Non-motor symptoms in Parkinson's disease

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Patient-reported autonomic symptoms in Parkinson disease

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Abstract

Objective: There is a wide range of autonomic symptoms (AS) in Parkinson disease (PD), but the full spectrum has never been evaluated with a validated instrument and in comparison with control subjects. In this study a reliable and valid instrument, the SCOPA-AUT, was used to evaluate the occurrence of AS in a large cohort of patients with PD and control subjects and to assess the relations with demographic, disease-related and clinical variables.

Methods: A cohort of 420 patients with PD was evaluated for the occurrence of AS, motor and nonmotor symptoms, as well as for demographic and disease-related characteristics. Results were compared with those of 150 control subjects. Associations between AS and demographic and clinical characteristics were also studied.

Results: For all autonomic domains, patients with PD reported more symptoms compared to control subjects, with the greatest differences in the gastrointestinal and urinary domain. Higher age, greater disease severity, and higher doses of dopaminergic medication were related to more autonomic problems. Autonomic symptom severity was associated with more motor dysfunction, depressive symptoms, cognitive dysfunction, psychiatric complications, nighttime sleep disturbances, and excessive daytime sleepiness (all p-values <0.01).

Conclusions: Autonomic symptoms (AS) are an important feature of Parkinson disease (PD) and increase with age, disease severity, and medication use. The prominent presence of AS warrants increased clinical awareness and highlights the need for efficacious therapies for the wide spectrum of problems related to this domain of PD.

Introduction

Autonomic symptoms (AS) occur in virtually all patients with Parkinson disease (PD) at some stage of their disease and contribute to the disease burden.[1,2] The autonomic domain is broad including symptoms and signs that relate to cardiovascular, gastrointestinal, urinary, thermoregulatory, pupillomotor, and sexual functioning.[3,4] The profile of AS is consistent with the results of neuropathological studies in PD, which have disclosed cell loss and Lewy bodies in autonomic regulatory regions, including the hypothalamus, sympathetic and parasympathetic system, the adrenal medulla, and in the neural plexi innervating the gut, heart, and pelvis.[4-6]

In spite of the recent increase in interest in autonomic impairment in PD, many aspects of this nonmotor domain are still unclear. The reported prevalence of autonomic impairment varies greatly between studies (14% to 80%)[5] and associations with age and disease-related variables (disease severity and medication use) are not consistent.[5,7-19] The discrepancies between studies are most likely explained by the use of different assessment methods (clinical tests or questionnaires) and the use of small patient groups, which are susceptible to selection or referral bias.

The therapeutic options for some of the AS are expanding and there is also growing interest to evaluate how potentially neuroprotective therapies differentially affect the motor and nonmotor symptoms.[2] Together these developments underscore the need for valid and reliable measures of the core AS in PD. Because no such instrument existed, a questionnaire that focuses on the AS in PD (SCOPA-AUT) was recently developed.[3]

The objective of this study was to evaluate the occurrence of AS in patients with PD, to compare this with the occurrence of AS in control subjects, and to assess the relations with demographic, disease-related, and clinical variables in a large cohort of patients with PD.

Methods

Study design

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of patients with PD, who are profiled on phenotype,

genotype, disability, and global outcomes of health using valid and reliable assessment instruments for PD. Findings obtained from the first annual evaluation of 421 patients who were assessed between May 2003 and March 2006 were used for analysis.

Study participants

All patients fulfilled the United Kingdom PD Society Brain Bank criteria for idiopathic PD.[20] Recruitment of patients was based on age at onset and disease duration, which are important determinants of disease course in PD and are related to various manifestations of the disease.[21,22] To obtain an adequate distribution of these characteristics across the cohort, we aimed to construct four strata, based on age at onset (onset of the first symptoms as perceived by the patient) (≤ / > 50 years) and disease duration (≤ / > 10 years). Recruitment stopped if approximately 100 patients per stratum were included. Because this number of patients could not be achieved in the principal center (Leiden University Medical Center (LUMC)), nearby university and regional hospitals were requested to participate in the recruitment of patients. No other selection criteria were applied. The majority of the patients were assessed at the LUMC. To avoid bias towards recruiting less severely affected patients, patients who were unable to come to the hospital were assessed at home. Control subjects were selected to match the overall age and sex distribution of the patients, and had no documented diseases of the CNS. One hundred control subjects were acquaintances (n=80) or relatives (n=20) of participating patients with sporadic PD. Fifty other control subjects were recruited from volunteers working in our hospital. The study was approved by the medical ethical committee of the LUMC and all participants gave informed consent.

