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Evaluation of cardiovascular risk in patients with Parkinson disease under levodopa treatment

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Abstract

Background Levodopa is the indispensable choice of medial therapy in patients with Parkinson disease (PD). Since L-dopa treatment was shown to increase serum homocysteine levels, a well-known risk factor for cardiovascular disorders, the patients with PD under L-dopa treatment will be at increased risk for future cardiovascular events. The objective of this study is to evaluate cardiovascular risk in patients with PD under levodopa treatment. **Methods** The study population consisted of 65 patients with idiopathic PD under L-dopa treatment. The control group included 32 age and gender matched individuals who had no cognitive decline. Echocardiographic measurements, serum homocysteine levels and elastic parameters of the aorta were compared between the patients with PD and controls. **Results** As an expected feature of L-dopa therapy, the Parkinson group had significantly higher homocystein levels (15.1 ± 3.9 μmol/L *vs.* 11.5 ± 3.2 μmol/L, P = 0.02). Aortic distensibility was significantly lower in the patients with PD when compared to controls (4.8 ± 1.5 dyn/cm^2 *vs.* 6.2 ± 1.9 dyn/cm^2, P = 0.016). Additionally, the patients with PD had higher aortic strain and aortic stiffness index (13.4% ± 6.4% *vs.* 7.4% ± 3.6%, P < 0.001 and 7.3 ± 1.5 *vs.* 4.9 ± 1.9, P < 0.001 respectively). Furthermore, serum homocysteine levels were found to be positively correlated with aortic stiffness index and there was a negative correlation between aortic distensibility and levels of serum homocysteine (r = 0.674, P < 0.001; r = −0.602, P < 0.001, respectively). **Conclusions** The patients with PD under L-dopa treatment have increased aortic stiffness and impaired diastolic function compared to healthy individuals. Elevated serum homocysteine levels may be a possible pathophysiological mechanism.

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Keywords: Aortic distensibility; Aortic stiffness; Cardiovascular risk; Homocysteine; Parkinson disease

1 Introduction

Parkinson disease (PD) is one of the most frequently seen neurodegenerative disorders affecting more than six million people worldwide. Although PD is primarily a movement disorder and its effects are prominent on neuromuscular system, cardiovascular disorders have also been widely investigated considering the risk of development of heart valve disease and heart failure especially in the patients using ergot-derived dopamine agonists (EDDA).[1−4] On the other hand, the corner stone therapy in PD, levodopa (L-dopa), has been shown to increase serum homocysteine levels.[5,6] Homocysteine is a well-established risk factor for cardiovascular disorders.[7] Therefore, management of PD with L-dopa may render patients at increased risk of atherosclerosis and coronary artery disease. However, the knowledge about the association between use of L-dopa, homocystein levels and atherosclerotic disorders is quite limited. The available data points an increased risk of vascular disease and this topic needs further evaluation.[7]

Propagation features of the pressure wave along the arterial tree reflect the intrinsic elasticity of the arterial wall. The elastic properties of the vessels and especially the aorta are good predictors of adverse cardiovascular outcomes across many different patient groups as well as in the general population.[8] Beside being an index of total mortality, aortic stiffness is also an important determinant for vascular diseases including cardiac failure, myocardial infarction,

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renal disease and stroke.[9–12]

Since the patients with PD are exposed to high doses of L-dopa which lead to an increase in serum homocystein levels, these patients are expected to have an increased cardiovascular risk. Herein, we designed this study to evaluate the cardiovascular risk profile of the patients with PD who are under L-dopa treatment by using aortic elastic parameters.

2 Methods

2.1 Study population

This study was designed with the collaboration of the Cardiology clinic and Movement Disorders Department of Neurology Clinic in Ordu University. The study population consisted of 65 patients with idiopathic PD who registered at our movement disorders outpatient clinic between June 2013 and January 2015. Uncooperative patients and the subjects who did not want to participate were excluded from the study. Also the patients with hypertension, diabetes mellitus, coronary artery disease, heart failure, chronic obstructive pulmonary disease, chronic kidney disease, atrial fibrillation, pacemaker or implantable cardioverter defibrillator, collagen vascular diseases, rheumatic heart valve disease, and heart valve prosthesis were excluded from the study in order to eliminate their effect on aortic stiffness. All patients in this study were using only L-dopa/dopa decarboxylase inhibitor (DDCI).

