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ORIGINAL COMMUNICATION

Heterogeneous pattern of autonomic dysfunction in Parkinson's disease

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Abstract

Dysautonomic symptoms are frequent non-motor complaints in patients with Parkinson's disease. Numerous neuropathological studies have shown that Lewy bodies and neurites, the pathological hallmarks of Parkinson's disease, are widely distributed throughout the peripheral autonomic nervous systems and across end organs. However, few investigations integrally explored the symptoms and physiology of dysautonomia in Parkinson's disease. We, therefore, performed a comprehensive evaluation of the autonomic function in a prospective group of 45 patients with idiopathic Parkinson's disease. Autonomic components (pupillomotor, tear, salivary, cardiovascular, digestive, urinary, sexual, sudomotor functions and skin sensitivity) were evaluated using questionnaires and functional tests. Skin biopsy was performed for intraepidermal nerve fibre density quantification. In addition, all patients underwent polysomnography and a complete neuropsychological and neurological assessment. The analysis association of autonomic components showed that dysautonomic signs and symptoms were heterogeneously distributed among patients. Skin denervation as assessed by intraepidermal nerve fibre density quantification was only associated with quantitative thermal sensory testing (OR = 12.0, $p = 0.02$), constipation (OR = 5.5, $p = 0.01$) and ocular dryness symptoms (OR = 8.29, $p = 0.04$). Cognitive alteration was associated with cardiovascular symptoms (OR = 4.33, $p = 0.03$) and dysfunction (OR = 5.83, $p = 0.02$) as well as with constipation (OR = 5.38, $p = 0.02$). Axial motor impairment and rapid eye movement (REM) sleep behaviour disorder were not related to any of the autonomic complaint or dysfunction. Our results show that autonomic functions are affected in a heterogeneous pattern in Parkinson's disease, thereby suggesting that the progression of autonomic dysfunction follows an erratic rather than a stepwise progression.

Keywords Dysautonomia · Electrophysiology · Intraepidermal nerve fibre density · Parkinson's disease · Cognitive alteration

Abbreviations

ANS	Autonomic nervous system
ENS	Enteric nervous system
IENF	Intraepidermal nerve fibre

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MDRS	Mattis dementia rating scale
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
NCV	Nerve conduction velocity
NMS-Quest	Non-motor symptoms questionnaire
PD	Parkinson's disease
QST	Quantitative thermal sensory testing
RBD	Rapid eye movement sleep behaviour disorder
REM	Rapid eye movement
SCOPA-Aut	SCales for Outcomes in PArkinson's disease-autonomic symptoms
SSR	Sympathetic skin response
UPDRS-III	Unified Parkinson's disease rating scale part III

Introduction

Autonomic involvement in Parkinson's disease (PD) is critical because it underlies several frequent and debilitating symptoms, such as orthostatic light-headedness, constipation, urinary problems, heat or cold intolerance, drooling, sweating and swallowing problems [1]. This wide variety in dysautonomic symptoms is likely to result from a dysregulation of more than one subdivision of the autonomic nervous system (ANS) [2]. Anatomically, the peripheral ANS can be divided into sympathetic (cholinergic and noradrenergic), parasympathetic pathways and the enteric nervous system (ENS). Dysfunction of a particular component causes characteristic signs and symptoms. ENS dysfunction is responsible for delayed gastric emptying and constipation. Parasympathetic cholinergic failure induces constipation, hyposialorrhea, an invariable pulse rate, urinary retention and erectile failure, while sympathetic cholinergic failure induces decreased sweating. Sympathetic noradrenergic failure presents as orthostatic intolerance and orthostatic hypotension [2]. Hence, in PD there seems to be a dysregulation of most if not all components of the autonomic nervous networks [3, 4] (Table 1).

