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Autonomic Function Tests and MIBG in Parkinson's Disease: Correlation to Disease Duration and Motor Symptoms

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SUMMARY

Aims: Disorders of the autonomic nervous system (ANS) have a variable degree of clinical relevance in patients with Parkinson's disease (PD). Here, we assessed whether subclinical autonomic dysfunction, as evaluated by a complete battery of autonomic function tests (AFTs), correlates with PD progression. **Methods:** A series of 27 consecutive patients with PD underwent extensive ANS investigations including the head-up tilt test (HUTT), Valsalva maneuver, deep-breathing test, and handgrip test (HG); further, they performed 123I-meta-iodobenzylguanidine (MIBG) scintigraphy. **Results:** Seven of the 27 patients showed orthostatic hypotension (OH) at HUTT and pathological responses to the deep-breathing and HG test and Valsalva maneuver. The majority of the remaining 20 patients with PD showed pathological responses to deep-breathing (n = 13) and/or HG (n = 11). Only 3 of 27 suffered relevant OH. MIBG uptake of myocardium was decreased in 19 patients with PD (H/M ratio 1.3 ± 0.2). Prolonged clinical observation (>3 years), persistent response to levodopa, and MIBG repetition allowed us to exclude negative MIBG as attributable to atypical Parkinsonism. MIBG uptake did not correlate with OH and other AFTs. Both HG test response and MIBG did correlate with the Unified Parkinson's Disease Rating Scale (UPDRS) motor score and disease duration. A positive correlation emerged between diastolic blood pressure (DBP) response to HG test and MIBG and with systolic blood pressure (SBP) response at tilt test. **Conclusions:** Our investigation suggests that ANS impairment affects the majority of patients with PD, even those PD patients showing negative MIBG, irrespective of clinical neurovegetative symptoms. The strict correlation that has been revealed with disease progression supports the routine utilization of AFTs as a reliable and inexpensive tool for monitoring peripheral sympathetic dysfunction in PD and optimizing therapy.

Introduction

Disorders of the autonomic nervous system (ANS) are common in patients with Parkinson's disease (PD) and represent an important feature of the spectrum of nonmotor signs [1]. However, the incidence and relevance of ANS deficits are still a matter of debate. Some groups underestimate cardiovascular ANS impairment, and it is only diagnosed in up to 30% of cases; yet, ANS involvement increases up to 70–80%, if sexual dysfunction, swallowing and gastrointestinal disorders, bowel and bladder abnormalities, and sleep disturbances are included [2].

Although the most disturbing symptom of cardiovascular autonomic dysfunction in PD is orthostatic hypotension (OH) [3], it is possible that a more subtle impairment, affecting either the sympathetic or para-sympathetic fibers, emerges only under specific conditions, such as developing comorbidities or sudden therapeutic changes [4].

It is perhaps more interesting to attempt to determine whether cardiovascular ANS deficits in PD correlate with disease clinical manifestations [5,6] or, more critically, with disease duration or severity. This latter issue is quite controversial, given that Lewy body deposition into catecholamine neurons, which had been considered a preclinical hallmark of PD [7], is now thought to develop and aggravate with disease progression [8,9].

A further uncertainty derives from the potential bias, in observational studies, of enrolling misdiagnosed patients, later identified as multiple system atrophy (MSA) [10]. With regard to this, 123I-meta-iodobenzylguanidine (MIBG) scintigraphy, by

evaluating cardiac sympathetic innervations differentiating preganglionic from postganglionic damage [11], represents a valuable diagnostic tool [12]. However, cardiac sympathetic neuroimaging may lack specificity in early disease stages [13] and is rather expensive and not available in most facilities.

A robust retrospective study has recently provided unequivocal evidence of the fact that a complete Ewing battery, when sequentially repeated, may indeed distinguish MSA-P from PD in the early stages [14]; this goes beyond the scope of our investigation, which aims to discuss whether a similar battery represents a reliable diagnostic approach in establishing even the subtle cardiovascular ANS involvement in well-established PD.

This study investigates two main issues; as both AFTs and MIBG explore the autonomic cardiovascular system, we aim (i) to assess a possible association between AFTs and MIBG uptake in patients with PD and (ii) to investigate to what extent specific alterations in ANS components may correlate with disease *progression*.

