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Cardiovascular Autonomic Dysfunction in Patients with Drug-Induced Parkinsonism

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Background and Purpose Recent studies have shown that several nonmotor symptoms differ between Parkinson's disease (PD) and drug-induced parkinsonism (DIP). However, there have been no reports on cardiovascular autonomic function in DIP, and so this study investigated whether cardiovascular autonomic function differs between PD and DIP patients.

Methods This study consecutively enrolled 20 DIP patients, 99 drug-naïve PD patients, and 25 age-matched healthy controls who underwent head-up tilt-table testing and 24-h ambulatory blood pressure monitoring.

Results Orthostatic hypotension was more frequent in patients with PD or DIP than in healthy controls. In DIP, orthostatic hypotension was associated with the underlying psychiatric diseases and neuroleptics use, whereas prokinetics were not related to orthostatic hypotension. The supine blood pressure, nighttime blood pressure, and nocturnal blood pressure dipping did not differ significantly between the DIP and control groups. Supine hypertension and nocturnal hypertension were more frequent in PD patients than in controls.

Conclusions The included DIP patients frequently exhibited orthostatic hypotension that was associated with the underlying diseases as well as the nature of and exposure time to the offending drugs. Clinicians should individualize the manifestations of DIP according to underlying diseases as well as the action mechanism of and exposure time to each offending drug.

Key Words Parkinson's disease, drug-induced parkinsonism, cardiovascular autonomic dysfunction.

INTRODUCTION

Drug-induced parkinsonism (DIP) is the second most common cause of parkinsonism in the elderly after Parkinson's disease (PD).[1] DIP is traditionally associated with old-generation (typical) antipsychotic agents, though it can also occur during the administration of several other classes of drugs including the newer (atypical) antipsychotic agents, gastrointestinal prokinetics, and calcium-channel-blocking agents.[2-4]

The clinical presentations of DIP and PD are very similar, and therefore patients with DIP are frequently misdiagnosed as having PD.[1] Although most DIP patients experience a full and long-lasting recovery from DIP with no subsequent PD after discontinuing the offending drugs, some patients develop persistent and worsening parkinsonian symptoms after drug discontinuation (i.e., subclinical parkinsonism or DIP unmasks PD) or experience the reappearance of PD after full remission from DIP (i.e., DIP antedates PD).[5]

Cardiovascular autonomic dysfunction is relatively common in patients with PD, and can occur independently of levodopa treatment and early in the course of the disease.[6] The manifestations of this dysfunction include orthostatic hypotension (OH), supine hyperten-

sion (SH), nocturnal hypertension (NH), and absence of a decrease in blood pressure (BP) during the night (nondipping).[6,7]

Recent analyses utilizing a nonmotor symptom questionnaire found that several nonmotor symptoms such as urinary and sleep symptoms and disturbances of taste or smell autonomic dysfunction occurred more frequent in patients with PD than in those with DIP.[8,9] However, cardiovascular autonomic function has not previously been assessed in patients with DIP.

In this study we evaluated the cardiovascular autonomic function during head-up tilt-table testing and performed 24-h ambulatory BP monitoring in PD and DIP patients as well as control subjects.

METHODS

Patients

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital, and each subject provided written informed consent to participate. Twenty patients with DIP were enrolled consecutively, in addition to 99 with PD who met the clinical diagnostic criteria of the UK Brain Bank between March 2014 and February 2015.[10] A clinical diagnosis of DIP was made based on the following diagnostic criteria:[4] 1) presence of at least two of the four cardinal signs (tremor, rigidity, bradykinesia, and impaired postural reflexes), 2) absence of a personal history of extrapyramidal disorders before receiving treatment with an offending drug, 3) onset of symptoms during the course of treatment with an offending drug, 4) reversal of parkinsonian symptoms (though not necessarily completely) after discontinuing offending drugs during a follow-up lasting more than 6 months, and 5) normal dopamine transporter positron-emission tomography scan using ^{18}F-N-(3-fluoropropyl)-2beta-carbon ethoxy-3beta-(4-iodophenyl) nortropane (FP-CIT). All of the PD patients exhibited a decreased uptake of FP-CIT in the basal ganglia.

