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Longitudinal assessment of autonomic dysfunction in early Parkinson's disease

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ABSTRACT

Introduction: Clinical correlates of autonomic nervous system (ANS) dysfunction in early Parkinson's disease (PD) have been addressed mainly in a cross-sectional way.
Methods: This is a combined cross-sectional and longitudinal prospective study of ANS dysfunction using the SCOPA-AUT in PD patients at the Hoehn and Yahr stage 1 with disease duration < 2 years. PD patients (n = 107) were compared to healthy controls (HC, n = 79), and then followed-up for over 3 years. The severity of PD, depression, anxiety, apathy and cognitive impairment were evaluated using rating scales.
Results: At least one symptom of ANS dysfunction was present in 71% of PD patients in comparison to 30.4% of HC, and in all PD patients after three years. The overall severity of dysautonomia symptoms was mild (SCOPA-AUT mean ± SD; 4.16 ± 5.0), but worsened by 23%, 86% and 0.3% during the 1st, 2nd and 3rd year respectively. Nighttime voiding (38.3%), constipation (30.8%) and straining for defecation (29%) were the most common symptoms. Prevalence and severity of urinary, gastrointestinal, and orthostatic symptoms increased, in contrast to thermoregulatory and pupillomotor symptoms. Frequency of symptoms suggestive of multi-domain ANS dysfunction rose from 49% to 79%. Psychiatric symptoms and age, but not motor impairment, were associated with dysautonomia symptoms.
Conclusion: Symptoms of ANS dysfunction were frequent in the initial motor stage of PD and progressed, yet remaining mild, within 3 years. An independent progression of dysautonomia symptoms from motor disability and its associations with non-motor, mainly psychiatric symptoms and age support the non-motor clustering in PD.

1. Introduction

Autonomic dysfunction, traditionally described as a feature of moderate-to-advanced Parkinson's disease (PD), may be present in the initial stages of PD or even in the premotor phase of the disease [1,2]. Specific abnormalities of the autonomic nervous system (ANS) observed at least 5 years before the onset of parkinsonism in patients with REM sleep behavior disorder [1], and an association of diminished heart rate variability with an increased risk of developing PD [3], suggested that autonomic dysfunction might be an early disease marker. Several cross-sectional studies reported more frequent symptoms of autonomic failure at the time of PD diagnosis in comparison to healthy subjects [2,4,5], in continuation with a recent evidence on the loss of post-ganglionic sympathetic skin nerve fibers and cardiac sympathetic and parasympathetic denervation in early PD [6,7]. Clinically significant dysautonomia occurred with a mean latency of 7 years after the diagnosis in post-mortem confirmed PD cases and was associated with more rapid disease progression [8]. Orthostatic hypotension (OH) had a negative prognostic value in PD, including worse quality of life, higher morbidity and shorter survival [9–11]. Therefore, early diagnosis and treatment of autonomic disorders in patients with PD is of paramount importance.

Since, at least to our knowledge, no prospective study on the natural history of autonomic dysfunction in early PD has been conducted, the aim of our study was to define prevalence, severity, evolution and predictors of dysautonomia symptoms in a cohort of PD patients recruited at the Hoehn and Yahr stage 1, that was prospectively followed for three years.

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2. Patients and methods

2.1. Recruitment of patients

Consecutive PD outpatients were recruited at the Institute of Neurology, School of Medicine (Belgrade), from January 1, 2012 to December 31, 2013, only if they were at the initial motor stage of the PD (Hoehn and Yahr stage 1). Neurologists in Serbia were encouraged to refer their newly diagnosed PD patients to us. The diagnosis of PD was (re)established in our Department according to step 1 of the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [12]. Patients with atypical and secondary parkinsonism, some genetic causes of parkinsonism (parkin, LRRK2, DJ1, PINK1, and VPS-35 mutations were excluded by genetic testing), dementia (according to the Movement Disorder Society Task Force recommendation criteria [13]), history of psychosis requiring neuroleptic treatment, concomitant neurologic disorders, alcohol or drug/substance dependence, history of head injury, metallic implants or pacemaker were excluded. The healthy control (HC) group consisted of age, sex and education group-matched healthy subjects (mainly spouses, friends, or hospital staff) who fulfilled the same exclusion criteria. Both patients and HC underwent 1.5T MRI of the brain to exclude extensive brain vascular damage or other major brain lesions. All patients and HC were free of diabetes mellitus or any other disease associated with autonomic neuropathy, and chronic treatment for hypertension, benign prostatic hyperplasia or erectile dysfunction. None of the subjects received anticholinergic drugs. Uterine prolapse was absent in all female subjects per history.

The study was approved by the Ethics Committee of School of Medicine, University of Belgrade, and all participants gave informed consent. The work has been carried out in accordance with the ethical standards of the Declaration of Helsinki.