Assessments

Within PROPARK, all patients received a standardized assessment, including evaluation of demographic and clinical characteristics, family history of PD, and medication. Measurement instruments for the different clinical domains of PD were derived from a prior project (SCales for Outcomes in PArkinson's disease; SCOPA).[23] For the current study, data obtained for autonomic function (SCOPA-AUT),[3] disease

severity (Hoehn & Yahr (H&Y)),[24] motor function (SPES/SCOPA-motor),[25] depressive symptoms (Beck Depression Inventory (BDI)),[26] cognition (SCOPA-COG),[27] psychiatric complications (modified-Parkinson Psychosis Rating Scale (modified-PPRS)),[28] and nighttime sleep and excessive daytime sleepiness (EDS) (SCOPA-SLEEP)[29] were used. For reasons of comparability, all patients who used antiparkinsonian medication were assessed while they benefited from their medication. Data of control subjects included data regarding autonomic function, demographic characteristics and medication use. All instruments were either self-administered (SCOPA-AUT, BDI, and SCOPA-SLEEP) or administered by trained research associates (H&Y, SPES/SCOPA-motor, SCOPA-COG, and modified-PPRS). The SCOPA-AUT is a questionnaire consisting of 23 items in six domains: gastrointestinal functioning (7 items), urinary functioning (6 items), cardiovascular functioning (3 items), thermoregulatory functioning (4 items), pupillomotor functioning (1 item), and sexual functioning (2 items for men and 2 items for women). The maximum score is 69, with a score range per item from 0 (never experiencing the symptom) to 3 (often experiencing the symptom). For reasons of comparability, scores of all instruments were converted into relative scores with a score range of 0 to 100. Except for the SCOPA-COG, higher scores indicate more severe impairment. To explore the influence of disease severity, patients were classified in groups based on H&Y stages in mild PD (H&Y stage 1 or 2), moderate PD (H&Y stage 3), or severe PD (H&Y stage 4 or 5). To evaluate the role of dopamine replacement therapy (DRT), patients were grouped according to their DRT use, resulting in four patient groups (patients who used both levodopa and dopamine agonists (combination therapy), patients with dopamine agonist monotherapy, patients with levodopa monotherapy, and patients without DRT).

Statistical analysis

If 25% or more of the data from a questionnaire or scale was missing, data from this scale for this patient were excluded from statistical analyses. The sexual items of the SCOPA-AUT include a response option "non-applicable"; if patients chose this option on one or both of the items, these items were excluded from statistical analyses.

SCOPA-AUT scores (total, domain, and item scores) of patients and control subjects were compared with student's T-tests for independent samples and SCOPA-AUT scores of the various patient groups were compared with analysis of covariance. Pearson's correlation coefficient or Spearman's rho was used to assess relations between SCOPA-AUT score and demographic, disease-related, and clinical characteristics.
To evaluate the relation between the autonomic domain and the motor and nonmotor domains of PD, patients were classified in subgroups, based on the quartiles of the SCOPA-AUT scores, resulting in the following subgroups: first quartile, minimal problems; second quartile, mild problems; third quartile, moderate problems; fourth quartile, severe problems.
Ordinal regression analysis was used to examine the relation between the quartile scores of the SCOPA-AUT and the scores of the other PD domains, including motor function, depressive symptoms, cognition, psychiatric complications, nighttime sleep, and EDS. A p-value < 0.05 was considered significant. All analyses were performed with Statistical Package for the Social Sciences 12.0.1 Software (SPSS 12.0.1).