These clinical observations are supported by neuropathological studies, which found Lewy bodies and neurites, the pathological hallmarks of PD, in various peripheral autonomic networks. Lewy pathology has been observed in a chain of neurons forming the sympathetic autonomic pathways including the intermedio lateral cell column of spinal cord [5, 6], sympathetic paravertebral ganglia [5, 7–9], epicardium [7, 8], adrenal medulla [5, 10] and skin nerve fibres [11]. This pathological process also reaches several structures of the parasympathetic nervous system [12–16] as well as the ENS [17–20] (Table 1). In addition, neuronal loss and/or denervation have been observed in the dorsal motor nucleus of the vagus [14, 21, 22], sympathetic ganglia [8], the epicardium [7, 8] and the skin [23] (Table 1).

Table 1 Possible clinico-pathological correlations of autonomic dysfunction in PD

Autonomic component	Autonomic dysfunction	ANS division	Lewy pathology
Pupillo-motor	Altered constriction	Parasympathetic	Edinger-Westphal nucleus [16]
	Altered dilation	Sympathetic	Spinal intermedio lateral cell column and SCG [6]
Tear	Dry eye	Parasympathetic	?
Salivary	Hyposialorrhea	Parasympathetic	Salivary glands [45, 46]
Cardio-vascular	Orthostatic hypotension	Sympathetic	Spinal intermedio lateral cell column [6], sympathetic paravertebral ganglia and adrenal gland [5, 9, 10]
	Invariable pulse rate	Parasympathetic	DMNV [15, 22] and vagus nerve [9]
Upper GI tract	Dysphagia	Parasympathetic	Somatic nervous system [47], DMNV [15, 22], vagus nerve [9] and ENS [17, 20]
	Gastroparesia	Parasympathetic	DMNV [15, 22], vagus nerve [9] and ENS [17, 20]
Lower GI tract	Faecal incontinence	Sympathetic	Spinal intermedio lateral cell column [6]
	Constipation	Parasympathetic	DMNV [15, 22], spinal sacral parasympathetic centres [6, 12] and ENS [17, 20]
Urinary	Urinary urgency	Sympathetic	Spinal intermedio lateral cell column [6], bladder [20]
	Urinary retention	Parasympathetic	Spinal sacral parasympathetic centres [6], preganglionic parasympathetic neurons [12, 48]
Sexual	Erectile failure	Parasympathetic	Spinal sacral parasympathetic centres [6], preganglionic parasympathetic neurons [12]
Skin sensitivity	Thermal intolerance	Sympathetic	Spinal intermedio lateral cell column [6] and skin nerve fibres [11]
	Unexplained pain	Sympathetic ?	Spinal intermedio lateral cell column [6] and skin nerve fibres [11]
Sudo-motor	Dyshidrosis	Sympathetic	Spinal intermedio lateral cell column [6] and skin nerve fibres [11]

DMNV dorsal motor nucleus of the vagus, *ENS* enteric nervous system, *GI* gastrointestinal, *SCG* superior cervical ganglia

The main limitation of most of previous reports on autonomic involvement in PD lies in the fact that they have focused on a single symptom and/or on a specific subdivision of the ANS. The purpose of the current study was therefore to perform a comprehensive assessment of the autonomic and non-motor features in a prospective group of idiopathic PD patients in order to explore autonomic dysfunction across PD population, its distribution and its relationship with disease progression and severity [cognitive alteration, axial motor impairment, rapid eye movement (REM) sleep behaviour disorder (RBD)].

Materials and methods

Study population

From February 2013 to February 2016, 50 patients aged 45–80 years with idiopathic PD as per the UK Brain Bank Criteria were prospectively screened for this cross-sectional study. Exclusion criteria were: (1) confounding factors for autonomic failure or neuropathy (autonomic active treatment, diagnosed peripheral neuropathy, renal failure, diabetes, alcoholic abuse and low levels of vitamin B12) (2) dementia (Mini-Mental State Examination (MMSE) < 24). Of the 47 patients who initially met inclusion criteria, two patients were subsequently excluded (one patient withdrew consent before ANS analysis and the diagnosis of PD was not further confirmed in another patient). This study was carried out in accordance with the Declaration of Helsinki, conducted with the approval of the local Ethical Committee (Comité de protection des personnes Ouest VI, France) and registered on ClinicalTrials.gov (identifier NCT01748409). Each participant gave written informed consent. This population was part of a previously published report [24].