2.2. Longitudinal assessment of clinical features and autonomic function

Autonomic function was assessed using the **SC**ales for **O**utcomes in **PA**rkinson's disease - autonomic (SCOPA-AUT) [14] (Serbian version), which consisted of 25 items including 3 orthostatic symptoms, 7 gastrointestinal, 6 urinary, 4 thermoregulatory, one pupillomotor and four sexual items, grouped into six domains. Occurrence of each symptom was scored 0 (never), 1 (sometimes), 2 (regularly) or 3 (often), allowing the severity rating. When a total score per domain was ≥ 1 (defined as at least one symptom occurring at least sometimes), the autonomic domain was considered as impaired. We checked on the cumulative number of reported dysautonomia symptoms (at least one point for each autonomic domain), resulting in the number of affected domains for each participant (i.e. 0–6 domains affected). The severity of PD was assessed using the MDS Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [15] in on state defined by subjective patient's perceptions and clinician's observations. Screening for depression and anxiety was done by the Hamilton Depression Rating Scale (HDRS) [16] and the Hamilton Anxiety Rating Scale (HARS) [17], and apathy was assessed by the Apathy Scale (AS) [18]. Levodopa equivalent dose (LED) was calculated using the standardized formula [19]. Cognitive evaluation was done using the Mini-Mental State Examination (MMSE) [20], and the revised version of Addenbrooke's Cognitive Examination (ACE-R) [21].

Patients with PD and HC were carefully examined at baseline evaluation. PD patients were further prospectively examined with the same battery of tests in the yearly intervals, during a 3-year follow-up. Semistructured interview was used for demographic and clinical features, as well as for current treatment at each visit.

2.3. Statistical analysis

The comparisons of relevant variables between groups were performed either by the ANOVA (numeric data) or χ^2 tests (nominal data). Results of baseline testing were calculated by linear regression method with the variable of interest as a dependent variable and group, and corresponding covariates as independent variables. Logistic regression models were used to identify risk factors for occurrence of different symptoms. Independent predictors of the ordinal-scaled measures were identified using a generalized linear mixed regression models that have been based on the proportional odds assumption and the correlation between the repeated measurements of a subject across the follow-up time points. Data analyses were performed using SPSS 17.0 (SPSS, Chicago, IL), and p-values below 0.05 were considered significant.

Table 1
Baseline demographic and clinical features of patients with Parkinson's disease and healthy controls.

	PD patients	Healthy controls	p
Number of patients	107	79	–
Males: Females	59:48	33:46	0.071
Age (years)*	61.5 ± 9.6	60.9 ± 11.1	0.399
Education (years)	13.1 ± 2.7	13.4 ± 2.5	0.421
Age at onset (years)*	59.3 ± 10.5	–	–
MDS-UPDRS motor score*	16.0 ± 4.6	–	–
MDS-UPDRS total score*	27.6 ± 9.7	–	–
LED*	216.6 ± 200.8	–	–
MMSE*	28.6 ± 1.5	29.8 ± 0.6	< 0.001
ACE-R*	91.0 ± 7.0	97.0 ± 2.4	< 0.001
HDRS*	5.9 ± 5.6	2.1 ± 3.4	< 0.001
HARS*	4.9 ± 4.8	3.1 ± 3.7	0.006
AS*	10.2 ± 7.8	1.4 ± 2.8	< 0.001

* Values presented as means ± SDs; MDS-UPDRS = Movement Disorders Society-Unified Parkinson's Disease Rating Scale; LED = levodopa equivalent dose; MMSE = Mini-Mental State Examination; ACE-R = Addenbrooke's Cognitive Examination-Revised Version; HDRS = Hamilton Depression Rating Scale; HARS = Hamilton Anxiety Rating Scale; AS = Apathy Scale.

3. Results

Study comprised 79 HC and 112 PD patients at baseline examination. Five patients initially diagnosed with PD who have changed their diagnoses after baseline evaluation (1 to multiple system atrophy, 1 to progressive supranuclear palsy and 3 to essential tremor) were excluded. A total of 107 patients with PD were included in the analyses. The PD patients endorsed more depressive symptoms, anxiety, apathy and cognitive dysfunction, when compared to HC (Table 1).

3.1. Baseline evaluation

Patients with PD had higher SCOPA-AUT total score in comparison to HC (4.16 ± 5.0 vs. 0.54 ± 1.04, $p < 0.001$; values presented as means ± SDs), including higher cardiovascular (0.33 ± 0.74 vs. 0.03 ± 0.16, $p < 0.001$), gastrointestinal (1.35 ± 1.90 vs. 0.18 ± 0.42, $p < 0.001$), urinary (1.63 ± 2.27 vs. 0.20 ± 0.52, $p < 0.001$), genital (0.87 ± 1.35 vs. 0.11 ± 0.39, $p < 0.001$) and thermoregulatory dysfunction scores (0.42 ± 0.94 vs. 0.06 ± 0.33, $p = 0.002$), whereas no difference was found for pupillomotor sensitivity score between the groups (0.005 ± 0.35 vs. 0, $p = 0.233$).