Results

Characteristics of the participants

Of the 421 patients with PD, one was excluded from the study because of too many missing values on the SCOPA-AUT. Thus, in total, 420 patients (64% men) and 150 control subjects (55% men) participated in the study (p=0.06). Patients were recruited from both university hospitals (n=251) and regional hospitals (n=169). The mean (SD) age was 61.1 (11.5) years in patients and 60.9 (9.9) years in control subjects (p=0.87). Patients had a mean (SD) disease duration of 10.5 (6.5) years and a mean (SD) age at onset of 50.6 (12.0) years. A total of 217 patients had mild PD, 110 patients had moderate PD, and 82 patients had severe PD (data were missing for 11 patients). A total of 287 (68%) patients used levodopa with a mean (SD) daily dose of 657.7 (370.3) mg, whereas 290 (70%) patients used dopamine agonists. Patients used combination therapy (n=204), dopamine agonist monotherapy (n=90), and levodopa monotherapy (n=84). Forty-two patients did not use any DRT.

Of these 42 patients, 11 used amantadine, 4 used trihexyphenidyl, 3 used propanolol, 1 used selegiline, and 23 did not use antiparkinsonian medication. Of all patients, 62 (15%) used anticholinergics, 44 as anti-parkinsonian medication and 18 for urinary problems. Furthermore, 85 patients (20%) used antihypertensive drugs, and 43 (10%) used heart medication.

The percentage of patients with too many missing values on other scales ranged from 0% (SCOPA-SLEEP) to 3% (modified-PPRS). Many participants answered "non-applicable" to one or both of the sexual items of the SCOPA-AUT (patients: 18% of the men and 42% of the women; control subjects: 12% of the men and 40% of the women). Patients who used the "non-applicable" option in one or both of the sexual items were older and had an older age at onset compared to the other patients (all p-values <0.01). Men with PD who responded with "non-applicable" also had a longer disease duration compared to the other men with PD (p=0.04), whereas women with PD who chose this option had more severe PD compared to the other women with PD (p=0.03).

Comparisons between patients and control subjects

Domain scores

In control subjects, no significant differences existed between relatives and non-relatives on the total SCOPA-AUT score and all domain scores. Patients had more AS compared to control subjects as measured by the total SCOPA-AUT score and domain scores (all p<0.01) (figure 1). Differences between patients and control subjects were most noteworthy for gastrointestinal symptoms (mean score patients vs control subjects: 23.6 vs 5.6 (difference in means; 18.0, 95% CI 16.1 to 19.8)) and urinary symptoms (37.4 vs 20.8 (difference in means; 16.6, 95% CI 13.5 to 19.6)).

The smallest differences between patients and control subjects were found for symptoms of the thermoregulatory (24.3 vs 13.5 (difference in means; 10.8, 95% CI 7.8 to 13.8)) and cardiovascular domain (12.9 vs 2.9 (difference in means; 10.0, 95% CI 8.4 to 11.7)). In both patients and control subjects, urinary symptoms were most frequent and cardiovascular symptoms were least frequent.

Item scores

Patients reported more problems on all items, except for vaginal lubrication (women) and problems with having an orgasm (women) (table 1). To obtain insight into the most relevant AS in PD, the percentages of patients and control subjects with scores ≥2 were compared. The largest differences in percentages were found for the items straining for defecation (36% vs 4%), frequency of urinating (43% vs 20%), urgency of urinating (25% vs 3%), sialorrhea (22% vs 0%), constipation (22% vs 1%), and cold intolerance (22% vs 2%) (all $p<0.01$).

In total, 21% (n=89) and 14% (n=59) of the patients used laxatives and medication for urinary symptoms, compared to 4% (n=6) and 3% (n=4) of the control subjects ($p<0.01$). Of the patients and control subjects who used laxatives, 51% (n=45) and 83% (n=5) never or sometimes experienced constipation. Similarly, 44% (n=26) of the patients and 50% (n=2) of the control subjects who used medication for urinary symptoms never or sometimes experienced urgency.

Correlations between age and total SCOPA-AUT score were 0.24 in patients ($p<0.01$) and 0.22 in control subjects ($p=0.01$). Total SCOPA-AUT scores did not differ between men and women in patients ($p=0.06$) and control subjects ($p=0.10$).