The DIP patients were subgrouped according to their underlying diseases (psychiatric diseases vs. functional dyspepsia or gastrointestinal prophylaxis) since patients with a psychiatric disease may experience some degree of autonomic dysfunction and most neuroleptics have the side effect of OH and act on dopaminergic, noradrenergic, cholinergic, and serotonergic pathways,[11-18] whereas most prokinetics mainly inhibit the dopamine D2 receptor in the central nervous system.[19-21] Twenty-five age-matched healthy subjects free from neurological disease were enrolled as controls.

Clinical information was collected, including age, sex, symptom duration, history of arterial hypertension, diabetes mellitus, cigarette smoking, and current medications. All pa-

tients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) Parts 1−3 and classified according to the modified Hoehn and Yahr (H&Y) stage. Patients with the following characteristics were excluded from the study: 1) history of diabetic neuropathy or other peripheral/autonomic neuropathy, 2) history of previous relevant cardiac disease, or any abnormalities on routine chest radiography or electrocardiography, and 3) taking medications known to influence cardiovascular autonomic function.

Suspected offending drugs were continued in DIP patients during all of the tests. Antihypertensive medications were discontinued 7 days before the BP tests in all subjects, and no serious clinical problems were observed during this period.

Tilt-table testing

The patients were examined in a temperature-controlled clinical investigation room after having fasted overnight (except for water). Electrocardiographic and noninvasive continuous-BP-monitoring leads were connected (YM6000, Mediana Tech, Redmond, WA, USA). After 30 minutes of supine resting, head-up tilt-table testing (20 minutes at 60°) was performed using a Manumed Special Tilt1-section tilt-table (ENRAF NONIUS, Rotterdam, the Netherlands). The BP was measured manually every 5 minutes before tilting, at 1, 3, 5, 10, 15, and 20 minutes during head-up tilting, at 1 minute after tilting, and as deemed necessary to ensure subject safety. The mean supine baseline and lowest tilt values for BP were recorded. Statistical analysis was applied to the lower values from 3 and 5 minutes.

OH was defined as a decrease in the systolic blood pressure (SBP) of at least 20 mm Hg or in the diastolic blood pressure (DBP) of at least 10 mm Hg between 2 and 5 minutes after the initiation of a head-up tilt.[22,23] Patients with SBP ≥140 mm Hg or DBP ≥90 mm Hg were considered to have SH.[24-26]

Ambulatory blood pressure monitoring

An automated 24-h BP recording instrument (Mobil-O-Graph NG, I.E.M., Stolberg, Germany) was used to measure the ambulatory BP every 15 minutes during the day and every 30 minutes during the night. The mean values of SBP, DBP, and heart rate during the daytime, nighttime, and over 24-h periods were evaluated. Nocturnal decreases in BP and heart rate were calculated as percentage changes between the daytime and nighttime mean values. Subjects with a <10% nocturnal decrease in mean BP were considered nondippers.[27] NH was defined according to the 2013 European Hypertension Society/European Cardiology Society guidelines (i.e., mean nighttime SBP/DBP ≥120/70 mm Hg).[28]

Data analysis

Statistical analyses were performed using SPSS (version 15.0 for Windows, SPSS Incorporated, Chicago, IL, USA). One-way analysis of variance was used to compare means between groups, and Pearson's χ^2 test was used to compare the frequencies of categorical variables. The Mann-Whitney nonparametric U test was also used to analyze DIP subgroups. Given the potential influence of age, sex, hypertension, and diabetes on the results of group comparisons, such comparisons were performed using analysis of covariance. Statistical significance was defined by a *p* value of less than 0.05.

RESULTS

Table 1 summarizes the clinical characteristics in the DIP, PD, and control groups. Men comprised 4 of the 20 DIP patients. The age at examination was similar among groups, but the disease duration was shorter in the DIP group than in the PD group. The UPDRS score and H&Y stage tended to be higher in DIP than in PD patients. In the DIP group, gastrointestinal prokinetics were the most common offending drugs (*n*=13), while antipsychotics were the second most common cause of DIP (*n*=7). Underlying diseases were functional dyspepsia (*n*=7) or psychiatric diseases (*n*=7). Six patients were prescribed a prokinetic drug for gastrointestinal prophylaxis. Exposure times and symptom durations varied among patients, but complete remission was observed in all of them. The dosage of each offending drug was within the therapeutic range of pharmaceutical introduction in all DIP patients.

