

Assessment of Autonomic Dysfunction in Parkinson Patients by Electrocardiogram

Arzu Şanlı Türk¹, Ayhan Köksal¹,
Özlem Altıokka¹, Fazilet Karademir¹,
Ayten Ceyhan Dirican¹,
Yavuz Altunkaynak¹,
Tamer Yazar², Sevim Baybaş¹

¹Neurologist, Prof. Dr. Mazhar Osman Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, ²nd Department of Neurology, İstanbul - Turkey

²Neurologist, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Department of Neurology, İstanbul - Turkey

ABSTRACT

Assessment of autonomic dysfunction in Parkinson patients by electrocardiogram

Introduction and Objective: In Parkinson's disease, autonomic involvement may be seen depending on degeneration of spinal autonomic neuron or side effects of treatment, as well as cardinal signs. Sudden death caused by autonomic dysfunction detected by QT interval has been reported in studies. In our study; we aim to investigate the degree of QT interval prolongation, and its relationship between gender, duration of disease, and treatment in patients with Parkinson disease to evaluate autonomic dysfunction.

Material and Method: Twenty patients with Parkinson's disease followed by the Movement Disorder Outpatient Clinic in the 2nd Neurology Department, at Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery were selected. Furthermore, 18 healthy controls were included in our study. None of the participants had cardiac disease, diabetes, hypertension, electrolyte imbalance, chronic liver and kidney diseases. They were not using any drug affecting QT interval. In electrocardiography (ECG) analyses, because previous RR interval affected QT interval, QT-c intervals calculated according to Bazett's formula ($QT_c = QT / (RR)^{1/2}$) were predicated. QT, QT-c and RR intervals were measured automatically by ECG machines.

Results: Twelve (60%) of patients were female and 8 (40%) patients were male. In the control group, there were 6 (33.3%) female and 12 (66.7%) male. The mean age was 69.8 (± 8.57) and 64.8 (± 8.71) in the patient and control groups, respectively. The mean duration of disease was 6.1 (± 3.1) years. QT, QT-c and RR intervals were not significantly correlated with duration of the disease. According to gender, QT, QT-c and RR intervals were compared in both groups, and there was not significant correlation. Means of QT-c interval were found very significantly longer in patients than controls, and means of QT interval were again found significantly longer in the patients. The RR intervals were measured in both groups and no significant correlation was found. The patients were using L-Dopa, Dopa agonist, MAO-B inhibitory drugs in similar doses and combinations, and the effects of the drugs on QT intervals could not have been compared. Among the study groups, means of QT and QT-c intervals were compared and they were found substantially longer in patients.

Conclusion: In Parkinson's disease, alternations of QT-c have an important role on cardioselective factors like pathologies of sympathetic and intrinsic neurons. For this reason, we think that QT-c measurement is an important parameter in terms of determining the risk of sudden death in Parkinson patients whose autonomic symptoms are prominent, and if there is a QT-c interval prolongation, these Parkinson patients must be followed by cardiologists as well.

Key words: Parkinson, autonomic dysfunction, QT interval, ECG

ÖZET

Parkinson hastalarında otonomik disfonksiyonun EKG ile değerlendirilmesi

Giriş ve Amaç: Parkinson hastalığında kardinal bulguların yanısıra; spinal otonom nöronlarda dejenerasyona veya tedaviye kullanılan ilaçların yan etkilerine bağlı olarak otonom belirtiler görülebilir. Parkinson hastalarında, otonomik disfonksiyona bağlı olarak QT intervalinde uzama saptanmış, bunun ani ölümlere yol açabildiği belirtilmiştir. Bu çalışmada, Parkinson hastalarında otonomik disfonksiyonu değerlendirmek amacıyla QT interval değişimleri ve bu parametrenin cinsiyet, hastalık süresi ve tedavi ile ilişkisinin araştırılması amaçlanmıştır.

