all patients including age, sex, body mass index (BMI), heart rate (HR), systolic blood pressure, and diastolic blood pressure were recorded carefully. Biochemical blood tests [(IB, total bilirubin (TB), fasting plasma glucose (FPG), aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP), lipid profiles, LDH, reticulocyte, hematologic parameters, hepatitis panel, vitamin B12, thyroid stimulating hormone (TSH)] and ECG (Pmax, Pmin, Pd, QTmax, QTmin, QTd) were obtained from the entire study population on admission.

Laboratory tests

The biochemical tests were performed with the *photometric* assays of the Abbott Architect C16000 analyzer (Abbott Diagnostics, USA), and the TSH and vitamin B12 tests were performed using the chemiluminescent microparticle immunoassay (CMIA) method of the Abbott Architect I 2000 immunology analyzer (Abbott Diagnostics, USA).

The CRP test was performed with the nephelometric method of the Coulter Image 800 device, and HBsAg, anti-HCV and anti-HIV were tested with the Roche Cobas E 601 microElisa device (Roche Diagnostics, England). The hematologic tests were performed using the Abbott Cell Dyn Ruby analyzer (Abbott Diagnostics, USA).

Diagnosis of GS

There is no indication for liver biopsy in patients with GS. If a biopsy is performed, it will show normal liver tissues (3). The

previous laboratory tests of patients who met the above criteria were reviewed, and the elevation of IB at least twice at different times was accepted as GS. Patients with elevated levels of IB, who had no previous laboratory results were called after 15 days for retesting and persistent elevation, were included in the study.

Electrocardiography

GS patients and the control group after resting were checked by 12 derivations and 3 channels using a Nikon Kohden ECG device (Japan) with amplitude of 1 mV/cm and a speed of 50 mm/sn. While performing the ECG, patients were not allowed to talk. All the derivations P-wave and QT interval were measured manually using an X10 magnifying glass. The measurements were done by a cardiologist and an internist who were not aware of the diagnosis given for the patients. Patients who had at least 8 derivations measured were included in the study.

The beginning and ending of P-waves were determined by the point of starting P-wave deflection with the isoelectric line, and the point of ending P-wave deflection with the isoelectric line. The patients with undetermined P-wave starting and ending points in the derivations were excluded from the study. Pd was calculated as the difference between Pmax and Pmin (20).

QT interval is defined as the distance between the point of starting Q wave and the point of ending T wave with the T-P isoelectric line. If there was a "U" wave, the end point of the "T" wave was determined as the lowest point between "T" and "U". Measurements were not taken in derivations if the end of T wave was not determined or the amplitude was low. QTd is defined as the difference between QTmax and QTmin (21). The intervals of QT were corrected according to heart rate (HR) using the Bazett formula "Corrected QT interval (QTc)=QT/ $\sqrt{}$R-R" and expressed as QTc. QTc $\leq$ 0.44 seconds were accepted to be within normal range.

Statistical analysis

The data analysis was performed using the statistical software SPSS for Windows (version 13.1; SPSS, Chicago, IL, USA). The results are reported as the mean±SD. All the results were analyzed by applying the Kolmogorov-Smirnov for the determination of normal and abnormal data distribution. Groups and subgroups showed normal distribution. The statistical significance of the differences in all parameters between the GS and the control groups were analyzed using the independent sample t-test. Subgroup's analyses were done by nested ANOVA, followed by Bonferroni posthoc analysis. The differences were considered significant at $p<0.05$.

Results

Clinical characteristics

Patient and control groups did not differ in terms of demographic and basal clinical analyses (Table 1).

However, when comparing the two groups, in the GS group TB ($p<0.001$), IB ($p<0.001$) and high density lipoprotein (HDL) ($p<0.012$), values were significantly high; low density lipoprotein (LDL) ($p<0.032$), CRP ($p<0.014$) values were significantly low as compared to controls

Electrocardiographic features

Analysis of ECG parameters demonstrated that Pd was significantly ($p<0.001$) higher, while Pmax ($p=0.02$), QTd ($p=0.038$), HR ($p=0.021$) were found decreased in patients with GS a compared to healthy subjects (Table 1, Fig. 1).