PD and DIP patients frequently had OH (controls vs. PD vs. DIP, 4.0% vs. 27.1% vs. 25.0%; χ^2=6.236, *p*=0.016). The orthostatic change in SBP (ΔSBP) was also greater in the PD and DIP groups than in the control group. SH and NH were more frequent in PD patients than in controls. Supine BP was higher in patients with PD than in controls and patients with DIP (Table 2). The proportions of SH, NH, and nondipping were similar in the DIP and control groups, and supine BP, nighttime BP, or nocturnal BP dipping did not differ significantly between these two groups (Table 2).

Among patients with DIP, OH was associated with underlying psychiatric disease and concurrent neuroleptics use (neuroleptic-induced parkinsonism, in 5 of 7 patients), whereas prokinetics were not related to OH (in 0 of 13 patients). Among patients with neuroleptic-induced parkinsonism, OH was related to mood disorders (four patients with depressive disorder and one with bipolar disorder). Patients with neuroleptic-induced parkinsonism displayed a higher ΔSBP during tilting than those with prokinetic-induced parkinsonism (Table 3). ΔSBP values during tilting did not differ significantly between patients with prokinetic-induced parkinsonism and normal healthy controls (6.7±7.3 mm Hg vs. 3.3±9.0 mm Hg, mean±standard deviation; *p*=0.210 in the Mann-Whitney U test).

Table 1. Demographics of age-matched controls and patients with Parkinson's disease (PD) and drug-induced parkinsonism (DIP)

	Controls (*n*=25)	PD (*n*=99)	DIP (*n*=20)	*p*	Post-hoc comparison		
					Controls vs. PD	Controls vs. DIP	PD vs. DIP
Age, years	67.4±10.9	68.9±10.1	67.6±17.0	0.767	1.000	1.000	1.000
Men*	6 (24.0%)	49 (49.5%)	4 (20.0%)	0.008	0.022	0.748	0.015
Disease duration, years	-	1.6±1.7	0.8±0.5	0.029	-	-	-
Hypertension*	6 (24.0%)	42 (42.4%)	7 (35.0%)	0.226	0.091	0.419	0.538
Antihypertensive agents used	ARB (*n*=4), CCB (*n*=2)	ARB (*n*=26), CCB (*n*=14), ACE (*n*=1), DU (*n*=1)	ARB (*n*=4), CCB (*n*=3)				
Diabetes mellitus*	4 (16.0%)	14 (14.1%)	5 (25.0%)	0.481	0.813	0.453	0.227
Current or ex-smoker*	7 (28.0%)	23 (23.2%)	1 (5.0%)	0.134	0.619	0.045	0.064
UPDRS score	-	22.2±15.4	31.1±17.3	0.018	-	-	-
UPDRS part 1 score	-	2.2±2.1	2.9±1.9	0.149	-	-	-
UPDRS part 2 score	-	6.1±4.8	9.1±1.9	0.012	-	-	-
UPDRS part 3 score	-	13.8±10.3	19.1±7.8	0.034	-	-	-
H&Y stage	-	1.5±0.7	1.9±0.5	0.018	-	-	-

Data are mean±SD or *n* (%) values.
One-way analysis of variance with Bonferroni post-hoc comparison, independent sample *t*-test, or *the χ^2 test.
ACE: angiotensin-converting enzyme inhibitor, ARB: angiotensin II receptor blocker, CCB: calcium channel blocker, DU: diuretic, H&Y: Hoehn and Yahr, UPDRS: Unified Parkinson's Disease Rating Scale.