Clinical-demographic data set

Collected demographic data included sex, age at onset and disease duration, treatments with L-dopa equivalent daily dosage and an approximation of lifetime cumulative dose of L-dopa.

Motor and cognitive function evaluation

All 45 patients were evaluated using the Unified Parkinson's disease Rating Scale part III (UPDRS-III) in ON state. UPDRS-III score was subdivided into an axial score (sum of items 18, 19, 22 and 27–30) that evaluates symptoms such as dysarthria or postural instability. Neuropsychological evaluation was carried out using the MMSE, Montreal cognitive assessment (MoCA) and Mattis dementia rating scale (MDRS).

Autonomic nervous system evaluation

ANS components (pupillomotor, tear, salivary, cardiovascular, digestive, urinary, sexual, sudomotor functions and skin sensitivity) were evaluated in 3 dimensions: symptoms, function and histology.

Dysautonomic symptoms were evaluated with the following questionnaires: SCOPA-Aut (Scales for Outcomes in PD-autonomic symptoms) [25], NMS-Quest (Non-motor symptoms questionnaire) [26] and Rome III constipation criteria [27]. Regarding dry eye, an additional question which followed the proposed options from SCOPA-Aut model (from never to often) was asked.

ANS functional testing was carried out between 9:30 am and 12:30 pm (total visit duration 2.5 h), in a temperature-controlled room set between 20 and 24 °C. It was divided into the assessment of pupillomotor function (pupillometry), tear secretion (Schirmer's test), saliva production (Saxon test), cardiovascular function (heart rate variability and orthostatic hypotension), skin sensitivity [Quantitative thermal sensory testing (QST) and nerve conduction velocity (NCV)] and sudomotor function [sympathetic skin response (SSR)]. Pupillometry was performed after 2 min adaptation in scotopic condition, binocular pupils were measured by infra-red illumination and a high-resolution camera (940 nm) at 30 images per second (Metrovision® Mon2012H, Perenchies, France), an average of at least ten validated recordings was registered for maximal and minimal diameters, constriction's amplitude, latency and velocity, dilation's latency and velocity. All data were compared to laboratory normative data for age-matched healthy controls and the test was considered abnormal when at least one abnormal value was observed. For Schirmer's test, strips were placed over the inferior lid margin of both eyes, eyes closed and tear level was measured at 5 min. Results were the mean value of both eyes (dry eyes under 5 mm, intermediate results between 5 and 10 mm). Saxon test was performed to evaluate the stimulated saliva flow volume by weighing a cotton pad before and after the participant had chewed on it for 2 min (normal value ≥ 2.75 g). For heart-rate variability, the RR interval was recorded with electrocardiogram electrodes placed on presternal region (Dantec™ Keypoint® G4, Natus, Paris, France) during 1 min in four conditions: normal breath (mean, variation max–min/mean, standard deviation), deep breath (mean, variation max–min/mean, standard deviation), 15 s Valsalva's manoeuvre (max/min) and standing up from sitting position (30th/15th battement ratio). The individual results were compared to laboratory normative data for age-matched healthy controls and the test was deemed abnormal when at least one abnormal value was observed. Orthostatic hypotension was defined as a decrease in systolic blood pressure ≥ 20 mm Hg and/or in diastolic blood pressure ≥ 10 mm Hg, and limited or

inappropriate rise in heart rate (< 15 beats per minute), from supine to active upright position at 1, 3 and 5 min. QST (Pathway system, Medoc, Abioz Technologies, France) was performed on hand and foot in predominant side of PD. The baseline temperature was 32 °C and the contact area of the thermode was 9.0 cm^2 with ramped stimuli (1 °C/s) ending when patient pressed a button. The mean threshold temperature of at least six consecutive measurements was calculated for cold and warm detection as well as for cold pain and heat pain. Range between detection and pain was calculated for cold and heat stimulation. Quartiles were compared between patients, lower quartiles in at least one of four conditions (cold and heat on hand, cold and heat on foot) were deemed abnormal. NCV (Dantec™ Keypoint® G4) was studied in two motor nerves (left fibular and right tibial) and in two sensory nerves (left sural and right radial). Individual results were compared to laboratory normative data for age-matched healthy controls, and classified as normal, axonal and/or demyelinating neuropathy. Sudomotor function was estimated by SSR (Dantec™ Keypoint® G4). The test was performed after a 15-min baseline resting period. Surface electrodes were placed on palms and plants, with reference electrodes placed on the dorsum, recorded 10-s signal after a 15-mA stimulation on the contralateral wrist. The widest amplitude response on three measurements was used, results were compared to laboratory normative data for age-matched healthy controls, and a reduction in amplitude or absence was considered as ANS dysfunction.