When the test population was divided into the subgroups GS males (GM), control males (CM), GS females (GF) and control females (CF); the values of Pd were found to be significantly lower in the GM and GF groups than the CF group ($p=0.001$) (Table 2).

Table 1. The main characteristics, laboratory and ECG parameters of the two groups

Variables	Gilbert's syndrome (n=61)	Healthy subjects (n=61)	*p
Age, years	29±8	27±4	0.139
Sex, M/F, n	30/31	30/31	1.00
BMI, kg/m^2	23.9±4.9	24.6±4.7	0.451
Systolic blood pressure, mm/Hg	107±14	108±14	0.868
Diastolic blood pressure, mm/Hg	70±9	71±9	0.663
HR, beat/min	74±8	78±10	0.021
Pmax, msec	97.70±19.7	108±18	0.002
Pmin, msec	61.90±16.7	56±15	0.079
Pd, msec	36±16.7	51±28	0.001
QTc, msec	418±29.5	422±23	0.440
QTd, msec	48.7±10.7	53±12	0.038
FPG, 70-110 mg/dL	93±9	94±8	0.822
AST, 0-55 IU/L	19±7	18±7	0.623
ALT, 5-34 IU/L	19±13	19±14	0.903
BUN, 15-43 mg/dL	28±7	27±6	0.067
Creatinine, 0.6-1.1 mg/dL	0.7±0.1	0.7±0.1	0.468
TB, 0.2-1.2 mg/dL	2±0.7	0.6±0.2	0.001
IB, 0.1-0.7 mg/dL	1.5±0.7	0.4±0.1	0.001
TC, 0-199 mg/dL	175±30	181±25	0.278
TG, 0-149 mg/dL	97±54	110±52	0.192
LDL, 0-130 mg/dL	102±25	111±23	0.032
HDL, 35-70 mg/dL	52±11	47±11	0.012
CRP, 0-0.8 mg/dL	0.2±0.2	0.3±0.3	0.014

Values are presented as mean±SD and proportions
*Student's t- test for independent samples
ALT - alanine aminotransferase, AST - aspartate aminotransferase, BMI - body mass index, BUN - blood urea nitrogen, CRP-C - reactive protein, ECG - electrocardiography, F - female, FPG - fasting plasma glucose, HDL - high density lipoprotein, HR - heart rate, IB - indirect bilirubin, LDL - low density lipoprotein, M - male, Pd - P-wave dispersion, Pmax - maximum P-wave duration, Pmin - minimum P-wave duration, QTc - corrected QT interval, QTd - QT dispersion, TB - total bilirubin, TC - total cholesterol, TG - triglycerides

Table 2. Subgroup analysis of ECG and laboratory parameters in Gilbert and the control groups

Groups	Pd, msec	QTd, msec	HR, beat/min	TB, 0.2-1.2 mg/dL	IB, 0.1-0.7 mg/dL
Gilbert's syndrome male, n=30	36.5±17.1	50.6±12.0	76±8	2.3±0.8	1.7±0.7
Gilbert's syndrome female, n=31	35.5±16.5	47.0±9.2	73±9	1.9±0.6[d]	1.3±0.5[e]
Healthy subject male, n=30	48.0±20.7	56.0±15.9[c]	78±10	0.6±0.2[ab]	0.4±0.1[ab]
Healthy subject female, n=31	55.1±19.9[ab]	50.5±6.2	79±9	0.5±0.2[ab]	0.3±0.1[ab]
*F	8.09	3.22	2.42	86.44	61.07
*p	0.001	0.025	0.069	0.001	0.001

HR - heart rate, IB - indirect bilirubin, Pd - P-wave dispersion. QTd - QT dispersion, TB - total bilirubin
Values are presented as mean±SD
*Nested ANOVA, posthoc Bonferroni test:
[a]comparison is made with GS male, p<0.001, [b]comparison is made with GS female, p<0.001, [c]comparison is made with GS female, p<0.015, [d]comparison is made with GS male, p<0.006, [e]comparison is made with GS male, p<0.005