DISCUSSION

Cardiovascular autonomic dysfunction occurs frequently in patients with PD, manifesting mainly as OH, SH, NH, non-dipping, and heart rate variability.[3,29] These abnormalities are associated with various nonmotor features such as cognitive impairment, dementia, depression, and sleep problems.[30-33] These dysfunctions in PD are related to cardiac and extracar-

Table 2. Blood pressure monitoring results of age-matched controls, patients with PD, and patients with DIP

	Controls (n=25)	PD (n=99)	DIP (n=20)	p	Post-hoc comparison		
					Controls vs. PD	Controls vs. DIP	PD vs. DIP
Orthostatic hypotension*	1 (4.0%)	32 (32.3%)	5 (25.0%)	0.016	0.004	0.039	0.519
Supine hypertension*	3 (12.0%)	39 (39.4%)	5 (25.0%)	0.024	0.010	0.257	0.224
Nondipper*	19 (76.0%)	81 (81.8%)	15 (75.0%)	0.683	0.511	0.938	0.481
Nocturnal hypertension*	2 (8.0%)	31 (31.3%)	4 (20.0%)	0.048	0.018	0.239	0.311
ΔSBP during tilting, mm Hg	3.3±9.0	15.8±16.8	16.7±22.0	0.001	0.001	0.019	1.000
Supine SBP, mm Hg	122.5±14.1	134.6±17.7	126.0±17.3	0.004	0.008	1.000	0.123
Nighttime SBP, mm Hg	107.1±11.6	114.1±14.7	106.3±14.9	0.037	0.146	1.000	0.121
Dipping, %	7.5±6.8	3.5±10.7	1.9±11.4	0.160	0.464	0.187	1.000

Data are mean±SD or n (%) values.
Analysis of covariance controlling for age, sex, hypertension, and diabetes mellitus, or *the χ^2 test.
DIP: drug-induced parkinsonism, PD: Parkinson's disease, SBP: systolic blood pressure.

Table 3. Demographics and autonomic function test results of patients with DIP categorized by underlying disease

	Psychiatric diseases (offending drugs: neuroleptics, n=7)	Functional dyspepsia or gastrointestinal prophylaxis (offending drugs: prokinetics, n=13)	p
Age, years	65.1±18.3	68.8±16.9	0.438
Men*	2 (28.6%)	2 (15.4%)	0.482
Disease duration, years	0.6±0.6	0.9±0.5	0.241
Hypertension*	0	7 (53.8%)	0.016
Diabetes mellitus*	2 (28.6%)	3 (23.1%)	0.787
Current or ex-smoker*	1 (14.3%)	0	0.162
UPDRS score	32.1±8.5	30.5±14.0	0.699
UPDRS part 1 score	3.3±1.4	2.7±2.2	0.275
UPDRS part 2 score	10.4±3.4	8.4±4.2	0.311
UPDRS part 3 score	18.4±4.8	19.5±9.2	0.588
H&Y stage	1.9±0.4	1.9±0.6	0.536
Underlying disease	Depressive disorder (n=4), bipolar disorder (n=1), schizophrenia (n=1), delusional disorder with agitation (n=1)	Functional dyspepsia (n=7), gastrointestinal prophylaxis with aspirin or nonsteroidal anti-inflammatory drug (n=6)	
Offending drugs	Chlorpromazine (n=2), sulpiride (n=1), haloperidol (n=1), aripiprazole (n=2), perphenazine (n=1)	Levosulpiride (n=9), clebopride (n=2), DA-9701 (herbal combination of Corydalis tuber and Pharbitis seed; n=2)	
Drug exposure time, years	4.5±2.0	1.6±1.5	0.011
Orthostatic hypotension*	5 (71.4%)	0	<0.001
Supine hypertension*	3 (42.9%)	2 (15.4%)	0.176
Nondipper*	4 (57.1%)	11 (84.6%)	0.176
Nocturnal hypertension*	1 (14.3%)	3 (23.1%)	0.639
ΔSBP during tilting, mm Hg	35.3±28.3	6.7±7.3	0.014
Supine SBP, mm Hg	129.6±13.7	124.1±19.1	0.438
Nighttime SBP, mm Hg	104.9±16.4	107.0±14.7	0.938
Dipping, %	0.8±14.6	2.5±9.9	1.000