A single skin biopsy was performed under local anaesthesia with 1% xylocaine, with a 4-mm punch on 7-mm depth, on the lower limb (10 cm above the lateral malleolus) on the side predominantly affected by PD. Immunofluorescence was performed using protein gene product 9.5 immunostaining and intraepidermal nerve fibre (IENF) density was quantified at high magnification (×400) with a light microscope by two blinded operators as previously described [28].

Rapid eye movement sleep behaviour disorder

Sleep clinical assessment comprised RBD history and severity by structured interview. Overnight video-polysomnography was performed and interpreted according to the recommendations of American Academy of Sleep Medicine. RBD was defined according to International Classification of Sleep Disorders–II diagnostic criteria. When REM sleep was considered absent or infrequent in polysomnographic recording (≤ 1%), the diagnosis of probable RBD was considered according to a clinical interview performed by a trained sleep specialist (LLV).

Statistical analysis

Continuous data were expressed as the mean ± standard deviation and categorical data were expressed as numbers and percentage. In order to explore clinical–functional correlations, we selected one or two representative items for each ANS component (pupillomotor, tear, salivary, cardiovascular, digestive, urinary, sexual, sudomotor functions and skin sensitivity) and dimension (symptoms, function) whenever possible. We performed association tests (Fisher tests for binary variables, Mantel-Haenzsel Chi-2 for ordinal variables and ordinal binary variables) between these items to explore autonomic failure associations, belonging either to the same ANS component (intra-component analysis, for example thermal intolerance and QST dysfunction) or to different ANS components (inter-component analysis, for example dry eye symptom and orthostatic hypotension). Clinical features of PD patients with and without skin denervation were compared with Chi-2 or Fisher's tests for categorical variable and Student's test for quantitative variable. Logistic regression models were performed to adjust these comparisons on disease duration. Logistic regression models were used to explore the associations of autonomic symptoms or dysfunctions with skin denervation (odds ratio and their 95% confidence interval were presented). Logistic regressions models were used to explore the associations of autonomic symptoms with severity criteria (odds ratio and their 95% confidence interval were presented). Correlation coefficients between SCOPA-Aut and continuous variables (age, disease duration, UPDRS III total and axial subscore, neuropsychological tests) were calculated with Spearman's test. For all statistical tests $p < 0.05$ was deemed significant. Statistical analysis was carried out using SAS software ® version 9.4.

Results

Population description

Among the 45 PD patients, 30 (66.7%) were men. The mean (± standard deviation) age was 60.4 ± 7.5 years and mean disease duration was 8.7 ± 6.5 years. Twenty-seven (60%) patients were treated with a combination of several antiparkinsonian medications, seven (15.6%) with levodopa only, ten (22.2%) with dopamine agonists only and one was untreated. Mean levodopa equivalent daily dose was 810.5 ± 532.9 mg. Eight (17.8%) patients were also treated by deep brain stimulation. Mean UPDRS-III score was 21.7 ± 11.9 and mean UPDRS-III axial subscore was 7 ± 4.2. Neuropsychological assessment showed altered MMSE score (< 26) in 5 patients (mean 28 ± 2), altered MoCA score (< 26) in 17 patients (mean 25.5 ± 3.7) and

altered MDRS score (< 135) in 9 patients (mean 138.2 ± 5). There were 30 (66.7%) patients with RBD (23 with polysomnographic-confirmed RBD and 7 with probable RBD) and 15 (33.3%) without RBD (one patient showed infrequent REM sleep on polysomnography and negative structured interview for RBD).