Discussion

In this study, the measurements of P-wave and QT interval were found to be lower in GS patients compared to the control group. Resting HR was found to be significantly lower in GS patients than the control group. These findings show that cardiac diseases such as AF may be lower in GS patients so they may have a higher life expectancy than healthy persons. In the current study, LDL and CRP were significantly lower in GS patients compared to the control group. The levels of HDL were found to be higher in the GS group than the control group. When divided into subgroups according to gender, the GF group had lower QTd than the CF group. Even statistically insignificant Pd and HR were lower in the GS group. The GM group had lower Pd, QTd and HR than the CM group; however, the results were statistically insignificant.

Increased resting HR has been shown to be related to cardiovascular mortality, non-cardiovascular mortality, sudden death and coronary artery disease in males and females (22). A study done by Framingham with a follow up of 30 years has shown that resting HR is a risk factor for all-cause mortality and that, additionally, it increases with age and is accompanied by a higher rate of mortality (23). HR is one of the most important determinants of myocardial oxygen consumption and energy requirements. Increased HR reduces diastole, ventricular filling becomes more difficult, coronary perfusion decreases, oxygen and energy consumption is increased, vascular resistance is impaired and shear stress increases. Lowering HR to 5-10 beat/min daily effectively reduces the workload of the heart. The GF and GM groups were found to have lower resting HR than normal persons. This result was not statistically significant, it is, however, quite important. The males had 2 beat/min and females had 5 beats/min lower values. When calculating these lower beats over days, months and years, we can say that GS patients experience a great protective effect from bilirubin. Normally, females have higher HR than males. The reason may be that females have smaller hearts than males and, to send blood to the peripheral parts of the body, the heart has to beat more.

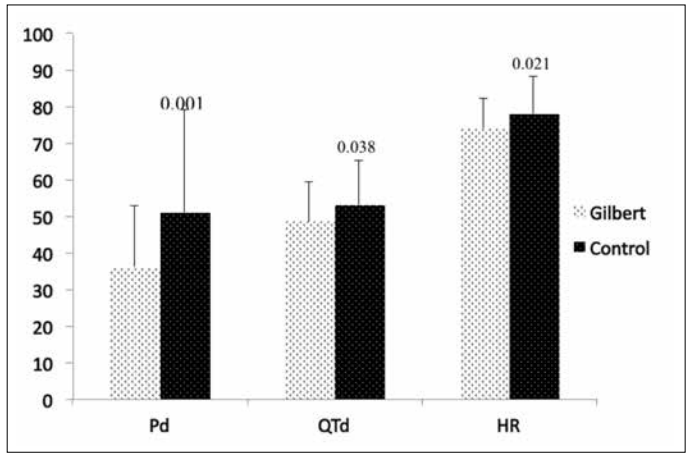

Figure 1. Comparison of Pd, QTd and HR values between GS and control groups
The results are presented as mean±SD
Independent samples t-test
GS - Gilbert`s syndrome, HR - heart rate, Pd - P-wave dispersion, QTd - QT dispersion

Therefore, males' and females' HR should be compared to subjects of the same sex. The fact that males have 2 beats/min and females have 5 beats/min lower than normal suggests that the bilirubin cardioprotective effect is more obvious in females.

P-wave abnormalities, detected from the ECG, have been thought to reflect left atrial enlargement, left atrial hypertension and altered conduction (24). Two simple ECG markers, Pmax and Pd, have been used to evaluate intraatrial and interatrial conduction times and the inhomogeneous propagation of sinus impulses are well known electrophysiologic characteristics of atriums prone to fibrillation (25, 26). In several studies, it has been reported that calculating Pmax and Pd by using surface ECG may be a simple and useful method to determine the risk of paroxysmal AF (27, 28). AF is the most common arrhythmia encountered in adult cardiology. Pd values of >40 msec were found to be correlated with AF, with a sensitivity of 74-83% and specificity of 81-85% (29). In our study, the Pd of the GS group was lower that the control group. The risk of AF may be lower in GS patients. There were no significant differences with regard

to gender among the GS patients. Sarı et al. (30) reported similar findings in a small group of healthy males and females. In contrast, Yıldız et al. (31) included a very large cohort and reported that the male gender was associated with higher Pd and Pmax values. In terms of gender differences, more studies with a broader range of subjects are needed.