Data are mean±SD or n (%) values.
Mann-Whitney nonparametric U test or *the χ^2 test.
DIP: drug-induced parkinsonism, H&Y: Hoehn and Yahr, SBP: systolic blood pressure, UPDRS: Unified Parkinson's Disease Rating Scale.

diac neuronal degeneration and the α-synuclein-related Braak pathological sequence.[34,35]

In contrast, although the pathology underlying DIP is not clear, temporary blockade of the dopamine D2 receptor by offending drugs can induce parkinsonian symptoms and other extrapyramidal manifestations.[36] We therefore speculated that patients with DIP would not have any other cardiovascular autonomic manifestations; however, to our surprise this was not the case—instead we frequently observed OH in patients with DIP. In particular, underlying psychiatric diseases and concurrent use of neuroleptics were more strongly associated with OH than gastrointestinal prophylaxis or treatment for functional dyspepsia and gastrointestinal prokinetics.

The DIP patients in this study who were taking neuroleptics exhibited a marked reduction in BP during orthostasis compared to healthy controls and DIP patients taking a prokinetic drug. The supine BP and nocturnal BP were higher in patients with PD—but not in those with DIP—compared to healthy controls, although the actual prevalence of SH/NH was higher in the DIP group than in the control group. The exposure time to the offending drug was significantly longer in patients with neuroleptic-induced parkinsonism than in those with prokinetic-induced parkinsonism. The psychiatric diseases are associated with dysfunction of the hypothalamic—pituitary axis, inducing increased secretion of cortisol, adrenaline, and noradrenaline, and eventually leading to increased sympathetic tone and decreased parasympathetic tone of the autonomic nervous system.[37] Therefore, depressive disorders and other mood disorders can be reportedly related to autonomic manifestations such as OH.[11-16] In addition, we should also consider the properties of each offending drug. Because most neuroleptics have pluripotent activities, including antidopaminergic activity as well as anticholinergic, antiserotonergic, and antinoradrenergic properties, they affect autonomic and neurobehavioral systems and can have many side effects such as autonomic dysfunction and cognitive problems.[17,18,38] Antidopaminergic gastrointestinal prokinetics [e.g., bromopride, cleboride, domperidone, levosulpiride, metoclopramide, and DA-9701 (Motilitone®, Donga ST, Seoul, Korea)] are understandably able to interact with other receptor systems [e.g., 5-hydroxytryptamine 3 (5-HT) and 5-HT4 receptors for metoclopramide, 5-HT4 receptors for levosulpiride, 5-HT1A, and adrenergic α2 receptors for DA-9701]. Although the antiserotonergic/antiadrenergic properties are mild, they can induce central side effects.[20,21] Finally, we cannot fully exclude the effect of the cumulative dosage burden and the exposure time to the offending drug.

Our study had several methodological limitations. First, because the study design was cross-sectional, we did not assess the autonomic function after complete remission of DIP.

Future longitudinal studies need to confirm the hemodynamic effects of offending drugs. Second, the sample for neuroleptic-induced parkinsonism was too small (*n*=7), which impairs the ability to generalize the results. To reduce selection bias, we enrolled consecutive PD and DIP patients who visited our movement disorder clinic during only 1 year. Third, our results should be interpreted with caution since the chronic use of antihypertensive medication can contribute to OH. In addition, because patients were tested after discontinuing antihypertensive medications for more than 7 days, the tested autonomic parameters could have been affected by drug withdrawal. In this study, none of the patients with neuroleptic-induced parkinsonism had arterial hypertension, and so the OH observed in patients with DIP was clearly associated with the underlying diseases and properties of the offending drugs.

In conclusion, the DIP patients in this study frequently had OH, and OH in DIP was associated with the underlying diseases and action mechanisms of the offending drugs. These findings have important implications for the diagnosis of PD. The simple application of autonomic function tests to differentiate DIP from PD can be frustrating—to care properly for patients with parkinsonism, the manifestation of DIP should be individualized according to the action mechanism of the offending drug.

Conflicts of Interest

The authors have no financial conflicts of interest.

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