Use of an anti-Parkinson drug except L-dopa/DDCI was the other exclusion criteria. The diagnosis of PD was confirmed by movement disorders specialists in neurology clinic, according to the UK Parkinson's Disease Society Brain Bank Criteria.[13,14] The severity of neurological impairment was assessed with the Unified Parkinson's Disease rating scale (UPDRS scale, ranging from 0 to 147) and the Hoehn-Yahr scale (HY scale, ranging from 0 to 5).[14,15]

The control group included 32 age and gender matched individuals who had no cognitive decline. The subjects in the control group were enrolled considering the same exclusion criteria. Baseline characteristics, echocardiographic measurements, serum homocysteine levels and elastic parameters of the aorta were compared between the patients with PD and controls. All patients and their carers read the information sheet provided before giving verbal and written consent to participate in the study. The study was approved by the institutional ethics committee of Ordu University.

2.2 Echocardiographic evaluation and assessment of aortic stiffness

Echocardiographic evaluation was performed in our cardiology department via a commercially available device (Philips, iE33, xMatrix Ultrasound, Andover, USA) using a 2.5–3.5 MHz transducer in the lateral decubitis position according to American Society of Echocardiography guidelines, with a simultaneously recorded electrocardiogram. The evaluation was performed by an experienced physician aware of study design. Left ventricle end-systolic diameter, left ventricle end-diastolic diameter, posterior wall and interventricular septum thickness were measured on the M-mode tracing at the papillary muscle level in the parasternal long axis view while left atrium diameter and aortic diameter were measured at the level of sinus valsalva. Transmitral flow samples were obtained by placing the sample volume of posterior wall Doppler to the edges of mitral leaflets in the apical four-chamber view. Mitral E, A waves, E/A ratio, isovolumetric relaxation time and DT were calculated from these tracings. Then, again in the apical four-chamber view, after appropriate gain settings were adjusted, lateral diastolic velocities (lateral Ea) were measured by tissue Doppler imaging. The cursor was placed in tricuspid valve lateral ring in the standard apical four chamber view for measurements of tricuspid annular plane systolic displacement (TAPSE) in the M-mode tracing. The scanning speed was kept as 75–100 m/s in order to reduce the margin of error.

The diameter of the ascending aorta was measured in the parasternal long axis view by the M-mode tracing at a level of 3 cm above the aortic valve. The systolic aortic diameter (AOS) was measured at the maximal anterior motion of the aorta, while the diastolic aortic diameter (AOD) was measured at the peak of the QRS complex on the simultaneously recorded electrocardiogram. Five consecutive measurements were averaged. Aortic elasticity parameters were calculated according to the following formulas:

Aortic strain = (AOS－AOD)/AOD

Aortic stiffness (β) index = Ln (systolic blood pressure/diastolic blood pressure)/aortic strain

Aortic distensibility = 2 × aortic strain/pulse pressure

2.3 Statistical analysis

Analyses were performed using the Statistical Package for Social Science program (SPSS for Windows, version 16.0). The data were tested for normal distribution using the Kolmogorov-Smirnov test. Comparisons between patients were made by using Student's independent *t*-test for normally distributed data and the Mann-Whitney *U* test for non-normal distributed data. Chi-square test was used to examine differences with categorical variables. The data were expressed as the mean ± SD for normally distributed variables and as median (minimum–maximum) for non-normally distributed variables. Pearson correlation coefficient

was used to measure of the strength of the association between homocystein levels, aortic distensibility and aortic stiffness. The results were regarded as significant when $P < 0.05$.

3 Results

The mean age in the Parkinson group was 70 ± 9 years while it was 69 ± 8 years in controls (Table 1). Comparision of the baseline characteristics between the patients with PD and controls is given in Table 2. There was no statistically significant difference between two groups in terms of smoking status, family history, body mass index (BMI), high density lipoprotein cholesterol (HDL-C) and triglyceride levels ($P > 0.05$). Additional systolic blood pressure and heart rate did not differ significantly between the two groups ($P > 0.05$). The Parkinson group had significantly higher levels of low density lipoprotein cholesterol (LDL-C) as well as higher diastolic blood pressure ($P = 0.023$ and $P = 0.032$, respectively). On the other hand, pulse pressure was significantly lower in Parkinson group compared to controls ($P = 0.021$). As an expected feature of L-dopa therapy, the Parkinson group had significantly higher homocystein levels (15.1 ± 3.9 μmol/L *vs.*11.5 ± 3.2 μmol/L, $P = 0.02$).