Araç ve Yöntem: Çalışmaya, Bakırköy Ruh ve Sinir Hastalıkları Hastanesi 2. Nöroloji Hareket Bozukluğu Polikliniğinden takipli, kardiyak hastalık, diyabet, hipertansiyon, elektrolit imbalansı, kronik karaciğer hastalığı ve böbrek yetmezliği öyküsü ve QT aralığını etkileyebilecek ilaç kullanımı olmayan 20 Parkinson hastası ve 18 sağlıklı kontrol grubu dahil edildi. EKG incelemesinde, QT intervali bir önceki RR intervalinden etkilendiği için, ölçümlerde Bazett's formülü ($QT_c = QT / (RR)^{1/2}$) ile hesaplanan QT-c değeri esas alındı. Otomatik analiz yapan EKG cihazı ile QT, QT-c ve RR ölçümleri yapıldı.

Bulgular: Hastaların 12'si kadın (%60), 8'i erkek (%40), kontrol grubunun 6'sı kadın (%33.3), 12'si erkek (%66.7) idi. Hastaların yaş ortalaması 69.8 (± 8.57), kontrol grubunun yaş ortalaması ise 64.8 (± 8.71) olarak saptandı. Ortalama hastalık süresi 6.1 (± 3.1) yıl idi. Hastalık süresi ile QT, QT-c ve RR değerleri arasında anlamlı korelasyon bulunmadı. Her iki grupta cinsiyet yönünden QT, QT-c ve RR değerleri kıyaslandı, ancak anlamlı fark bulunamadı. Her iki grupta QT ve QT-c ortalamaları değerlendirildi. Hasta grubunda QT-c ortalamasının ve QT ortalamasının, normal gruptan anlamlı olarak ileri düzeyde yüksek olduğu görüldü. Her iki grupta R-R mesafesi ölçüldü ve anlamlı fark bulunmadı. Hastalar; L-Dopa, Dopa agonisti, MAO-B inhibitörü ilaçları benzer kombinasyonlarda kullanmakta idi. Kullanılan ilaçların QT intervali üzerine etkisi kıyaslanamadı. Hasta ve normal gruplarda QT ve QT-c ortalamaları kıyaslanmış ve hastaların QT ve QT-c ortalamasının normalden ileri düzeyde yüksek olduğu saptanmıştır.

Sonuç: Parkinson hastalarında QT-c değişikliklerinin; postganglionik sempatik ve intrinsik nöronlardaki patolojik değişiklikler gibi kardiyoselektif faktörler üzerinde önemli rolü vardır. Bu nedenle, otonom bulguları belirgin olan Parkinson hastalarında QT-c ölçümünün, ani ölüm riski açısından anlamlı olabileceğini ve QT-c intervalinde uzama saptanması halinde, hastaların kardiyoloji ile birlikte takibinin uygun olacağını düşünüyoruz.

Anahtar kelimeler: Parkinson, otonomik disfonksiyon, QT interval, EKG

Address reprint requests to:
Neurologist Özlem Altıokka, Prof. Dr. Mazhar Osman Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, 2nd Department of Neurology, İstanbul - Turkey

Phone: +90-212-543-6565/1920

E-mail address:
ozlemaltiokka@gmail.com

Date of receipt:
June 14, 2011

Date of acceptance:
September 27, 2011

INTRODUCTION

Parkinson's disease (PD) was first described by British physician James Parkinson as "shaking palsy" in 1817. Cardinal symptoms of the disease are resting tremor, reduction in voluntary and associated movements, increase in tonus as rigidity and postural instability. In addition to these symptoms, autonomous symptoms and signs due to degeneration of spinal autonomous neurons and side effects of medications used to treat the disease particularly in advanced stages of disease (1,2). Prolongation of QT interval due to autonomic dysfunction was observed in Parkinson patients in the literature and sudden deaths due to this finding were reported (1).

In this study, we aimed to investigate QT interval changes and relationship of this parameter with gender, disease duration and treatment in order to evaluate autonomic dysfunction in Parkinson patients.

METHODS

Twenty Parkinson patients who were being followed-up by Movement Disorders Outpatient Clinic of Prof. Dr. Mazhar Osman Bakırköy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, 2nd Department of Neurology and not having history of cardiac disorder, diabetes, hypertension, electrolyte imbalance, chronic liver disease and renal failure and medication use affecting QT interval and 18 healthy people as the control group were included in the study. In ECG examination, due to negative effect of QT interval by previous RR interval, QT-c (corrected QT dispersion) which was calculated by Bazett formula ($QT-c = QT/(RR)^{1/2}$) was used in

assessments. QT, QT-c and RR assessments were done by auto-analyzing ECG device.