Seventy six PD patients (71%) and 24 HC (30.4%) scored at least „one“ on the SCOPA-AUT scale ($\chi^2 = 37.77$, $p < 0.001$). The most frequent symptom of dysautonomia in PD patients was nighttime voiding in 41 patients (38.3%), followed by constipation in 33 (30.8%) and straining for defecation in 31 patients (29%) (Table 2). Increased urinary frequency was present in 28 PD patients (26.2%). Lightheadedness on standing-up (18 patients; 16.8%) and hyperhidrosis during the day (14 patients; 13.1%) were the most frequent symptoms of OH and impaired thermoregulation respectively. Among symptoms of sexual dysfunction, ejaculation (15 patients; 25.4%), but not erection problems (21 patients; 35.6%), were also more frequent in PD when compared to HC (Table 2).

Cumulative number of symptoms attributable to affection of

Table 2
Frequency of dysautonomia symptoms in patients with Parkinson's disease and healthy controls at baseline, and in Parkinson's disease patients during 3-year follow-up.

	Healthy controls	PD-baseline	PD-baseline vs. HC; *p value*	PD-year 1	PD-year 2	PD-year 3	P value (change over time)
Number of patients	79	107	–	98	92	86	–
Cardiovascular dysfunction	2 (2.5%)	23 (21.5%)	0.006	22 (22.4%)	35 (38.0%)	34 (39.5%)	0.002
Light-headed when standing-up	1 (1.3%)	18 (16.8%)	0.002	19 (19.4%)	35 (38.0%)	30 (34.9%)	< 0.001
Light-headed when standing for some time	1 (1.3%)	13 (12.1%)	0.021	11 (11.2%)	17 (18.5%)	13 (15.1%)	0.231
Syncope	0	1 (0.9%)	0.389	2 (2%)	2 (2.2%)	3 (3.5%)	0.284
Gastrointestinal dysfunction	13 (16.5%)	52 (48.6%)	< 0.001	55 (56.1%)	64 (69.6%)	68 (79.1%)	< 0.001
Swallowing/chocking	0	11 (10.3%)	0.003	16 (16.3%)	21 (22.8%)	21 (24.4%)	0.006
Sialorrea	0	16 (14.9%)	0.005	23 (23.5%)	31 (33.7%)	35 (40.7%)	< 0.001
Dysphagia	0	8 (7.4%)	0.046	12 (12.2%)	17 (18.5%)	15 (17.4%)	0.097
Early satiety	0	5 (4.7%)	0.150	2 (2.1%)	12 (13%)	12 (14%)	0.003
Constipation	9 (11.4%)	33 (30.8%)	0.004	29 (29.6%)	45 (48.9%)	47 (54.7%)	< 0.001
Straining for defecation	5 (6.3%)	31 (29%)	0.001	25 (25.5%)	45 (48.9%)	42 (48.8%)	< 0.001
Faecal incontinence	0	1 (0.9%)	0.389	0	5 (5.4%)	5 (5.8%)	0.047
Urinary dysfunction	13 (16.5%)	52 (48.6%)	< 0.001	64 (65.3%)	68 (73.9%)	70 (81.4%)	< 0.001
Urgency	0	15 (14%)	0.002	17 (17.3%)	34 (37%)	44 (51.2%)	< 0.001
Urge incontinence	0	2 (1.9%)	0.222	4 (4.1%)	11 (12%)	13 (15.1%)	0.001
Incomplete emptying	5 (6.3%)	18 (16.8%)	0.062	22 (22.4%)	22 (23.9%)	23 (26.7%)	0.197
Weak stream of urine	2 (2.5%)	16 (15%)	0.015	12 (12.2%)	15 (16.3%)	15 (17.4%)	0.367
Frequency	1 (1.3%)	28 (26.2%)	< 0.001	34 (34.7%)	39 (42.4%)	38 (44.2%)	0.017
Nighttime voiding	8 (10.1%)	41 (38.3%)	< 0.001	51 (52.0%)	62 (67.4%)	64 (74.4%)	< 0.001
Thermoregulatory dysfunction	3 (3.8%)	25 (23.4%)	< 0.001	17 (17.3%)	28 (30.4%)	24 (27.9%)	0.120
Hyperhidrosis during the day	0	14 (13.1%)	0.011	9 (9.2%)	17 (18.5%)	15 (17.4%)	0.105
Hyperhidrosis during the night	0	9 (8.4%)	0.030	7 (7.1%)	16 (17.4%)	9 (10.5%)	0.023
Cold intolerance	3 (3.8%)	6 (5.6%)	0.570	5 (5.1%)	6 (6.5%)	14 (16.3%)	0.020
Heat intolerance	2 (2.5%)	7 (6.5%)	0.404	7 (7.1%)	5 (5.4%)	10 (11.6%)	0.449
Sexual dysfunction*	7 (8.9%)	27 (25.2%)	0.004	27 (25.2%)	40 (44.9%)	41 (47.7%)	0.443
Erection problem	7 (21.9%)	21 (35.6%)	0.415	20 (38.5%)	27 (56.3%)	28 (58.3%)	0.001
Ejaculation problem	0	15 (25.4%)	0.006	15 (28.8%)	25 (52.1%)	24 (50%)	0.002
Vagina lubrication	0	3 (6.3%)	0.376	6 (13.3%)	13 (31.7%)	13 (34.2%)	0.300
Problem with orgasm	0	3 (6.3%)	0.376	5 (11.1%)	13 (31.7%)	13 (34.2%)	0.183
Pupillomotor dysfunction	0	2 (1.9%)	0.222	2 (2%)	5 (5.4%)	4 (4.7%)	0.934
Oversensitiveness to bright light	0	2 (1.9%)	0.222	2 (2%)	5 (5.4%)	4 (4.7%)	0.934
Total autonomic dysfunction	24 (30.4%)	76 (71.4%)	< 0.001	84 (85.7%)	84 (91.3%)	86 (100%)	0.001