Materials and Methods

Subjects

Twenty-seven patients with PD with a mean age of 61 ± 10 referred to our Department of Neurology were consecutively included in this study (Table 1). All patients fulfilled the UK Parkinson's Disease Society Brain Bank criteria for diagnosis [12]. The patients' clinical stage was assessed using the Hoehn and Yahr (H&Y) scale, and their motor disability was quantified using the Unified Parkinson's Disease Rating Scale motor score (UPDRS, part III) (Table 1). All patients were under levodopa/dopadecarboxylase inhibitor and/or dopamine agonist therapy. None of the patients had any further medical conditions nor were they taking medication known to affect ANS or the myocardial MIBG uptake. Exclusion criteria (to ensure compliance) were mini-mental state examination (MMSE) <24 and major depression (here considered as Beck's score >13) [15]. Our control group included 31 healthy age-matched subjects (Table S1). This study was approved by our local Ethical Committee at the University of Rome Tor Vergata. The protocol details were explained fully to each patient, and full consent was given.

Autonomic Function Tests (AFTs)

All patients were studied in a temperature-controlled room (23 ± 1°C). They were asked to abstain from alcohol and caffeine for at least 24 h before the investigations. All tests were carried out in the morning between 8 and 10 o'clock. For ethical reasons, patients were free to take their usual medications with the exception of the morning they performed the autonomic tests. Continuous noninvasive measurement of systolic and diastolic blood pressure (SBP and DBP) was obtained by an infrared photoplethysmograph (Finometer, Model-1 TNO Biomedical Instrumentation, Amsterdam, the Netherlands). ECG (Click ECG USB 3-12 Leads – ET Medical Devices SpA) was monitored by standard methods. Respiration rate was also monitored continuously using a nasal thermocouple respiration flow sensor (SleepSense®). AFTs were performed using standard procedures [16–18]. The results of each test were automatically calculated by means of Light-SNV software®. After 30 min of supine rest, the subject was tilted up at 65° on a tilt table for 10 min. At each minute of head-up tilt test (HUTT), the changes in SBP, DBP, and heart rate (HR) were calculated with respect to basal values. Pre-HUTT supine values (baseline) for SBP, DBP, and HR, were set at 0, and changes were expressed as Δ (raw data) from baseline. Abnormal response was defined as a decrease in SBP ≥20 mmHg or in DBP ≥10 mmHg or an increment of HR ≥30 beats per minute (bpm). The Valsalva maneuver was performed by blowing through a mouthpiece attached to a manometer and maintaining a pressure of 40 mmHg for 15 seconds. The following indices of autonomic activity were considered: the ratio between HR in phases II and IV (Valsalva ratio, VR), the DBP in phase II, and the overshoot (OV) during phase IV (difference between the highest SBP after the expiratory effort and the basal value). The responses were considered normal if the DBP increased before the end of straining and if SBP during phase IV increased to a value exceeding the baseline during not more than 7 seconds. We considered values of VR >1.21 normal. In the deep-breathing test, the subject breathed deeply six times a minute while supine. The sinus arrhythmia calculated in bpm was evaluated. The difference between the maximum HR during inspiration and minimum HR during expiration, that is inspiration–expiration difference (I-E), in an individual respiratory cycle was measured and expressed as the mean of the differences in ten respiratory cycles. We considered IE difference ≥15 bpm to be normal values in the handgrip test, and the patient exerted 30% of maximal voluntary contraction of the dominant hand for 3 min on a dynamometer. DBP and SBP were measured in the nonexercising arm at rest and at the third minute of the test. A rise of DBP >15 mmHg was considered normal.

Table 1 Demographic and clinical data of patients with PD

	PD study cohort (n = 27)	
	Mean (SD)/*n*	Range (min-max)
Age (years)	61.2 (10.1)	41.0 – 79.0
Gender (male/female)	15/12	–
Disease duration (years)	4.3 (4.5)	0.5 – 21.0
Hoehn & Yahr stage	2.4 (1.1)	1.0 – 4.0
Motor score of UPDRS	28.7 (14.4)	10.0 – 53.0

PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale.