Statistical Analysis

SPSS (11.5 version) package software was used for biostatistical analyses. When study data were being evaluated, in addition to descriptive statistical methods (mean, standard deviation) Student's t-test was used to compare quantitative data and inter-group comparisons of parameters having normal distribution. Chi-square test was used to compare qualitative data. Significance level was taken as $p < 0.05$. Spearman correlation test was used for correlation analysis (r value).

RESULTS

There were 12 women (60%) and 8 men (40%) at the patient group and 6 women (33.3%) and 12 men (66.7%) at the control group. Mean age was 69.8 (± 8.57) at the patient group and 64.8 (± 8.71) at the control group. Mean disease duration was 6.1 (± 3.1) years. No significant correlation was found between disease duration and QT, QT-c and RR values ($p > 0.05$) (Table 1). QT, QT-c and RR values were compared for gender at both groups and no significant difference was found ($\chi^2 = 0.70$, $p = 0.10$). QT and QT-c mean values were assessed at both groups.

Table 1: Relationship between disease duration and ECG characteristics

n=20		QT	QT-c	RR
Disease duration	r	-0.143	0.22	-0.21
	p	0.549	0.20	0.29

QT duration: Duration between initiation of Q wave and termination of T wave in ECG.

QT-c: Corrected QT duration.

RR Interval: Duration between R waves of two consecutive QRS complexes in ECG.

Table 2: Mean values of patient and control group according to ECG characteristics

	Patient n=20	Normal n=18	t	p
	Mean \pm Standard deviation	Mean \pm Standard deviation		
Age	69.80 \pm 8.57	64.88 \pm 8.71	1.751	>0.05
Disease duration (year)	6.10 \pm 3.11			
QT (milliseconds)	397.70 \pm 16.14	374.44 \pm 19.88	3.932	<0.001
QT-c (milliseconds)	423.75 \pm 16.59	404.16 \pm 16.58	3.635	<0.001
RR (milliseconds)	847 \pm 120.57	791.11 \pm 89.76	1.630	>0.05

QT duration: Duration between initiation of Q wave and termination of T wave in ECG, QT-c: Corrected QT duration, RR Interval: Duration between R waves of two consecutive QRS complexes in ECG, t: Student T Test

Mean QT-c value of patients (423.75 msec.) was significantly higher ($p<0.001$) than the control group (404.16 msec.) and also mean QT value of patients (397.70 msec.) was significantly higher ($p<0.001$) than the control group (374.44 msec.). R-R interval was calculated at each group and no significant difference was found ($p=0.12$) (Table 2). Patients were using combinations of L-Dopa, Dopa agonists, MAO-B inhibitors so their effects on QT interval could not be assessed.

DISCUSSION

QT interval of ECG represents total ventricular myocardial depolarization and repolarization duration (3,4). Prolongation of QT interval which is concomitant with ventricular arrhythmia has been related to unexpected cardiovascular deaths (1). QT prolongation and sudden death have been reported due to autonomic dysfunction in patients with PD and multi-system atrophy (MSA) in the literature (1,3-6). For this reason, QT interval is important for follow-up and treatment of these patients. QT-c and R-R interval assessments were performed in studies done with patients with PD and MSA and prolongation of QT-c interval was detected compared to control group but no significant difference was found at R-R interval and QT (7). In PD, QT-c interval was compared between patients who are taking anti-Parkinsonian medications and unmedicated group: no significant difference was found. In our study, we also found a highly significant difference of mean QT-c in PD compared to healthy controls which is consistent with the literature. However, mean QT was also found significantly

higher than healthy control group contrary to the literature (7). No significant difference was found at R-R interval assessments at both groups, and this is also consistent with the literature. In another study, QT-c interval length was found to be correlated with disease duration (7). No significant correlation was found in our study. No correlation was found between medications used in the treatment and QT-c interval in the same study (8,9). Effect of anti-Parkinsonian medications on QT-c interval could not be compared statistically due to similar combination of medications being used in our patient group.