Values presented as number of subjects with an item or domain score ≥1 with percentage in parentheses; *Answers to questions regarding sexual dysfunction were available from 59, 52, 48 and 48 male PD patients at baseline, year 1, year 2 and year 3, respectively, and from 48, 45, 41 and 38 female PD patients at year 1, year 2 and year 3, respectively.

multiple autonomic domains significantly differed between PD patients and HC ($\chi^2 = 38.11$, $p < 0.001$). Twenty-seven PD patients (25.2%) reported symptoms reflecting dysfunction of one autonomic domain, 21 (19.6%) of two, 19 (17.8%) of three, and 11 (10.3%) of four ANS domains. One patient (0.9%) had symptoms related to the dysfunction of five ANS domains. There were 28 PD patients (26.2%) and 55 HC (69.6%) with no scorable symptoms on the SCOPA-AUT.

Thirty four PD patients (31.8%) were drug naive at the time of assessment. Among treated patients, 27 (25.2%) were receiving the combination of levodopa and dopamine agonists, 19 patients (17.8%) and 27 patients (25.2%) were on dopamine agonists and levodopa monotherapy respectively. Drug-naive and treated patients did not differ in the total SCOPA-AUT score ($p = 0.468$), but the latter group showed more problems related to the dysfunction of cardiovascular ($p = 0.021$) and pupillomotor systems ($p = 0.041$). Male and female patients did not differ in terms of autonomic symptoms, including sexual dysfunction ($p = 0.139$).

Linear regression analyses revealed that age ($\beta = 0.034$, 95% CI: 0.016–0.052, $p = 0.001$), age at disease onset ($\beta = 0.040$, 95% CI: 0.015–0.064, $p = 0.002$), depression ($\beta = 0.104$, 95% CI: 0.070–0.139, $p < 0.001$) and anxiety ($\beta = 0.073$, 95% CI: 0.031–0.115, $p = 0.001$), but not the MDS-UPDRS motor score, LED, apathy and the total ACE-R score, were significant predictors of higher total scores of autonomic dysfunction.

3.2. Longitudinal evaluation

Only 98 (91.6%), 92 (86%) and 86 (80.3%) out of 107 initially recruited PD patients were available in the 1st, 2nd and 3rd year of follow-up respectively (all of them on dopaminergic therapy). One patient was surgically treated for acute abdomen due to gall bladder perforation and died two days later. A total of 8 patients could not be reached anymore, 7 patients withdrew informed consent and 5 patients changed their place of living. Over three years PD patients demonstrated progression of motor impairment ($p < 0.001$), had higher LED values ($p < 0.001$), depressive symptoms ($p = 0.004$) and apathy ($p < 0.001$). The MDS-UPDRS motor score deteriorated by 43%, 11% and 18% during 1st (16.0 ± 4.6 to 22.9 ± 8.3), 2nd (22.9 ± 8.3 to 25.5 ± 9.9) and 3rd year (25.5 ± 9.9 to 30.2 ± 11.2) of follow-up respectively. No significant cognitive decline was observed either on the ACE-R ($p = 0.159$) or the MMSE ($p = 0.448$). The overall severity of dysautonomia symptoms worsened by 23%, 86% and 0.3% during 1st (4.16 ± 5.0 to 5.11 ± 4.30), 2nd (5.11 ± 4.30 to 9.51 ± 7.30) and 3rd year (9.51 ± 7.30 to 9.54 ± 7.20) from the baseline respectively. In respect to the SCOPA-AUT domains, mean urinary (1.63 ± 2.27 to 3.55 ± 3.22, $p < 0.001$), gastrointestinal (1.35 ± 1.90 to 3.02 ± 2.67, $p < 0.001$), cardiovascular (0.33 ± 0.74 to 0.71 ± 1.07, $p = 0.001$) and sexual dysfunction scores (0.87 ± 1.35 to 2.12 ± 2.38, $p = 0.008$) increased, while thermoregulatory (0.42 ± 0.94 to 0.61 ± 1.20, $p = 0.081$) and pupilomotor scores (0.005 ± 0.35 to 0.02 ± 0.15, $p = 0.528$) remained stable (Fig. 1).