Echocardiographic evaluation of the subjects is given in Table 3. Both Parkinson and control groups had similar left ventricular ejection fraction, left ventricular end diastolic diameter, left ventricular end systolic diameter, left atrial diameter, left ventricular mass index, interventricular and posterior wall thickness ($P > 0.05$). Right ventricular function was also similar since TAPSE and estimated pulmonary artery systolic pressure values did not differ between the two groups ($P > 0.05$). Beside preserved systolic function in both Parkinson and control groups, the prevalence of diastolic dysfunction was significantly higher in the patients with PD. Tissue Doppler measurements revealed lower Ea and higher E/Ea values in the Parkinson group (9.2 ± 0.6 cm/s *vs.* 12.1 ± 0.9 cm/s and 9.5 ± 1.2 cm/s *vs.* 7.8 ± 1.1 cm/s, $P = 0.01$ and $P = 0.01$, respectively).

When elastic parameters of the aorta were evaluated, aortic distensibility was significantly lower in patients with PD when compared to controls (6.2 ± 1.9 dyn/cm^2 *vs.* 4.8 ± 1.5 dyn/cm^2, $P = 0.016$). Additionally, the patients with PD had higher aortic strain and aortic stiffness index (13.4% ± 6.4% *vs.* 7.4% ± 3.6%, $P < 0.001$ and 7.3 ± 1.5 *vs.* 4.9 ± 1.9, $P < 0.001$, respectively) (Table 4). Furthermore, serum homocysteine levels were found to be positively correlated with aortic stiffness index and there was a negative correlation between aortic distensibility and levels of serum homocysteine ($r = 0.67$, $P < 0.001$, $r = –0.60$, $P < 0.001$, respectively).

Table 1. Demographics and characteristic features of the patients with PD (n = 65).

Mean age, yrs (min-max)	70 ± 9 (42–85)
Gender	
Male	41 (63%)
Female	24 (37%)
Age of onset of disease, yrs	65.0 ± 7.4 (49–84)
Duration of PD, yrs	5.32 ± 3.67 (1–14)
Mean levodopa dosage, mg/day	504.67 ± 267.71 (25–1100)
Stage of disease	
1 (HYS)	20 (31.4%)
2 (HYS)	30 (45.7%)
3 (HYS)	13 (20.0%)
4 (HYS)	2 (2.8%)
UPDRS	
UPDRS total	29.04 ± 17.15 (8–99)
UPDRS cognitive	1.96 ± 1.27 (0–5)
UPDRS motor sections	18.02 ± 11.03 (5–60)
UPDRS activities of daily living	8.01 ± 7.12 (1–36)
UPDRS complication of treatment	0.58 ± 1.26 (0–6)

Data are expressed as n (%) or mean ± SD (min-max). HYS: Hoehn-Yahr scale; PD: Parkinson disease; UPDRS: unified Parkinson's disease rating scale.

Table 2. Baseline characteristics of Parkinson and control groups.

	Parkinson group (n = 65)	Control (n = 32)	P value
Age, yrs	70 ± 9	69 ± 8	0.804
Male gender	41 (63%)	24 (64%)	0.612
Smoking	7 (21%)	7 (22%)	0.701
Family history	16 (25%)	7 (23%)	0.345
BMI, kg/m^2	25 ± 4	24 ± 3	0.273
LDL-C, mg/dL	145 ± 32	131 ± 31	0.023
HDL-C, mg/dL	44 (25–76)	47 (28–77)	0.853
Triglycerides, mg/dL	174 (135–215)	162 (138–214)	0.046
SBP, mmHg	137 ± 9	139 ± 9	0.280
DBP, mmHg	79 ± 8	69 ± 7	0.032
Pulse pressure, mmHg	58 ± 6	70 ± 6	0.021
HR, beats/min	72 ± 5	71 ± 7	0.320
Homocysteine, μmol/L	15.1 ± 3.9	11.5 ± 3.2	0.002
Vitamin use (folic acid, B12, B6)	12 (18%)	6 (20%)	0.278

Data are expressed as n (%), mean ± SD, or median (interquartile range). BMI: body mass index; DBP: diastolic blood pressure; HDL-C: high density lipoprotein cholesterol; HR: heart rate; LDL-C: low density lipoprotein cholesterol; SBP: systolic blood pressure.