Associations between dysautonomic symptoms and functional testing

As expected, intra-component analysis showed associations between symptoms and functional measures of several ANS components, including tear and cardiovascular functions (Supplementary Table 1). By contrast, no significant association was observed between abnormal QST measurements, pain and skin sensitivity complaints. Regarding loco-regional ANS impairment, associations were observed between pupillomotor dysfunction and dry eye complaint, dysphagia and reduced salivary flow and hyperhidrosis and altered QST (Supplementary Table 1). Multiple association tests revealed a heterogeneous pattern of autonomic failure: pupillomotor symptoms were associated with early abdominal fullness and thermal intolerance; orthostatic hypotension with constipation and cardiovascular symptoms with thermal intolerance (Supplementary Table 1). Abnormal heart-rate variability, urinary symptoms, sexual symptoms and pain were not associated with any of ANS symptoms or dysfunctions (Supplementary Table 1).

Associations between dysautonomia and peripheral ANS denervation

As a measure of small fibre neuropathy, 13 (29%) PD patients showed reduced IENF density in skin biopsy. PD patients with skin denervation were more likely to be male, had longer disease duration and higher L-dopa lifetime cumulative dose, showed poorer MDRS score and displayed more frequently non-motor symptoms (Table 2). After adjustment on disease duration, only poorer MDRS score remained significant. Axonal neuropathy was diagnosed on NCV study in 15 (34%) patients, without difference between patients with and without skin denervation (46.2 vs 29%, respectively, $p = 0.31$). There were no demyelinating neuropathies. When autonomic components were compared between patients with and without skin denervation, only dry eye complaint, constipation and QST alterations were more frequent in PD patients with skin denervation (Table 3). Three out of four QST ranges were altered in patients with skin denervation when compared to patients without skin denervation, reflecting functional-histological correspondences (heat on hand, $p = 0.03$, cold on hand, $p < 0.01$, cold on foot, $p = 0.03$). Of note was the absence of relationship between skin denervation, thermal intolerance and pain (Table 3).

Table 2 Main clinical features of PD patients with and without skin denervation

	PD + SD	PD − SD	*p* value	Adjusted *p* value‡
Number, %	13 (29%)	32 (71%)		
Sex, % male	12 (92.3%)	18 (56.3%)	**0.03**	0.05
Age, years	62.2 (7.9)	59.7 (7.4)	0.31	0.45
Disease duration, years	11.9 (5.6)	7.3 (6.5)	**0.03**	/
L-dopa therapy (no, %)	12 (92%)	22 (69%)	0.14	0.39
L-dopa lifetime cumulative dose, kg	1.9 (1.4)	0.8 (1.1)	**< 0.01**	0.19
UPDRS part III 'on'				
Total	22.1 (9.6)	21.6 (12.9)	0.90	0.35
Axial	7.2 (3.4)	6.9 (4.5)	0.84	0.24
Neuropsychological tests				
MMSE < 26	3 (23.1%)	2 (6.3%)	0.13	0.13
MoCA < 26	6 (46.2%)	11 (34.4%)	0.51	0.39
MDRS < 135	6 (46.2%)	3 (9.4%)	**0.01**	**0.03**
Overall non motor symptoms				
SCOPA-Aut	22.9 (8.0)	19.1 (7.7)	0.14	0.33
NMS	15.3 (3.4)	12.1 (4.7)	**0.04**	0.09

PD + SD Parkinson's disease patients with skin denervation, PD – SD Parkinson's disease patients without skin denervation. Data are mean (standard deviation) or number (%)