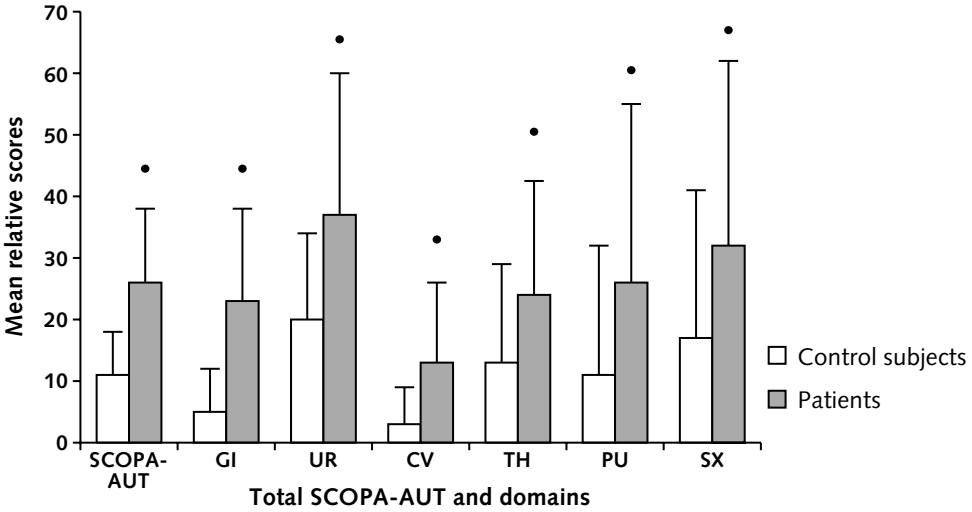
Influence of disease severity

Analysis of covariance, with age and medication use included as covariates, was used to compare patient groups with mild, moderate, or severe PD, with respect to AS. For both the total SCOPA-AUT score and all domain scores, except for the pupillomotor and sexual domains, scores increased with increasing disease severity. No significant differences were found between mildly and moderately affected patients for any domain. Compared to patients with mild and moderate PD, patients with severe PD experienced significantly more gastrointestinal, cardiovascular, thermoregulatory, and pupillomotor problems. Compared to patients with mild PD, patients with severe PD also experienced significantly more urinary problems.

For the sexual domain scores, no significant differences were found between the

different severity groups (table 1). The correlation coefficient between the total SCOPA-AUT score and the H&Y score was moderate (0.35, $p<0.01$).

Figure 1. Total SCOPA-AUT and domain scores in patients and control subjects



Mean group scores and standard deviations for patients and control subjects expressed in relative scores (range 0 to 100) on the total SCOPA-AUT and its domains. A higher score indicates more problems. Differences between groups are analyzed with student's T-test for independent samples.

•: difference ($p<0.05$) between groups

GI: gastrointestinal functioning; UR: urinary functioning; CV: cardiovascular functioning; TH: thermoregulatory functioning; PU: pupillomotor functioning; SX: sexual functioning

Dopamine replacement therapy

Analysis of covariance, with age and disease severity as covariates, was used to compare patient groups based on type of DRT, with respect to AS. Patients without DRT experienced significantly less gastrointestinal problems compared to patients with levodopa monotherapy and combination therapy and they also experienced less urinary problems compared to patients with combination therapy. Patients with

dopamine agonist monotherapy experienced significantly less thermoregulatory problems compared to patients with combination therapy. No significant differences between patient groups were found for the cardiovascular, pupillomotor, and sexual domain (table 2). The correlation coefficient between the total SCOPA-AUT score and the levodopa dose was moderate (0.34, $p<0.01$).

In order to evaluate the severity of AS in de novo patients, patients without antiparkinsonian medication (n=23) were compared to control subjects, with analysis of covariance with age and sex included as covariates. Patients without antiparkinsonian medication had a mean (SD) age of 53.0 (8.2) years with a mean (SD) disease duration of 4.8 (2.7) years. They experienced more gastrointestinal ($p<0.01$) and cardiovascular ($p=0.02$) problems. No significant differences were found for the urinary, thermoregulatory, pupillomotor, and sexual domains.

Table 1. Frequency of autonomic symptoms in control subjects and (groups of) patients (% with an item score ≥1)

		Patients			
Item	**Control subjects (n=150)**	**Total (n=420)**	**H&Y 1&2 (n=217)**	**H&Y 3 (n=110)**	**H&Y 4&5 (n=82)**
Gastrointestinal domain					
Swallowing/choking	19	55*	49†	54†	72
Sialorrhea	7	73*	66†	74	88
Dysphagia	9	38*	34†	34†	56
Early abdominal fullness	24	51*	44†	56	63
Constipation	11	50*	43†	46†	71
Straining for defecation	35	72*	65†	77	87
Fecal incontinence	3	11*	9	7	17