^{123}I MIBG Scintigraphy

Each PD patient was i.v. injected for 60 seconds with 111 MBq (3 mCi) of ^{123}I MIBG (General Electric). The radio-labeled compound was administered at the same time of the day and under the same experimental conditions for each patient. Data were collected by means of a dual-head gamma-camera (Millennium VG; General Electric Medical Systems, Milwaukee, WI, USA) equipped with low-energy high-resolution parallel-hole collimators with static planar images in a 128 × 128 matrix. Images were acquired 30 min (early images) and 4 h (delayed images) after the injection of the radio-labeled

compound for both PD and control [19]. A region of interest (ROI) was manually drawn over the myocardium including the left ventricular cavity; ROIs were set over the upper mediastinum, and a heart-to-mediastinum (H/M) count ratio was calculated, which was defined as the average counts/pixel in the myocardium divided by that of the upper mediastinum [19].The H/M ratio was compared to the normal range of >1.7 (4 h p.i. [12]). To assess the evolution of the MIBG uptake, selected patients underwent a repeated procedure at 2 years (see results).

Statistical Analysis

Mean, standard deviations, and range (min/max) were calculated for the quantitative variables, and proportions for the qualitative variables. Comparison of DBP data between PD and the healthy control was performed by a two-tail Student's *t*-test. The data followed a normal distribution as attested by a Kolmogorov–Smirnov test. Pearson's correlation coefficients were used to examine the correlation between autonomic test results and demographic/clinical variables. The significance level was set at $P < 0.05$. Analyses were conducted with SPSS 18 (IBM SPSS, New York, NY, USA).

Results

Autonomic Function Tests

Table 2 reveals the main ANS finding. Seven of twenty-seven patients fulfilled the criteria of OH at the HUTT and only three reported symptomatic episodes (dizziness and fainting). The same patients showed a decreased VR, abnormal DBP and SBP responses in both phases III and IV of the Valsalva maneuver and pathologic responses to deep-breathing and HG test. Among the remaining twenty patients, thirteen showed pathological responses to deep-breathing and eleven to the HG test (Table 2).

MIBG

MIBG uptake of myocardium was decreased in 19 PD patients with a mean delayed H/M ratio 1.3 ± 0.2 (below the cut-offset in our center) [13]. The remaining 8 patients showed a mean delayed H/M ratio 2.0 ± 0.3 (Table 3). Of these 8 patients, only one was revealed as likely MSA in the following 2 years (* in Table 3). The others still have a PD diagnosis with a H&Y stage of 1.5–2 and respond well to dopaminergic agents. In

Table 2 Results of autonomic function tests

	HUTT			Valsalva		Deep breathing	Isometric HG
Pts	Δ SBP	Δ DBP	Δ HR	OV	VR	I-E	Δ DBP
1	−31	−11	3	0	1.12	4	7
2	−41	−8	4	0	1.16	8	1
3	−6	0	15	26	1.92	7	3
4	−22	−8	11	0	1.18	9	−2
5	−81	−29	12	0	1.1	3	2
6	−35	−14	8	0	1.19	10	8
7	−1	6	11	45	1.47	8	41
8	−11	−2	9	20	1.38	6	5
9	−12	−7	2	10	1.1	9	5
10	−4	8	4	9	1.43	10	10
11	−1	−5	8	11	1.15	6	15
12	−12	−8	6	27	1.5	13	15
13	5	3	13	29	1.46	41	−2
14	−11	−8	3	11	1.12	2	12
15	14	4	1	14	1.37	34	12
16	−20	0	17	0	2.25	10	12
17	−8	−5	7	33	1.85	17	20
18	3	−1	2	0	1.16	21	45
19	−5	−6	9	0	1.18	4	4
20	0	−2	12	33	1.71	18	26
21	3	3	5	27	1.57	9	23
22	−12	−1	4	10	1.36	0	3
23	6	−1	10	51	1.86	9	8
24	29	−2	6	13	1.3	4	31
25	−13	−3	4	26	1.31	6	22
26	−6	0	1	31	2.17	16	10
27	−20	−8	5	0	1.07	5	8

Δ SBP, changes in systolic blood pressure; Δ DBP, changes in diastolic blood pressure; Δ HR, changes in heart rate; OV overshoot; VR, Valsalva ratio; I-E, inspiration–expiration difference.

particular, they all show at least a 33% motor amelioration to a submaximal dose of levodopa (250 mg, in CAPIT). Moreover, three patients repeated the MIBG at 24 months and uptake had deteriorated (H/M ratio <1.55 Table 3).