All PD patients (100%) scored at least „one“ on the SCOPA-AUT scale in the 3rd year of the follow-up. Symptoms attributable to the urinary and gastrointestinal dysfunction were present in 70 (81.4%) and 68 (79.1%) patients, respectively, whereas sexual (41 patients; 47.7%), cardiovascular (34 patients; 39.5%), thermoregulatory (24 patients; 27.9%) and pupillomotor symptoms (4 patients; 4.7%) were

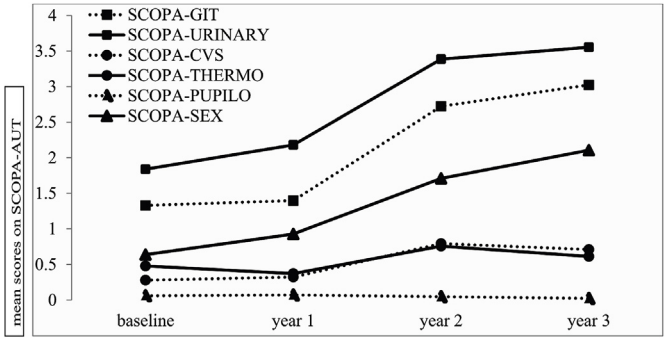

Fig. 1. Progression of autonomic dysfunction in patients with Parkinson's disease over the three-year follow-up period.

less common (Table 2). Frequency of positive answers on all SCOPA-AUT items regarding gastrointestinal dysfunction significantly increased over time, except for dysphagia ($p = 0.097$). Similarly, frequency of nighttime voiding ($p < 0.001$), urgency ($p < 0.001$), frequency ($p = 0.017$) and incontinence ($p = 0.001$) also increased. Among symptoms of cardiovascular autonomic dysfunction, only lightheadedness on standing-up occurred more frequently over time ($p < 0.001$). Higher prevalence of hyperhydrosis during night ($p = 0.023$) and cold intolerance ($p = 0.020$) were also found. Frequency of sexual problems in men increased (i.e. for erection problem $p = 0.001$; for ejaculation problem $p = 0.002$), whereas in female patients remained stable (Table 2).

Cumulative number of symptoms reflecting affection of particular ANS domains increased over time in PD. Symptoms suggestive of multi-domain autonomic dysfunction were present in 68 patients (79.1%): 15 patients (17.4%) had symptoms of two, 25 (29.1%) of three, 22 (25.6%) of four, and 5 (5.8%) of five domains of ANS affected after a three-year follow-up. One patient (1.2%) had symptoms that reflected a widespread dysfunction affecting all six SCOPA-AUT domains.

Psychiatric symptoms including depression [$F(1,80) = 12.170$, $p = 0.001$], anxiety [$F(1,80) = 6.271$, $p = 0.014$) and apathy [$F(1,80) = 5.562$, $p = 0.021$] were significantly associated with the total SCOPA-AUT score over time. Age and age at onset were significant predictors of symptoms of gastrointestinal [$F(1,81) = 5.783$, $p = 0.018$ and $F(1,81) = 7.380$, $p = 0.008$, respectively], urinary [$F(1,81) = 15.800$, $p < 0.001$ and $F(1,81) = 20.365$, $p < 0.001$ respectively] and sexual dysfunction [$F(1,81) = 13.889$, $p = 0.001$ and $F(1,81) = 10.214$, $p = 0.004$ respectively]. Depression and anxiety were related both to the symptoms of urinary [$F(1,81) = 11.847$ $p = 0.001$ and $F(1,81) = 5.095$, $p = 0.027$ respectively] and gastrointestinal dysfunction [$F(1,81) = 7.206$, $p = 0.009$ and $F(1,81) = 6.868$, $p = 0.010$ respectively], while apathy only predicted the latter [$F(1,81) = 4.424$, $p = 0.039$]. Higher doses of dopaminergic medication [$F(1,81) = 5.773$, $p = 0.019$], apathy [$F(1,81) = 10.471$, $p = 0.002$] and the total ACE-R score [$F(1,81) = 19.178$, $p < 0.001$] appeared to be significant predictors of cardiovascular dysautonomia symptoms three years from the disease onset.

4. Discussion

Since the progression of dysautonomia symptoms in early stages of PD has not been thoroughly examined, the main finding of our study was that at least one symptom of ANS dysfunction was present in 71% of patients at the initial motor stage of PD (Hoehn and Yahr 1), and in all of them (100%) three years later. Although initially mild, ANS symptoms worsened by 23%, 86% and 0.3% during 1st, 2nd and 3rd year respectively. Both the prevalence and severity of symptoms related to the urinary, gastrointestinal and cardiovascular dysfunction increased after three years. The frequency of symptoms that reflect multi-domain dysfunction rose from 49% to 79%, suggesting possible progression to a widespread ANS affection already in early PD.