‡Adjusted p-value on disease duration

Associations and correlations between dysautonomia and PD severity

The presence of axial symptoms in PD patients has been consistently associated with disease severity and poor prognosis [29, 30]. Regarding non-motor features, cognitive impairment and RBD have been identified in a subset of parkinsonian patients in whom a rapid progression rate could be expected [31]. We, therefore, investigated the possible correlation between dysautonomia and these three severity criteria of PD, i.e. cognitive alteration (MoCA < 26), axial motor impairment (UPDRS-III axial subscore ≥ 10) and RBD. Cognitive alteration was associated with cardiovascular symptoms (light headed when standing up) and dysfunction (orthostatic hypotension) as well as with constipation (Table 4). Conversely, axial motor impairment and RBD were not related to any of the autonomic complaint or dysfunction (Table 4). There were no correlations between total SCOPA-Aut and age ($p = 0.12$), disease duration ($p = 0.07$), cognitive alteration (MoCA, $p = 0.58$; MDRS, $p = 0.21$; MMSE, $p = 0.53$) or axial sub-score ($p = 0.17$); however, SCOPA-Aut was correlated with total UPDRS score ($r = 0.32$, $p = 0.03$).

Table 3 Associations between autonomic symptoms and dysfunctions and skin denervation

Component		Item	Odds ratio	*p* value
Pupillo-motor	Symptom: oversensitivity to bright light	SCOPA-Aut Q19	1.99 [0.51–7.79]	0.33
	Dysfunction: altered pupillometry		0.49 [0.09–2.69]	0.41
Tear	Symptom: dry eye	"do you complain from dry eye?"	**8.29 [1.65–41.58]**	**0.01***
	Dysfunction: abnormal Schirmer's test		7.20 [0.83–62.55]	0.07
Salivary	Symptom: sialorrhea	SCOPA-AUT Q2	1.88 [0.47–7.41]	0.37
	Dysfunction: abnormal sialometry	Saxon's test	1.71 [0.47–6.25]	0.42
Cardio-vascular	Symptom: light-headed when standing up	SCOPA-AUT Q14	2.25 [0.57–8.82]	0.24
	Symptom: light-headed when standing for some time	SCOPA-AUT Q15	1.03 [0.28–3.75]	0.96
	Dysfunction: orthostatic hypotension		1.93 [0.44–8.42]	0.38
	Dysfunction: abnormal heart-rate variability		1.67 [0.37–7.44]	0.50
Upper digestion symptom	Difficulty swallowing or choking	NMS Q3	1.43 [0.39–5.26]	0.59
	Early abdominal fullness	SCOPA-AUT Q4	3.33 [0.77–14.42]	0.11
Lower digestion symptom	Faecal incontinence	SCOPA-AUT Q7	5.64 [0.46–68.46]	0.17
	Constipation	Rome III criteria	**5.50 [1.05–28.88]**	**0.04***
Urinary symptom	Urgency	SCOPA-AUT Q8	1.50 [0.41–5.48]	0.54
	Weak stream of urine	SCOPA-AUT Q11	1.60 [0.43–5.96]	0.48
Sexual symptom	Difficulty to have sex	NMS Q19	1.83 [0.48–6.90]	0.37
Skin sensitivity	Symptom: cold intolerance	SCOPA-AUT Q20	0.39 [0.10–1.46]	0.16
	Symptom: heat intolerance	SCOPA-AUT Q21	0.97 [0.27–3.54]	0.96
	Symptom: unexplained pain	NMS Q10	0.77 [0.17–3.45]	0.73
	Dysfunction: altered QST		**12.0 [1.39–> 99.99]**	**0.02***
Sudo-motor	Symptom: hyperhidrosis	NMS Q28	0.74 [0.19–2.94]	0.67
	Dysfunction: abnormal SSR		1.93 [0.28–13.30]	0.50

Q item number of the questionnaire

Discussion

The widespread autonomic dysregulation encountered in parkinsonian patients prompted us to carry out a comprehensive evaluation of autonomic symptoms and signs in a prospective sample of patients affected by PD. We observed several ANS inter-component associations that were heterogeneously distributed, following either a locoregional or a remote distribution pattern. Apart from its expected association with skin sensitivity, skin denervation was only associated with constipation and dry eye. In line with previous studies [32], reduced IENF density cannot be ascribed to L-dopa potential toxicity, as L-dopa cumulative doses were similar after adjustment on disease duration. Cardiovascular symptoms, orthostatic hypotension and constipation were more likely to occur in PD patients with cognitive alteration; however, autonomic complaints and dysfunctions were not associated with the two other criteria of disease severity, namely axial motor impairment and RBD [29, 31].