Correlation between Clinical and AFTs Parameters and MIBG

Positive correlation emerged between DBP response to HG test and MIBG ($r = 0.524$, $r^2 = 0.27$; $P < 0.01$) and with ΔSBP at tilt test ($r = 0.451$, $r^2 = 0.20$; $P < 0.05$) (Table 4). A significant negative correlation between DBP response to hand grip and H&Y ($r = -0.630$, $r^2 = 0.40$; $P < 0.001$), UPDRS III ($r = -0.548$, $r^2 = 0.30$; $P < 0.01$), and disease duration ($r = -0.391$, $r^2 = 0.15$; $P < 0.05$) was found (Table 4). Moreover, a negative significant correlation between MIBG and H&Y ($r = -0.558$, $r^2 = 0.31$; $P < 0.01$), UPDRS III ($r = -0.440$, $r^2 = 0.19$; $P < 0.05$), and disease duration ($r = -0.471$, $r^2 = 0.22$; $P < 0.05$) was also revealed (Table 4).

We found no correlation between myocardial MIBG uptake, OH, and other AFTs.

Table 3 Clinical and scintigraphic results

Pts	H&Y	MIBG H/M ratio (240 min)
1	3	1.76
2	1	1.44
3	4	1.06
4	3	1.03
5	3	1.37
6	2.5	1.51
7	1	2.33
8	2	1.4
9	1	1.49
10	2	1.53
11	4	1.15
12	1.5	2.26
13	1	1.35
14	3	1.07
15	2	1.65
16	2	1.62
17	1	2.04*
18	1	1.74†
19	2	1.22
20	1	1.8
21	2	1.16
22	4	1.02
23	1.5	1.67
24	1	2.24†
25	1	1.07
26	2	1.52
27	1.5	2.03†

H&Y, Hoehn and Yahr scale stage; H/M ratio, heart/mediastinum ratio; *At present, diagnosed as MSA-P; †In these patients with PD, the new MIBG, 30–36 months later, revealed H/M values <1.55.

Table 4 Pearson's correlation coefficients between autonomic test results and demographic/clinical data

	Age	Disease duration	UPDRS III
Tilt			
Δ SBP	−0.217	−0.174	−0.194
Δ DBP	−0.284	−0.088	−0.138
Δ HR	−0.133	0.216	0.064
Valsalva			
VR	−0.470*	0.021	−0.241
OV	−0.373	−0.170	−0.337
Deep breathing			
I-E	−0.175	−0.374	−0.306
HG			
Δ DBP	−0.048	−0.391*	−0.548†
MIBG			
H/M ratio	−0.180	−0.471*	−0.440*

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate, VR, Valsalva ratio; OV overshoot; I-E, inspiration–expiration difference; HG, hand grip; H/M ratio, heart/mediastinum ratio. *$P < 0.05$. †$P < 0.01$.

Discussion

This study has addressed the correlation between different approaches, AFTs and MIBG scintigraphy, both capable of targeting some aspects of the ANS, and PD progression. If MIBG uptake represents a reliable index of cardiac postganglionic sympathetic innervations, AFTs provide a more detailed examination, including parasympathetic innervations to heart and sympathetic innervations to vessels. In the present study, the sympathetic branch was assessed by the blood pressure response to HUTT, Valsalva maneuver, and HG test. The parasympathetic cardiovagal axis was assessed by the HR variation during deep breathing and by the VR.

The relevance of autonomic cardiovascular dysfunction in patients with PD, considering both the sympathetic and the parasympathetic elements, is well established [20], and our study supports this. However, it goes beyond the available literature in several respects.

Firstly, the abnormal responses to AFTs found in our PD cohort were rather heterogeneous, implying that the involvement of different components of ANS occurs neither in the same way nor at the same time in the course of PD. Although the vast majority of patients manifested pathological responses to deep-breathing and to HG test, they rarely complained of symptomatic impairment of cardiovascular ANS. As a matter of fact, only a low percentage of those PD patients featuring abnormal responses to HG and to deep-breathing test in fact showed OH at tilt table testing (of whom, only three were symptomatic). Interestingly, OH occurred in <30% of patients, which is a percentage slightly lower than reported in previous studies [20–22]. On the other hand, there is a general agreement that the presence of sympathetic and parasympathetic dysfunctions, albeit subclinical, is typical of PD as a "multisystemic disorder," and the comparison with age-matched healthy subjects (Table S1) reinforces this contention. Consistently, in our series, the abnormal response to

deep-breathing, index of vagal efferent pathway, and to HG test, mediated by efferent sympathetic pathways to vessels, coexists from the early stages of PD. Currently, a neuropathological staging system of Parkinson's disease-related lesions in the central nervous system postulates six stages based on topographical distribution pattern and extent of lesions [7]. The dorsal motor vagal (DMV) nucleus is almost always involved in stage 1. In addition to the Lewy neurites (LNs) in DMV, LNs may be detected in the ventrolateral surface of the lower brain stem [7] where catecholaminergic melanized neurons provide descending input to preganglionic sympathetic neurons in the intermediolateral cell column of the spinal cord [23]. In subsequent stages, the disease process takes an ascending route in the brain stem nuclei and finally reaches the neocortex, affecting structures of the central autonomic network such as hypothalamus, amygdala, and anterior cingulate cortex [24].