It has been shown that overall severity of symptoms and indices of autonomic dysfunction increased with progression of motor stages according to the Hoehn and Yahr staging [22]. Also, the longer disease duration, the more severe motor impairment and the older age of patients, the more prevalent was multi-domain versus single-domain autonomic affection [11]. Merola et al. reported 20% increase in the severity of dysautonomia over 12 months in consecutive PD patients in different motor stages and with disease duration ranging from one to 26 years [11], significantly influencing activities of daily living and the quality of life.

In line with previous evidence [2,5,23], nighttime voiding, constipation and straining for defecation affected up to 50% of our patients. Nighttime voiding remained the most common symptom over follow-up period, with the highest prevalence in the final year of follow up (74.4%). Frequency of other storage symptoms (i.e. urgency and frequency) also increased significantly (Table 2). Urge incontinence, usually associated with advanced PD, was rare in our patients at baseline (1.9%), but progressed to 15% after three years. Results of Picillo et al. [23] suggesting a stable urinary dysfunction (with an exception of mild worsening of nighttime voiding and urgency), over a 2-year observation period in a large PD cohort, contradicted our data, although their patients had a longer disease duration. Therefore, we suggested that progression of urinary symptoms probably occurred earlier in the course of the disease. Supportive of this observation was the small progression of the mean SCOPA-AUT score from the 2nd to the 3rd year of follow-up in our PD patients. Nevertheless, both studies questioned the utility of the urine storage symptoms in a differential diagnosis of parkinsonian patients in early phases of the disease. Most of the symptoms of the upper and lower gastrointestinal tract dysfunction became more frequent during the follow-up (i.e. constipation, impaired swallowing, sialorrea and early satiety). Fecal incontinence was rare at baseline and, similar to dysphagia, did not progress.

Orthostatic symptoms, found in 21% of our patients at baseline evaluation, mainly presented as a lightheadedness on standing-up and worsened over the follow-up, affecting 39% of our patients, while the syncope was rare. Khoo et al. [2] reported orthostatic symptoms in 33% of their early PD patients whose disease duration was longer than in our patients. Even among drug-naive PD patients, 18% reported clinically relevant symptoms of OH [5], whereas additional 37% had asymptomatic OH verified by head-up tilt test [24]. An association between cognitive impairment and hypotension has been previously recognized [8,10,24] and confirmed in our cohort. However, the suggested role of the white matter hyperintensities in this association [24] could not be evaluated in our study since MRI-confirmed vascular damage was an exclusion criterion.

Several other findings deserve to be mentioned: (a) different progression of symptoms of ANS subdomains affection during the follow-up (symptoms attributable to the urinary, gastrointestinal, cardiovascular and sexual dysfunction progressed, while thermoregulatory and pupillomotor symptoms remained stable); (b) different rates of progression of motor and autonomic symptoms over time; and (c) non-motor symptoms, particularly psychiatric disturbances such as depression, anxiety and apathy, as well as age and age at PD onset, predicted global, but also specific urinary, gastrointestinal and genital autonomic symptoms, reflecting certain grouping of NMS [25]. In continuation with previous findings [26], sexual dysfunction was a single domain related to the motor impairment at baseline. Our data suggested that deterioration of the ANS dysfunction might occur independently of motor deterioration, with a predominant motor progression in the 1st year, and prevailing deterioration in autonomic dysfunction in the 2 nd year of the follow-up. Association between diminished heart rate variability and motor impairment in both untreated and treated early PD patients explained less than 10% of the MDS-UPDRS variance in the latter group [27]. We hypothesized that at least some of the mechanisms such as variability in alpha-synuclein distribution, comorbid

pathology, and variable rates of neurodegeneration of nigral neurons and central and peripheral postganglionic autonomic neurons, might account for the diverse progression of autonomic and motor features, underpinning the concept of non-motor subtyping within the early PD [28,29]. For example, associations between depression, OH and attenuated cardiovagal response during ambulatory BP monitoring [30] or nighttime urination and anxiety [31] supported further investigation of the NMS clustering in a recently described subtype of PD with predominant autonomic dysfunction [29]. Dopaminergic therapy in our study might alleviate motor disability, while aggravating an impairment in cardiovascular autonomic control.

Among the limitations of our study was a fact that the assessment of autonomic dysfunction was restricted to a questionnaire with dependence on the symptom recall, that might lead to an underestimation of symptom frequency. Dizziness and lightheadedness have low specificity and may be attributable to imbalance and gait problems in patients who do not have OH. Thus, the frequency of symptoms suggestive of cardiovascular autonomic dysfunction might be overestimated. Other limitations include potential selection bias of tertiary center and a relatively small number of drug-naive patients at baseline. Also, a minimal clinically relevant deterioration in the SCOPA-AUT score and cut-off scores for mild, moderate and severe dysautonomia have not been determined yet. However, our intention was to investigate a burden of autonomic symptoms in early PD patients using the SCOPA-AUT that is reliable, sensitive and easy to implement scale recommended for the assessment of dysautonomia symptoms in patients with PD [32,33]. We believed that our data were important since this was the first study to prospectively evaluate both a prevalence and severity of symptoms reflecting ANS dysfunction in PD from the Hoehn and Yahr stage 1.

