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Normal Cardiovascular Reflex Testing in Patients With *parkin* Disease

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Abstract: The objective of this study was to investigate cardiovascular autonomic function in patients with *parkin* disease. Ten patients with a genetically confirmed diagnosis were compared to 11 healthy controls. Symptoms related to autonomic dysfunction were collected by structured interviews. Cardiovascular autonomic reflex function was evaluated using a standard battery of eight tests. Autonomic tests included the study of sympathetic function through the analysis of blood pressure responses to head-up tilt, standing, isometric hand grip, cold pressor, mental arithmetic, Valsalva maneuver (Valsalva overshoot), and the study of parasympathetic function through the analysis of heart rate responses to deep breathing, hyperventilation, and Valsalva ratio. Seven out of 10 patients reported symptoms involving different aspects of autonomic function, while 5 out of 11 controls reported symptoms related exclusively to orthostatic dizziness and constipation. Symptoms related to bladder dysfunction were the most frequent autonomic abnormality occurring in six patients, followed by orthostatic dizziness and dry mouth (in four patients each). Constipation occurred in three patients, sialorrhea in two, and erectile dysfunction, dry eye, and warm intolerance in one each. Cardiovascular reflex testing revealed no difference between patients and controls in quantitative assessment of both sympathetic and parasympathetic functions, except for diastolic blood pressure after isometric hand grip that did not increase normally in *parkin* patients compared to controls ($P = 0.007$). These data show that cardiovascular dysautonomia is not associated to the *parkin* phenotype, whereas urinary complaints are more frequently reported by *parkin* patients than by controls. Urinary dysautonomia warrants further investigation in patients with *parkin* disease. © 2007 Movement Disorder Society

Key words: *parkin* disease; autonomic nervous system; cardiovascular reflex test; orthostatic hypotension; dysautonomia

Parkin disease (PARK2; OMIM 602544) is the most frequent monogenic early-onset parkinsonism (EOP), accounting for approximately 49% of familial EOP.[1] Pathological features of *parkin* disease resemble those of idiopathic Parkinson's disease (PD) in that they show degeneration of neurons in the substantia nigra pars compacta and in the locus coeruleus,[2] and occasionally Lewy bodies.[3] The typical clinical phenotype shows early onset of parkinsonian features, usually before the age of 40, benign clinical course, dystonia at onset, increased tendon jerks, sleep benefit, early motor fluctuations, and susceptibility to levodopa-induced dyskinesias.

Autonomic dysfunction is frequently observed in PD, varying from very mild nonsymptomatic abnormality of autonomic testing to a more severe sympathetic dysfunction.[4] It has been recently observed that patients with *parkin* disease may have some autonomic symptoms resembling those observed in PD.[5,6] In order to confirm if autonomic dysfunction is part of the clinical spectrum of parkin disease, we evaluated cardiovascular reflex testing in 10 carriers of *parkin* mutations and compared the results with a group of age-matched controls.

PATIENTS AND METHODS

Subjects

Ten consecutive patients with *parkin* disease were compared to 11 age- and sex-matched healthy controls.

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All subjects gave written informed consent. Patients with history or signs of heart disease, hypertension, neuropathy, or other medical disorders that could alter autonomic function (e.g., diabetes, hematological disorders, collagen diseases, malignancies) were excluded. Control subjects had no history or signs of medical disorders.

The patients had a complete neurological examination, including the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS),[7] and an internal physical examination with assessment of orthostatic hypotension. A structured interview allowed the assessment in each patient the severity of symptoms in the following domains: postural hypotension, gastrointestinal function, bladder and erectile function, sweating, and thermoregulation.