Table 3. Hemodynamic findings and echocardiographic parameters of Parkinson and control groups.

	Parkinson group, *n* = 65	Control group, *n* = 32	*P* value
Echocardiographic measurements			
EF	62.4% ± 3.4%	61.5% ± 3.8%	0.427
LA diameter, mm	3.5 ± 0.6	3.4 ± 0.5	0.578
LVEDD, mm	43 ± 2.5	44.7 ± 3.4	0.624
LVESD, mm	25.9 ± 3.7	26.6 ± 3.6	0.478
LVMI, g/m^2	109 ± 16.9	108.5 ± 18.4	0.285
IV*S*, mm	9.8 ± 1.8	9.5 ± 1.1	0.848
PW, mm	9.7 ± 1.0	9.4 ± 0.9	0.789
TAPSE, cm	1.98 ± 0.45	1.88 ± 0.36	0.124
ePASP, mmHg	18 ± 5	19 ± 5	0.235
Cardiac output, L/min	4.95 ± 1.2	5.28 ± 1.1	0.120
Stroke volume, mL	69 ± 5.1	67 ± 4.2	0.235
Mitral inflow parameters			
E, cm/s	60.3 ± 13.0	83.0 ± 14.5	0.001
A, cm/s	82.3 ± 15.1	84.2 ± 15.5	0.657
E/A ratio	0.7 ± 0.15	0.9 ± 0.28	0.011
IVRT, ms	128 ± 11	106 ± 9	< 0.001
DT, ms	179 ± 32	134.5 ± 30.7	0.012
Tissue doppler parameters			
Ea, cm/s	9.2 ± 0.6	12.1 ± 0.9	0.001
Aa, cm/s	9.6 ± 0.4	8.6 ± 0.6	0.024
E/Ea ratio	9.5 ± 1.2	7.8 ± 1.1	0.001

Data are expressed as mean ± SD. A: mitral late-diastolic velocity; Aa: late diastolic velocity of mitral annulus; DT: decelaration time; E: mitral early-diastolic velocity; Ea: early diastolic velocity of mitral annulus; EF: ejection fraction; ePASP: estimated pulmonary artery systolic pressure; IVRT: Isovolumetric relaxation time; IVS: interventricular septum; LA: left atrium; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVMI: left ventricular mass index; PW: posterior wall; TAPSE: tricuspid annular plane systolic displacement.

Table 4. Evaluation of aortic elastic parameters of Parkinson and control groups.

	Parkinson group, *n* = 65	Control group, *n* = 32	*P* value
Aortic velocity, m/s	1.2 ± 0.9	1.3 ± 0.5	0.574
Aort diameter in systole, mm	35.6 ± 2.5	36.5 ± 3.4	0.203
Aort diameter in diastole, mm	33.6 ± 2.5	31.6 ± 2.8	0.044
Aortic strain, %	13.4 ± 6.4	7.4 ± 3.6	< 0.001
Aortic distensibility ($cm^2.dyne^{-1}.10^{-6}$)	4.8 ± 1.5	6.2 ± 1.9	0.016
Aortic stiffness index	7.3 ± 1.5	4.9 ± 1.9	< 0.001

Data are expressed as mean ± SD.

4 Discussion

The results of our study demonstrated that the patients with PD under L-dopa therapy have impaired aortic elasticity and diastolic function. Elevated serum homocystein levels in this patient population was also another noteworthy finding of our study. It can be hypothesized that increased aortic stiffness and impaired diastolic function may be secondary to elevated homocysteine levels.