Most of the existing studies on ANS complaints or dysfunctions in PD have focused on single or dual components of dysautonomia, and especially on cardiovascular dysfunction. Cardiovascular dysfunction in PD, indicating predominantly parasympathetic (heart-rate variability) or sympathetic (orthostatic hypotension) dysfunction [33], has been shown to be associated with disease severity. This includes, for example, the higher risk of developing dementia in patients with orthostatic hypotension [34] and the higher Hoehn and Yahr stage in patients with cardiovagal autonomic dysfunction [35]. Our results, which showed that orthostatic hypotension was strongly associated with cognitive alteration in our PD sample, are, therefore, in line with these previous observations. A few studies have attempted to correlate sudomotor and skin vasomotor dysfunction with disease severity in PD [36] and with dementia [37]. They showed that skin vasomotor function was more severely affected in PD patients with dementia than without and an inverse correlation between the amplitude of sympathetic sweat response and Hoehn and Yahr stage. Contrasting with these results, we did not observe any association between SSR and MoCA.

Numerous pathological studies have shown that every single component of the ANS may be affected by PD pathology (reviewed in [38]). It is suggested that this widespread distribution of Lewy pathology throughout the central and peripheral autonomic networks is responsible for the

Table 4 Associations between autonomic symptoms and dysfunctions and PD severity criteria

Component		Cognitive alteration		Axial motor impairment		RBD	
		Odds ratio	*p* value	Odds ratio	*p* value	Odds ratio	*p* value
Pupillo-motor	Symptom: oversensitivity to bright light	0.73 [0.22–2.46]	0.61	0.28 [0.06–1.32]	0.11	0.57 [0.16–2.08]	0.40
	Dysfunction: altered pupillometry	0.95 [0.23–3.95]	0.95	0.79 [0.14–4.55]	0.80	0.33 [0.08–1.34]	0.12
Tear	Symptom: dry eye	1.42 [0.32–6.22]	0.65	1.18 [0.20–6.98]	0.85	0.55 [0.12–2.45]	0.43
	Dysfunction: abnormal Schirmer's test	0.61 [0.16–2.27]	0.46	4.00 [0.45–35.79]	0.21	0.50 [0.11–2.19]	0.36
Salivary	Symptom: sialorrea	1.64 [0.44–6.08]	0.46	1.30 [0.27–6.22]	0.74	0.73 [0.19–2.79]	0.64
	Dysfunction: abnormal sialometry	0.36 [0.10–1.30]	0.12	0.29 [0.05–1.57]	0.15	0.39 [0.11–1.38]	0.14
Cardio-vascular	Symptom: light-headed when standing up	**4.33 [1.13–16.68]**	**0.03***	1.00 [0.23–4.35]	1.00	1.14 [0.33–3.97]	0.83
	Symptom: light-headed when standing for some time	3.20 [0.89–11.56]	0.08	2.00 [0.43–9.26]	0.38	1.49 [0.43–5.19]	0.53
	Dysfunction: orthostatic hypotension	**5.83 [1.25–27.16]**	**0.02***	2.07 [0.41–10.39]	0.38	1.22 [0.27–5.58]	0.80
	Dysfunction: abnormal heart-rate variability	1.50 [0.38–6.00]	0.57	0.67 [0.13–3.33]	0.62	0.89 [0.22–3.61]	0.87
Upper digestion symptom	Difficulty swallowing or choking	2.37 [0.69–8.20]	0.17	4.00 [0.85–18.84]	0.08	1.53 [0.42–5.58]	0.52
	Early abdominal fullnes	1.07 [0.32–3.64]	0.91	0.28 [0.06–1.32]	0.11	1.97 [0.56–6.94]	0.29
Lower digestion symptom	Faecal incontinence	3.60 [0.30–43.06]	0.31		0.97		0.98
	Constipation	**5.38 [1.26–22.98]**	**0.02***	1.43 [0.31–6.64]	0.65	2.29 [0.64–8.11]	0.20
Urinary symptom	Urgency	1.03 [0.31–3.43]	0.97	2.80 [0.60–13.01]	0.19	0.67 [0.19–2.32]	0.53
	Weak stream of urine	0.67 [0.20–2.24]	0.51	1.12 [0.26–4.86]	0.88	2.25 [0.63–7.97]	0.21
Sexual symptom	Difficulty to have sex	**0.22 [0.06–0.83]**	**0.02***	0.94 [0.20–4.39]	0.94	1.07 [0.30–3.84]	0.92
Skin sensitivity	Symptom: cold intolerance	1.80 [0.50–6.50]	0.37	2.50 [0.45–13.76]	0.29	0.48 [0.12–1.84]	0.28
	Symptom: heat intolerance	1.03 [0.31–3.43]	0.97	5.50 [1.00–30.36]	0.05	1.00 [0.29–3.46]	1.00
	Symptom: unexplained pain	1.25 [0.32–4.82]	0.75	0.74 [0.13–4.20]	0.74	0.38 [0.10–1.47]	0.16
	Dysfunction: altered QST	1.80 [0.50–6.50]	0.37	1.27 [0.27–5.93]	0.76	0.75 [0.20–2.75]	0.66
Sudo-motor	Symptom: hyperhidrosis	0.64 [0.18–2.34]	0.50	0.88 [0.19–4.14]	0.88	0.75 [0.21–2.70]	0.66
	Dysfunction: abnormal SSR	1.19 [0.18–8.00]	0.86	0.97 [0.09–9.91]	0.98	**0.10 [< 0.01–0.98]**	**0.05***