Molecular Genetic Analysis

Parkin mutations were identified on DNA obtained from peripheral lymphocytes. Single-strand conformation polymorphism (SSCP) analysis of the 12 exons was followed by nucleotide sequencing whenever an SSCP band shift was observed. To detect alterations of gene dosage (deletions and duplications), a quantitative RT-PCR assay was performed.[8]

Autonomic Tests

Autonomic testing was performed according to standard clinical methodology.[9] Caffeine-containing beverages, cigarettes, and alcohol were not allowed for at least 24 hours before testing. Subjects were studied while taking their usual antiparkinsonian medication. Drugs that can modify autonomic responses (e.g., α-adrenoceptor blockers) were withdrawn before the autonomic assessment in advance of three times the drug's half-life. All tests were conducted in the morning, at least 2 hours after a light breakfast, in a quiet and temperature-controlled laboratory (21–24°C). Patients were placed in the supine position on the horizontal electrical tilt table and told to be relaxed and stay silent during the whole period of the examination. A finger cuff of an infrared photoplethysmograph sensor for blood pressure (Finometer; FMS Finapres Medical System, Arnhem, The Netherlands) was then placed on the third finger of the nondominant hand to provide noninvasive continuous beat-to-beat finger arterial pressure measurement and recording; heart rate was derived from the beat-to-beat arterial pressure wave. Basal measurements were performed with the subject lying supine for at least 15 minutes, in order to stabilize blood pressure (BP) and heart rate (HR).

Each patient underwent a standard battery of eight noninvasive tests assessing the cardiovascular autonomic nervous system function, as outlined hereafter.[9,10] Head-up tilt: the patient was tilted 60° upright, and BP and HR were continuously measured in this position for 9 minutes. Mental arithmetic: the patient was asked to subtract 7 or 17 from a suitable starting number (e.g., 100 or 400), depending on the patient's level of education, and after a period of 2 minutes, the BP and HR were measured. Cold pressor: ice packs were placed over and under the patient's hand and forearm for 90 seconds, taking a BP and an HR recording during the last 30 seconds. Isometric hand grip: patient was asked to squeeze maximally a cloth sphygmomanometer cuff, and afterward to squeeze at 1/3 maximum power for 3 minutes, BP and HR were recorded during the last 30 seconds of isometric exercise. Hyperventilation: patient was asked to hyperventilate for 1 minute and BP and HR were recorded during the last 30 seconds. Deep breathing: patient was asked to breathe deeply at six breaths per minute for 1 minute and the difference between the maximum and minimum heart rates was estimated. Valsalva maneuver: the patient was asked to inspire deeply, then a mouthpiece was placed in the patient's mouth and the patient was asked to expire forcefully through, so as to raise the mercury column to 40 mm Hg. The pressure was maintained at 40 mm Hg for 15 seconds followed by normal breathing. The Valsalva ratio (the ratio of the maximal heart rate in phase II to the minimal heart rate in phase IV) and the presence of BP overshoot (the rising of BP over the baseline value) during the IV phase were recorded. Standing: the patient was asked to stand for up to 5 minutes and BP and HR were recorded after 2 and 5 minutes. In between each test, the patient was allowed to rest for at least 15 minutes in order to achieve baseline measurements.

Statistical Analysis

Two-sided *t* test was used for analyzing BP and HR variations between *parkin* patients and controls. Between-group differences in the frequency of altered phase IV of Valsalva maneuver (absence of BP overshoot) were assessed using 2×2 χ^2 analysis. A P value of less than 0.05 was considered statistically significant. The statistical package SPSS for Windows (SPSS, Chicago, IL), version 12.0, was used.

RESULTS

Ten patients (F:M ratio 1.00) carried mutations in the *parkin* gene. Seven were homozygous or compound heterozygous, and three had only one heterozygous mutation. The control group was composed of 11 healthy subjects (4 men and 7 women; mean age, 43.2 ± 5.7 years; range, 30–53). There were no differences between patients and controls for age or gender. The clinical and

TABLE 1. *Demographics and clinical features of* parkin *patients*

	Homozygous/compound heterozygous	Simple heterozygous	Total
Sex	2.5:1	2:1	1:1
Age at onset of motor signs (yr)	31 ± 9.5	38.6 ± 9.1	33.3 ± 9.6
Duration of motor signs (yr)	15.1 ± 10.4	16.0 ± 1.0	15.4 ± 8.5
UPDRS motor score (on)	22.1 ± 10.5	29.7 ± 9.1	24.4 ± 10.3
Levodopa-equivalent daily dose	735.7 ± 257.7	428.3 ± 325.0	697.5 ± 221.2
Motor fluctuations (number of patients)	5	3	
Dystonia at onset (number of patients)	4	0	
Sleep benefit (number of patients)	0	1	

genetic features of the patients are summarized in Table 1.