Urinary domain					
Urinary urgency	21	67*	59†	73	78
Urinary incontinence	22	51*	43†	52†	70
Incomplete emptying	25	52*	48	57	55
Weak stream of urine	33	61*	56	65	67
Frequency	75	90*	89	91	92
Nocturia	89	87*	82	92	95
Cardiovascular domain					
Lightheaded when standing up	16	56*	56	51†	67
Lightheaded when standing for some time	9	35*	28†	36†	57
Syncope	1	4*	2	3	7
Thermoregulatory domain					
Hyperhidrosis during the day	29	46*	42†	48	54
Hyperhidrosis during the night	36	55*	50†	56	62
Cold intolerance	27	52*	50	53	60
Heat intolerance	41	46*	39†	49	63
Pupillomotor domain					
Oversensitive to bright light	27	54*	50†	49†	71
Sexual domain					
Men: erection problem	27	55*	53	56	71
Men: ejaculation problem	24	42*	39	40	57
Women: vaginal lubrication	34	26	25‡	34	20
Women: problem with orgasm	31	31	38	30	25

*: difference vs control group ($p<0.05$; student's T-test for independent samples)

†: difference vs severe group ($p<0.05$; analysis of covariance with age and medication use as covariates)

‡: difference vs moderate group ($p<0.05$; analysis of covariance with age and medication use as covariates)

H&Y: Hoehn & Yahr

Table 2. Frequency of autonomic symptoms in groups of patients with different types of dopamine replacement therapy (% with an item score ≥1)

	Patient groups			
Item	No DRT (n=42)	Dopamine agonist monotherapy (n=90)	Levodopa monotherapy (n=84)	Combination therapy (n=204)
Gastrointestinal domain				
Swallowing/choking	52	53	54	57
Sialorrhea	62	58	77	80†
Dysphagia	26	38	42	39
Early abdominal fullness	26	51*	54*	56*
Constipation	26	43	54	56*
Straining for defecation	43	69*	81*	76*
Fecal incontinence	0	7	7	16
Urinary domain				
Urinary urgency	33	68*	67*	74*
Urinary incontinence	12	43	56*	60*
Incomplete emptying	33	46	56	57*
Weak stream of urine	43	43	67	69
Frequency	93	84	87	93
Nocturia	81	80	91	91
Cardiovascular domain				
Lightheaded when standing up	45	54	60	58†
Lightheaded when standing for some time	14	29	48	37†
Syncope	0	1	6	4
Thermoregulatory domain				
Hyperhidrosis during the day	38	40	39	53
Hyperhidrosis during the night	43	46	48	64
Cold intolerance	57	50	58	50
Heat intolerance	31	47	46	49

Pupillomotor domain				
Oversensitive to bright light	45	46	58	58
Sexual domain				
Men: erection problem	29	29	26	43
Men: ejaculation problem	12	22	20	34*
Women: vaginal lubrication	14	16	2†	9
Women: problem with orgasm	7	18	4	12

*: difference vs no DRT group ($p<0.05$; analysis of covariance with age and disease severity as covariates)