In conclusion, symptoms of dysautonomia, were mild but frequent in the initial motor stage of PD and tended to progress both in terms of prevalence and severity, particularly within the first two years of the disease course. Non-motor, mainly psychiatric symptoms were associated with different symptoms of autonomic dysfunction, supporting the non-motor clustering in PD. The impact of dopaminergic medications was limited, with the exception of aggravated symptoms of cardiovascular derangement, suggesting that autonomic dysfunction was an integral part of the initial motor phase of PD.

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Disclosures

Dr. Stanković reports no disclosures.

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Author contributions

1. Research project. Conception: VSK, IS. Organization: IS, VSK. Execution: IS, IP, VM, TS, NDM, MS, VSK.
2. Statistical Analysis. Design: TP, IS, IP, VM, TS, VSK. Execution: TP, IS, VM. Review and Critique: TP, IS, VM, TS, IP, VSK.
3. Manuscript Preparation. Writing of the first draft: IS, IP, VSK. Review and Critique: IP, TP, VM, TS, NDM, MS, VSK.

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References

[1] R.B. Postuma, J.F. Gagnon, A. Pelletier, J. Montplaisir, Prodromal autonomic symptoms and signs in Parkinson's disease and dementia with Lewy bodies, Mov. Disord. 28 (2013) 597–604.
[2] T.K. Khoo, A.J. Yarnall, G.W. Duncan, S. Coleman, J.T. ÒBrien, D.J. Brooks, R.A. Barker, D.J. Burn, The spectrum of nonmotor symptoms in early Parkinson disease, Neurology 80 (2013) 276–281.
[3] A. Alonso, X. Huang, T.H. Mosley, G. Heiss, H. Chen, Heart rate variability and the risk of Parkinson's disease: the atherosclerosis risk in communities (ARIC) study, Ann. Neurol. 77 (2015) 877–883.
[4] D. Verbaan, J. Marinus, M. Visser, S. van Rooden, A. Stiggelbout, J. van Hilten, Patient-reported autonomic symptoms in Parkinson disease, Neurlogy 69 (2007) 333–341.
[5] B. Muller, J. Larsen, T. Wentzel-Larsen, G. Skeie, O. Tysnesfor T.P.S. Group, Autonomic and sensory symptoms and signs in incident, untreated Parkinson's disease: frequent but mild, Mov. Disord. 26 (2011) 65–72.
[6] M. Nolano, V. Provitera, F. Manganelli, R. Iodice, A. Stancanelli, G. Caporaso, A. Saltalamacchia, F. Califano, B. Lanzillo, M. Picillo, P. Barone, L. Santoro, Loss of cutaneous large and small fibers in naive and L-dopa – treated PD patients, Neurology 89 (2017) 776–784.
[7] S. Orimo, A. Takahashi, T. Uchihara, F. Mori, A. Kakita, K. Wakabayashi, H. Takahashi, Degeneration of cardiac sympathetic nerve begins in the early disease process of Parkinson's disease, Brain Pathol. 17 (2007) 24–30.
[8] E. De Pablo-Fernandez, C. Tur, T. Revesz, A.J. Lees, J.L. Holton, T. Warner, Association of autonomic dysfunction with disease progression and survival in Parkinson disease, JAMA 74 (2017) 970–976.
[9] D. Goldstein, C. Holmes, Y. Sharabi, T. Wu, Survival in synucleinopathies: a prospective cohort study, Neurology 85 (2015) 1554–1561.
[10] A. Fanciulli, S. Strano, C. Colosimo, C. Caltagirone, G. Spalletta, F.E. Pontieri, The potential prognostic role of cardiovascular autonomic failure in alpha-synucleinopathies, Eur. J. Neurol. 20 (2012) 231–235.
[11] A. Merola, A. Romagnolo, M. Rosso, R. Suri, Z. Berndt, S. Maule, L. Lopianno, A. Espay, Autonomic dysfunction in Parkinson's disease: a prospective cohort study, Mov. Disord. 33 (2018) 391–397.
[12] A. Hughes, S. Daniel, L. Kilford, A. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. 55 (1992) 181–184.
[13] B. Dubois, D. Burn, C. Goetz, D. Aarsland, R.G. Brown, G.A. Broe, D. Dickson, C. Duyckaerts, J. Cummings, S. Gauthier, A. Korczyn, A. Lees, R. Levy, I. Litvan, Y. Mizuno, I.G. Mckeith, C.W. Olanow, W. Poewe, C. Sampaio, E. Tolosa, M. Emre, Diagnostic procedures for Parkinson's disease dementia: recommendations from the movement disorder society Task Force, Mov. Disord. 22 (2007) 2314–2324.
[14] M. Visser, J. Marinus, A.M. Stiggelbout, J.J. van Hilten, Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT, Mov. Disord. 19 (2004) 1306–1312.
[15] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. Lapellefor the M.D.S.U.R.T. Force, Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 23 (2008) 2129–2170.
[16] M. Hamilton, A rating scale for depression, J. Neurol. Neurosurg. Psychiatry 23 (1960) 56–62.
[17] M. Hamilton, The assessment of anxiety states by rating, Br. J. Med. Psychol. 32 (1959) 50–55.
[18] S. Starkstein, H. Mayberg, T. Preziosi, P. Andrezejewski, R. Leiguarda, R. Robinson, Reliability, validity, and clinical correlates of apathy in Parkinson's disease, J. Neuropsychiatry Clin. Neurosci. 4 (1992) 134–139.
[19] C.L. Tomlinson, R. Stowe, S. Patel, C. Rick, R. Gray, C.E. Clarke, Systematic review of levodopa dose equivalency reporting in Parkinson's disease, Mov. Disord. 25 (2010) 2649–2685.
[20] M. Folstein, S. Folstein, P. McHugh, 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician, J. Psychiatr. Res. 12 (1975) 189–198.
[21] E. Mioshi, K. Dawson, J. Mitchell, R. Arnold, J. Hodges, The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening, Int. J. Geriatr. Psychiatry 21 (2006) 1078–1085.
[22] J. Bin Kim, B.J. Kim, S.B. Koh, K.W. Park, Autonomic dysfunction according to disease progression in Parkinson's disease, Park. Relat. Disord. 20 (2014) 303–307.