Parkinsonian features started before the age of 50 in all patients; mean age at disease onset was 33.3 ± 9.6 years (range, 22–49 years). In 8 patients, onset was before age 40. The presenting parkinsonian picture was asymmetrical in all, with the exception of Patient 1, who presented axial dystonia and postural instability at onset. Cognitive functions were normal in all patients (Mini-Mental State Examination was 30 in all cases). Disease duration at the time of clinical evaluation was 15.4 ± 8.5 years (range, 1–29 years). All patients had resting tremor, akinesia, and rigidity. Gait impairment was present in 7 patients (associated with freezing in 4). Pyramidal signs were found only in 1 patient. At the time of the study, all patients were under multiple antiparkinsonian medication: their clinical response to treatment was excellent and sustained in all cases. Motor fluctuations occurred in all patients but two, and *on* state dyskinesias were also reported by all patients but one.

In the structured questionnaires, 7 patients and 5 controls reported signs indicating possible dysautonomia. Four *parkin* patients reported orthostatic dizziness, and two of them also noted blurring of vision on standing. Fainting or syncope was never reported. Three control subjects complained of orthostatic dizziness, with occasionally orthostatic visual disturbances. Constipation occurred in 3 patients and 2 controls, who reported frequent straining at stools. No control subject complained of bladder dysfunction that was accounted for by 6 patients, who reported incontinence or urgency. Dry mouth was reported by 4 patients and sialorrhea by 2. The following features occurred in one patient each: erectile dysfunction, eye dryness, and intolerance to warm. All patients and controls correctly performed the complete test battery and tolerated the procedure well.

The results of group comparisons are summarized in Table 2. Quantitative assessment of sympathetic function did not reveal differences between patients and controls for blood pressure variations during head-up tilt test or active standing, systolic blood pressure variation after cold pressor test, or after mental arithmetic. No difference between patients and controls was found in blood pressure response during phase IV of the Valsalva maneuver. The only variation found in *parkin* patients compared to controls was a lack of increase of diastolic blood pressure during isometric hand grip ($P = 0.007$). Quantitative parasympathetic assessment revealed no difference between patients and controls in mean heart rate response during Valsalva maneuver, hyperventilation, or deep breathing. Analysis of the subgroup of three simple heterozygous *parkin* patients confirmed the results obtained in the complete series of patients for tests of sympathetic and parasympathetic function.

DISCUSSION

Parkin disease is a progressive disorder leading to early-onset parkinsonian features that share many features with other early-onset forms of PD.[11] Information on autonomic failure in *parkin* disease is scanty. Original series have not mentioned autonomic dysfunction in these patients with the exception of urinary urgency in 11% of cases,[1,12] but later studies have suggested that symptoms related to dysautonomia, particularly genitourinary, may occur in as many as 60% of *parkin* disease patients.[6]

The present series shows that symptoms of cardiovascular dysautonomia are as common in *parkin* patients as in controls, that erectile dysfunction is also uncommon in *parkin* patients, whereas urinary complaints occurred in 60% of the patients and not in controls. This is partly in keeping with earlier reports based on retrospective reviews of medical records, which reported a prevalence of 45% for urge incontinence and of 28% for erectile dysfunction.[6] The same series, however, mentioned a 13% incidence of orthostatic faintness in *parkin* patients. Diagnosis of orthostatic hypotension based on history taking may detect nonspecific dizziness instead of orthostatic hypotension.[13] The symptoms of dysautonomia reported by *parkin* patients in the present series are

TABLE 2. *Summary of cardiovascular autonomic testing in* parkin *patients and controls*