QTc and QTd indicate ventricular repolarization time and heterogeneity. Increased QTc and/or QTd are known to be the cause of ventricular arrhythmia in various systemic diseases and lead to an increase in mortality and morbidity. Increased QTd has been shown to be an important prognostic factor in several cardiovascular conditions such as coronary artery disease, congestive heart failure and cardiomyopathy (21, 32). Literature reviews found the QTd to vary mostly between 30 and 60 msec in normal subjects, although average values around 70 msec were also reported (33). In the current study, QTd was found to be significantly lower than the control group. This decrease may lower risk of ventricular arrhythmias, coronary artery disease and MI in patients with GS. When analyzing according to gender GF and GM groups had similar QTd levels. Reports show either no statistically significant difference in QTd between the genders (34). Compared to the GS and control subgroups, the GF group had significantly lower QTd than the CM group. The GF group had lower QTd than the CF group; however, these results demonstrated no statistically significant difference. The GM group had lower QTd than the CM group; however, this was not statistically a significant difference.

As a result, the GF group may benefit from a higher cardioprotective effect than that of the GM group. However, it is known that endogenous and exogenous estrogen increase QTd (35) while testosterone decreases it (36). The Pd values were higher in healthy females whereas in the GF group, it was similar to that of GM group. Estradiol is known to reduce bilirubin glucuronidation (37, 38). In addition to this, the fact that bilirubin glucuronidation is low in GF patients means that IB may be more effective than expected. At the same time, the QTd of the GM group was statistically significant; however, it was insignificant with other groups. This effect may be related to the synergism between testosterone and bilirubin. The cardioprotective effect of bilirubin is well known (9, 35), GS patients have high indirect bilirubin due to the defect of the UDP glucuronosyl transferase enzyme. In these patients, it has been reported that decreased lipid peroxidation and inflammation have a cardioprotective effect (7). Oxygen free radicals have been considered as a promoter of the altered relationship between conduction time and repolarization time in the hypertrophied myocardium. Previous studies have shown that antioxidant agents, while lowering oxidative stress, decrease QTd (39-41). Bilirubin levels in GS patients show a cardioprotective effect without reaching a pathological level. As the incidence of atherosclerosis events is low in GS patients, in addition to lower values of Pd and QTd, than in healthy subjects, the risk of arrhythmia may therefore be lower.

Endothelial dysfunction via lipid peroxidation and inflammation is a marker for atherosclerosis. Elevated levels of circulated LDL increase lipid peroxidation. The CRP level demonstrates the intensity of inflammation. In this study, levels of LDL and CRP were found to be significantly low. High levels of HDL have been shown to be related to a decrease in cardiovascular events. In the current study, in comparison to the control group, higher levels of HDL have been found. So increasing levels of bilirubin, which is a potent antioxidant, in GS patients prevents adverse cardiovascular events. The cardioprotective effect of bilirubin has been demonstrated in previous studies (42, 43). Due to the results being significant, low levels of CRP and LDL may be related to the antioxidant effect of bilirubin and may be the reason that cardiovascular events are less likely to occur in GS patients.

Study limitations

Although the number of the subjects in our study is not enough to represent the population, this is a pilot study on this issue. A long-term follow-up of patients with GS has not been carried out so it cannot be concluded that AF and ventricular arrhythmia are seen less in these patients. This study may suggest the idea that the risk of arrhythmia in this group of patients may be decreased.

Conclusion

In GS patients, increased bilirubin levels are associated with decrease in HR, Pd and QTd, which consequently might decrease the incidence of cardiac arrhythmias and coronary artery disease. Further studies are needed to clarify the protective role of bilirubin in risk of arrhythmias in this category of patients.

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