[23] M. Picillo, R. Palladino, P. Barone, R. Erro, C. Colosimo, R. Marconi, L. Morgante, A. Antonini, On behalf of the P.S. Group, the PRIAMO study: urinary dysfunction as a marker of disease progression in early Parkinson's disease, Eur. J. Neurol. 24 (2017) 788–795.
[24] J.S. Kim, Y.S. Oh, K.S. Lee, Y.I. Kim, D.W. Yang, D.S. Goldstein, Association of cognitive dysfunction with neurocirculatory abnormalities in early Parkinson disease, Neurology 79 (2012) 1323–1331.
[25] K. Zhu, J.J. van Hilten, J. Marinus, Associated and predictive factors of depressive symptoms in patients with Parkinson's disease, J. Neurol. 263 (2016) 1215–1225.
[26] X. Deng, B. Xiao, H. Li, Y. Lo, L. Chew, K. Prakash, E. Tan, Sexual dysfunction is associated with postural instability gait difficulty subtype of Parkinson's disease, J. Neurol. 262 (2015) 2433–2439.
[27] W. Maetzler, M. Karam, M. Fruhmann Berger, T. Heger, C. Maetzler, H. Ruediger, J. Bronzova, P. Pita Lobo, J.J. Ferreira, T. Ziemssen, D. Berg, Time- and frequency-domain parameters of heart rate variability and sympathetic skin response in Parkinson's disease, J. Neural Transm. 122 (2014) 419–425.
[28] R. Erro, M. Picillo, C. Vitale, R. Palladino, M. Amboni, M. Moccia, M.T. Pellecchia, P. Barone, Clinical clusters and dopaminergic dysfunction in de-novo Parkinson disease, Park. Relat. Disord. 28 (2016) 137–140.
[29] A. Sauerbier, P. Jenner, A. Todorova, K.R. Chaudhuri, Non motor subtypes and Parkinson's disease, Park Relat Disord. Suppl 1 (2016) S41–S46.
[30] H.E. Park, J.S. Kim, Y.S. Oh, I.S. Park, J.W. Park, I.U. Song, K.S. Lee, Autonomic nervous system dysfunction in patients with Parkinson disease having depression, J. Geriatr. Psychiatry Neurol. 29 (2016) 11–17.
[31] A.Q. Rana, D.A. Paul, A.M. Qureshi, A. Ghazi, S. Alenezi, M.A. Rana, M. Moazen, S. Akhter, A. Owlia, M.R. Akhter, S. Randhawa, Z.M. Moosavi, A.N. Rana, Association between nocturia and anxiety in Parkinson's disease, Neurol. Res. 37 (2015) 563–567.
[32] M.L. Evatt, K.R. Chaudhuri, K.L. Chou, E. Cubo, V. Hinson, K. Kompoliti, C. Yang, W. Poewe, O. Rascol, C. Sampaio, G.T. Stebbins, C.G. Goetz CG, Dysautonomia rating scales in Parkinson's disease: sialorrhea, dysphagia, and constipation - critique and recommendations by Movement Disorders Task Force on rating scales for Parkinson's disease, Mov. Disord. 24 (2009) 635–646.
[33] A. Pavy-Le Traon, G. Amarenco, S. Duerr, H. Kaufmann, H. Lahrmann, S.R. Shaftman, F. Tison, G.K. Wenning, C.G. Goetz, W. Poewe, C. Sampaio, A. Schrag, G.T. Stebbins, O. Rascol, The Movement Disorders Task Force review of dysautonomia rating scales in Parkinson's disease with regard to symptoms of orthostatic hypotension, Mov. Disord. 26 (2011) 1985–1992.