PD is a neurodegenerative disorder and commonly seen in elder population.[1–3] Coronary heart disease also affects individuals in the same decades.[16] Therefore, concomitance of these two clinical entities is highly probable. The studies investigating the association between them are quite limited. Liang, *et al*.[17] demonstrated a high risk of myocardial infarction in patients with PD when compared to healthy subjects. Another study found that PD was associated with an increased risk of ischemic heart disease–related death.[18] Although these two studies revealed the fact that myocardial infarction and death secondary to ischemia are common in patients with PD, the underlying mechanism of this process has not been clearly identified.[17,19]

Orthostatic hypotension, oxidative stress and inflammation are thought to be the underlying mechanisms in the studies revealing increased frequency of coronary heart disease and mortality in patients with PD.[17,19] Oxidative stress and inflamation cause atherosclerosis secondary to endothelial dysfunction. On the other hand, ortostatic hypotension results in cardiac sympathetic denervation, extracardiac noradrenergic denervation, and baroreflex failure leading to decreased diastolic perfusion pressure on myocardial blood flow.[16,20–22]

Homocysteine has been identified as a risk factor for atherosclerotic vascular disease and hypercoagulability states since 1990. It is a sulphur-containing aminoacid and produced in the metabolism of the essential aminoacid methionine.[6,23,24] Coagulation cascade activation, production of inflammatory mediators, ROS generation and endothelial dysfunction have been proposed to explain the link between hyperhomocysteinemia and coronary artery disease.[23] The sulfhydryl group of homocysteine has redox potential and causes formation of reactive oxygen species resulting in substantial impairment of endothelial function and subsequent atherosclerosis.[24] Endothelial dysfunction and atherosclerosis are well identified etiological factors of impaired aortic elasticity.[25,26]

Randomized and prospective studies have also demonstrated the association between hyperhomocysteinemia and increased aortic stifness as well as adverse cardiovascular events.[27,28] A moderately elevated homocysteine level indicates high risk of CVD (coronary, heart, cerebrovascular and peripheral artery diseases).[6,29] However, to settle the pure clinical effects of PD is tough since the anti-Parkinson

drugs have already been shown to have substantial effects on cardiovascular system. The overlooked feature in PD is elevation of serum homocysteine levels resulting from use of L-dopa. Although its initial impressive therapeutic efficacy within a few years is typically interrupted due to development of motor complications such as fluctuations or abnormal movements and other neurological problems, L-dopa remains to be the first-line and gold- standard therapy in PD.[30,31] L-dopa therapy has been shown to increase serum homocytesine levels. The pathophysiological mechanism is that O-methylation of L-dopa to 3-O-methyldopa is associated with conversion of S-adenosylmethionine to S-adenosylhomocysteine and subsequently homocysteine.[5,7,32] The knowledge about L-dopa therapy and homocysteine makes us speculate an increased risk of cardiovascular disorders in patients with PD under L-dopa treatment. Our study results demonstrated that patients with PD under L-dopa treatment had increased aortic stiffness.

The other prominent finding of our study was deterioration of diastolic function in patients with PD. Diastolic dysfunction is a significant predictor of fatal and nonfatal cardiovascular events.[33] Several trials have depicted a negative correlation between serum homocysteine levels and diastolic function.[34,35] Also, in our study, elevated homocysteine levels may be the reason of impaired diastolic function.

Consequently, we hypothesize that increased aortic stiffness and impaired diastolic function in patients with PD under L-dopa treatment may be secondary to elevated serum homocysteine levels.

4.1 Limitations

Lack of a more sophisticated method in assessment of aortic elastic parameters is a limitation of this study as we do not own the required equipment for oscillometric and tonometric measurement of arterial stiffness. Besides, evaluation of aortic stiffness through echocardiographic measurements is a well-established and commonly used method. On the other hand, in addition to increased aortic stiffness, high frequency of diastolic dysfunction was another indicator of increased cardiovascular risk in the Parkinson group. Since PD patients were free of hypertension, use of L-dopa can be the reason for impaired diastolic function. Furthermore, the number of patients was relatively small and this cross-sectional study was not designed to establish causal relationship, which should be confirmed by longitudinal and interventional studies.

4.2 Conclusions

Patients with PD under L-dopa treatment have increased aortic stiffness and impaired diastolic function compared to healthy individuals. Elevated serum homocysteine levels may have played a role in the pathophysiological mechanism. Considering the cross-sectional design of the present study, the contributions of serum homocysteine measurement in impaired aortic elasticity and diastolic function in patients with PD under L-dopa treatment requires further investigation by prospective, interventional studies.

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