Tests	*Parkin* patients	Controls	*P*
Sympathetic function tests			
Tilt test 60°			
Systolic pressure variation at 2 minutes (mean mm Hg)	0.1 ± 7.1	−2 ± 7.2	0.50
Diastolic pressure variation at 2 minutes (mean mm Hg)	6.6 ± 4.9	4.5 ± 3.7	0.26
Heart rate variation at 2 minutes (mean beats/min)	9.8 ± 7.1	10.8 ± 8.2	0.76
Systolic pressure variation at 5 minutes (mean mm Hg)	2.3 ± 5.5	−0.1 ± 7.7	0.44
Diastolic pressure variation at 5 minutes (mean mm Hg)	6.1 ± 5.8	4.3 ± 3.3	0.38
Heart rate variation at 5 minutes (mean beats/min)	9.9 ± 7.0	11.0 ± 8.2	0.74
Standing			
Systolic pressure variation at 5 minutes (mean mm Hg)	−1.2 ± 8.2	1.9 ± 5.7	0.32
Diastolic pressure variation at 5 minutes (mean mm Hg)	6.1 ± 5.4	6.1 ± 6.4	0.99
Heart rate variation at 5 minutes (mean beats/min)	13.8 ± 7.0	12.7 ± 8.9	0.73
Isometric exercise			
Diastolic pressure variation at 3 minutes (mean mm Hg)	12.9 ± 5.1	21.8 ± 7.9	0.007
Cold pressure test			
Systolic pressure variation at 90 sec (mean mm Hg)	5.0 ± 4.5	5.1 ± 3.6	0.96
Mental arithmetic			
Systolic pressure variation at 2 minutes (mean mm Hg)	18.6 ± 14.1	13.0 ± 10.7	0.31
Altered phase IV of Valsalva maneuver (%)	40.0	27.3	0.53
Parasympathetic function tests			
Valsalva ratio	1.6 ± 0.2	1.7 ± 0.2	0.67
Deep breathing			
Heart rate difference at 1 minute (mean beats/min)	20.5 ± 11.7	17.0 ± 5.2	0.42
Hyperventilation			
Heart rate variation at 1 minute (mean beats/min)	28.9 ± 19.9	21.9 ± 11.1	0.33

milder than those reported by PD patients, notwithstanding a longer disease course.[14] Features observed in PD include chronic constipation in more than 50% of cases,[15] urinary urgency and incontinence in about 50%,[16] erectile failure in 60% to 70%,[17] and orthostatic hypotension in 47%.[18]

Cardiovascular reflex testing revealed no difference between patients and controls in quantitative assessment of both sympathetic and parasympathetic functions, with the exception for diastolic blood pressure after isometric hand grip that did not increase normally in *parkin* patients. It is unlikely hat this isolated anomaly indicates a mild sympathetic cardiovascular dysfunction, because the test battery was performed on a group of *parkin* patients with an average disease duration of 15.4 years. Cardiovascular dysautonomia occurs early in the course of PD.[19] In keeping with this is also the observation that *parkin* patients without symptoms of cardiovascular dysautonomia have normal ^{123}iodine-labeled metaiodobenzylguanidine (^{123}I-MIBG) myocardial uptake.[20,21] This would set a difference with PD and PINK1 disease, where postganglionic sympathetic denervation has been detected.[22,23] By contrast, in multiple-system atrophy, sympathetic denervation is preganglionic.[24] Further support to the observation that cardiovascular dysautonomia is not associated to the *parkin* phenotype is provided by our observation of normal cardiovascular testing in simple heterozygous patients, who may have milder parkinsonian phenotype and later onset of motor symptoms.[25,26] *Parkin* disease is phenotypically more homogeneous than classical PD, particularly for dysautonomia that has been reported to occur with varying severity.[27] Earlier PD series, particularly those reporting a low average age at onset, probably included *parkin* and other monogenic parkinsonian patients in addition to classic nongenetic forms.

The present data raise the issue whether urinary, but not cardiovascular, dysautonomia is a feature of *parkin* disease. In keeping with this, a *parkin* patient with bladder and pelvic floor symptoms (constipation and frequency of urination) was reported to have normal ^{123}I-MIBG scan.[20,21] Quantitative analysis of urinary autonomic function is warranted in patients with *parkin* disease.

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