The AFTs detailed here [25] are largely utilized also in the identification of cardiac autonomic neuropathy (CAN). In CAN, deep-breathing test seems to be the most effective of all the subtests [26]; this may explain the predominance of abnormal responses to deep-breathing test in our sample, where cardiovagal efferent involvement is due to degeneration of DMV.

Our data highlight the possibility that specific AFTs may not only be significantly impaired from the early phases of disease, but also correlate with disease duration and motor severity. In particular, a striking inverse correlation linked DBP response to HG and H&Y ($P = 0.000$) as well as to UPDRS III ($P = 0.003$) and disease duration ($P = 0.043$). These findings seem to be in contrast with a recent contribution in which HR variability (HRV) and sympathetic skin response were significantly affected in PD compared to control, but did not correlate with the clinical scores [27]. However, the same authors found that low-frequency components of HRV, reflecting mostly sympathetic activity, tended to be lower with increasing disease duration.

A critical issue targeted by our study concerns the specific roles played by the different diagnostic approaches utilized during the course of PD. Although captured in a relatively small sample, we found a positive correlation between MIBG uptake reduction and blood pressure response to HG test and to SBP responses to HUTT, while no significant correlation with other AFTs was seen. A possible explanation of these results is that HG test explores efferent sympathetic pathways to vessels and is an index of peripheral noradrenergic activity similar to MIBG scintigraphy, which investigates postganglionic noradrenergic nerves of the heart [18]. The positive correlation with SBP responses at HUTT is attributable to the fact that sympathetic vasomotor control plays a central role in the maintenance of arterial pressure during prolonged standing. On the other hand, the initial blood pressure responses to HUTT and blood pressure responses to Valsalva maneuver are not purely mediated by efferent pathways, but involve baroreceptor reflex and, therefore, have central and afferent connections as well [18,28]. As no correlation between MIBG and OH was found, our study supports the concept that cardiac denervation occurs independently of OH in PD, in line with some reports [29], but in conflict with others [30], possibly as a result of different inclusion criteria.

The most relevant and original aspect of our study remains the correlation of both approaches with PD disease duration and motor impairment. Both MIBG and DBP response to HG test correlated with PD progression and severity. These results reinforce the claim that MIBG is a useful diagnostic tool in advanced stages of PD, as recently reported [9,10]. However, HG disclosed more sensitivity, given its stronger correlation with disease severity. This finding does not present, *per se*, any conflict with previous studies inferring that in early stages, MIBG uptake in patients with PD is significantly lower than in MSA patients [31]. In other words, the degree of MIBG uptake impairment contributes to differential diagnosis; yet, when the diagnosis of PD is solid, as in this series, the acquisition of a full AFT spectrum allows for a more complete, and prospective, definition of neurovegetative deficits.

In this article, the specificity of MIBG or AFTs in movement disorders is not under scrutiny; on the contrary, here we are discussing the use of *both* techniques. Our confidence in the solid diagnosis of PD in all but one patient renders the early utilization of MIBG of little use [13]; therefore, the results of a full AFT spectrum would appear more pertinent.

For the time being, isometric HG could be a useful, simple, and inexpensive autonomic tool for evaluating peripheral sympathetic dysfunction in PD. It is worth recalling the recent European diagnostic recommendations [32], which claimed: "at the moment, there is insufficient evidence to provide a level of recommendation for AFTs in PD" [32]. Our results suggest that this sort of recommendation might turn out to be obsolete in the near future. Not only do extensive AFTs, performed longitudinally, provide an early opportunity to differentiate between PD and MSA-P [14,33], but a consistent investigation of ANVs might also contribute to better identifying PD phenotypical subtypes and to the fine monitoring of the clinical impact of pharmacological [4,16,34] and even nonpharmacological strategies [35].

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Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

The following supplementary material is available for this article:

Table S1. Comparison of HG Δ DBP between PD and healthy age-matched control subjects.