Cardio-selective sympathetic denervation in PD can be explained by a number of characteristics. First, catecholaminergic cells in basal ganglia decrease proportionally by increasing severity of PD. Another characteristic is presence of Lewy bodies in cardiac plexus in PD (10,11). Oxidative or neurotoxic processes leading to cellular degeneration at central nervous system in PD may also lead to impairment of adrenergic tracts (12,13). Post-ganglionic sympathetic fibers are affected by this route. Rapid oxidative deamination of noradrenalin in cardiac sympathetic nerves has a role in cardio-selective denervation in PD (14).

In conclusion, QT-c changes in PD have an important role in cardio-selective factors such as pathological changes in post-ganglionic sympathetic and intrinsic neurons. For this reason, assessment of QT-c in Parkinson patients with predominant autonomic symptoms may be important for risk of sudden death and when prolongation of QT-c interval was detected, follow-up of patients with cardiology department will be appropriate.

REFERENCES

1. Iodice V, Low DA, Vichayanrat E, Mathias CJ. Cardiovascular autonomic dysfunction in MSA and Parkinson's disease: similarities and differences. *J Neurol Sci* 2011; 310:133-138.
2. Mehndiratta M, Garg RK, Pandey S. Nonmotor symptom complex of Parkinson's disease: an under-recognized entity. *J Assoc Physicians India* 2011; 59:302-308.
3. Schouten EG, Dekker JM, Meppelink P, Kok FJ, Vandenbroucke JP, Pool J. QT interval prolongation predicts cardiovascular mortality in an apparently healthy population. *Circulation* 1991; 84:1516-1523.
4. Choy AM, Lang CC, Roden DM, Robertson D, Wwood AJ, Robertson RM, Biaggioni I. Abnormalities of the QT interval in primary disorders of autonomic failure. *Am Heart J* 1998; 136:664-671.
5. Schwartz PJ, Snebold NG, Brown AM. Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold. *Am J Cardiol* 1976; 37:1035-1040.
6. Ishizaki F, Harada T, Yoshinaga H, Nakayama T, Yamamura Y, Nakamura S. Prolonged QTc intervals in Parkinson's disease: relation to sudden death and autonomic dysfunction. *No To Shinkei* 1996; 48:443-448.

7. Lo SS, Mathias CJ, Sutton MS. Qt interval and dispersion in primary autonomic failure. *Heart* 1996; 75:498-501.
8. Oka H, Mochio S, Sato H, Katayama K. Prolongation of QTc interval in patients with Parkinson's disease. *Eur Neurol* 1997; 37:186-189.
9. Deguchi K, Sasaki I, Tsukaguchi M, Kamoda M, Touge T, Takeuchi H, Kuriyama S. Abnormalities of rate-corrected QT intervals in Parkinson's disease-a comparison with multiple system atrophy and progressive supranuclear palsy. *J Neurol Sci* 2002; 199:31-37.
10. Komai N. Surgical treatment of Parkinson's disease. *Nihon Rinsho* 1993; 51:2940-2946.
11. Iwanaga K, Wakabayashi K, Yoshimoto M, Tomita I, Satoh H, Takashima H, Satoh A, Seto M, Tsujihata M. Lewy body-type degeneration in cardiac plexus in Parkinson's and incidental Lewy body diseases. *Neurology* 1999; 52:1269-1271.
12. Hirsch EC. Why are nigral catecholaminergic neurons more vulnerable than other cells in Parkinson's disease? *Ann Neurol* 1992; 32:88-93.
13. Hirsch EC. Does oxidative stress participate in nerve cell death in Parkinson's disease? *Eur Neurol* 1993; 33:52-59.
14. Eisenhofer G, Esler MD, Meredith IT, Dart A, Cannon RO, Quyyumi AA, Lambert G, Chin J, Jennings GL, Goldstein GL. Sympathetic nervous function in human heart as assessed by cardiac spillovers of dihydroxyphenylglycol and norepinephrine. *Circulation* 1992; 85:1775-1785.