disabling dysautonomic symptoms observed in parkinsonian patients [39]. At first glance, these neuropathological observations appear to be at odds with our findings, which show a patchy and heterogeneous pattern of dysautonomic signs and symptoms in PD. However, it should be kept in mind that the mere presence of Lewy pathology in a subset of neurons does not necessarily imply that these neurons are dysfunctional. For example, the motor symptoms of PD are driven primarily by neuronal loss rather than Lewy pathology in the *substantia nigra* [40]. As such, an evaluation of the density of the autonomic neurons in the different components of the peripheral ANS will be a critical step toward understanding the pathophysiology of dysautonomic symptoms in PD.

We confirm the results of a number of studies, which have shown a reduction of distal IENF in PD patients and a correlation of IENF density with disease duration and disease severity [41, 42]. In addition, we show in the current survey that skin denervation is poorly related to dysautonomic signs and symptoms, as ocular dryness and constipation were the only signs to be significantly associated with IENF density.

There are some limitations of this study. First, we did not perform any functional evaluation of the lower urinary tract and digestive systems, as urodynamic testing and colonic manometry were considered too invasive. Another aspect is the relatively small sample size of PD patients, which hinders us from further stratification of patients into subgroups with different motor severity and/or disease duration. Finally, alpha-synuclein deposition in skin biopsies was not evaluated in our study. The principal reason for not performing this evaluation is that there is still an open debate about the optimised immunohistochemical method that should be used for the detection of alpha-synuclein in skin nerve fibres

[43, 44]. On the other hand, our study has several strengths. All patients in our study had a comprehensive assessment of the ANS, addressing a variety of non-motor outcomes. In addition, all patients also had a precise evaluation of cognitive function with three different validated scales and a confirmation of RBD by polysomnography.

In summary, our results show that autonomic functions are affected in a heterogeneous pattern in PD. They suggest that autonomic dysfunction in PD progresses in an erratic rather than a stepwise fashion, pointing out the complexity of the pathophysiology of disease progression. They also imply that it is not possible in a single patient with PD to predict the progression pattern of dysautonomia.

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Compliance with ethical standards

Conflicts of interest Authors report no disclosure relevant to the research covered in this article.

Ethical standard statement This study was carried out in accordance with the Declaration of Helsinki, conducted with the approval of the local Ethical Committee (Comité de protection des personnes Ouest VI, France).

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