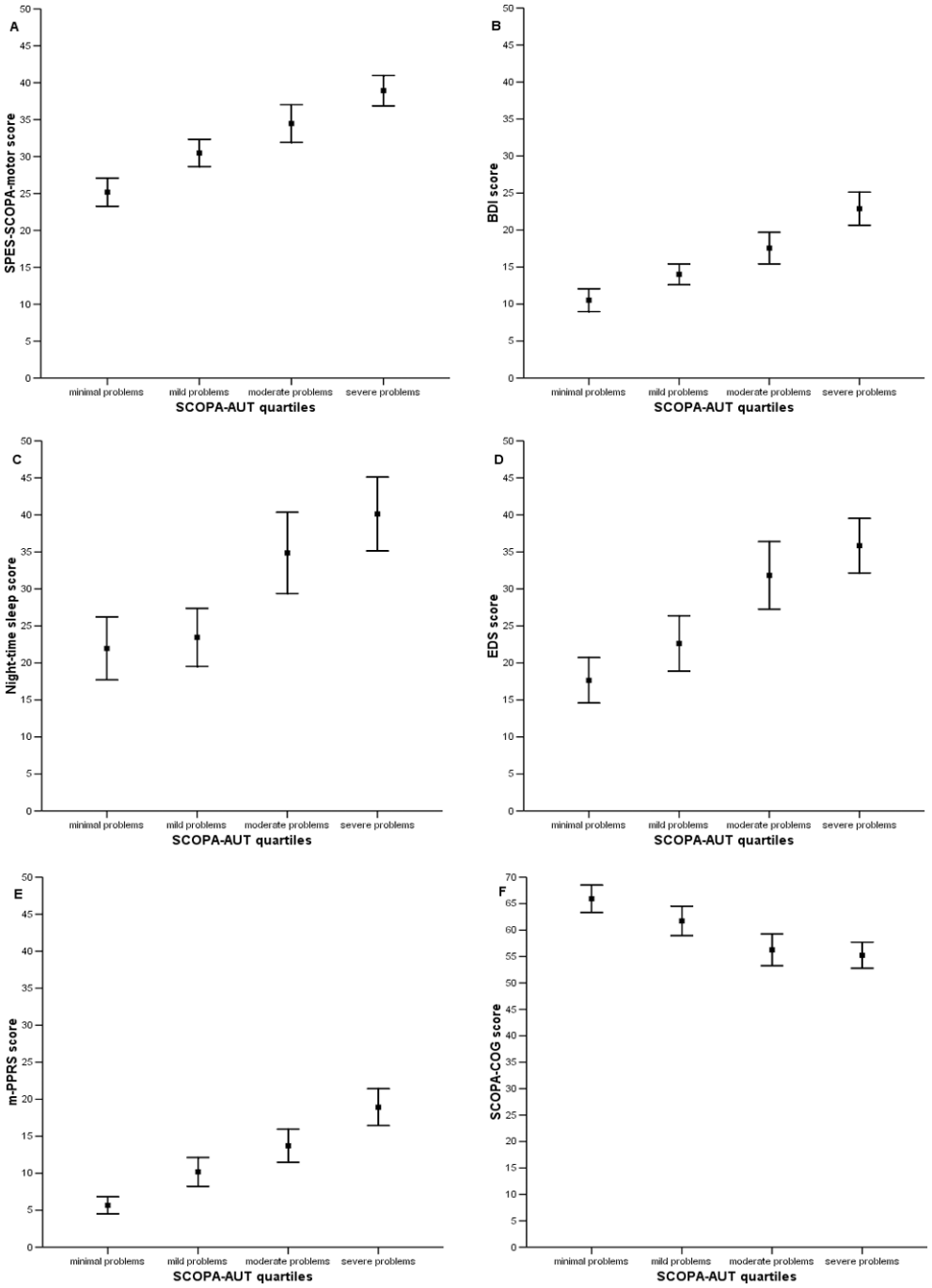
†: difference vs dopamine agonist monotherapy group ($p<0.05$; analysis of covariance with age and disease severity as covariates)

DRT: dopamine replacement therapy

AS in relation to other impairments

To evaluate the relation of the autonomic domain with motor and nonmotor domains of PD, patients were classified in subgroups, based on the quartiles of the SCOPA-AUT scores (first quartile: minimal problems, second quartile: mild problems, third quartile: moderate problems, fourth quartile: severe problems). More AS were associated with more problems on all other PD impairment domains (all trends: $p<0.01$; all goodness of fit: $p>0.05$) (figure 2). Correlations between the total SCOPA-AUT score and other PD impairment scores were all moderate (depressive symptoms 0.48, psychiatric complications 0.48, motor function 0.44, EDS 0.32, nighttime sleep 0.29 and cognition -0.29, all $p<0.01$).

Figure 2. Clinical characteristics of subgroups of patients based on quartiles of SCOPA-AUT scores



Mean group scores expressed in relative scores (range 0 to 100) for motor function (SPES/SCOPA-motor), depressive symptoms (BDI), nighttime sleep and excessive daytime sleepiness (SCOPA-SLEEP), psychiatric complications (modified-PPRS), and cognition (SCOPA-COG). A higher score indicates worse performance, except for the SCOPA-COG.

Discussion

In this clinic-based study, AS were assessed in a large cohort of patients with PD. To obtain an adequate distribution of important determinants of the disease course, patients were recruited in strata based on age at onset (≤ / > 50 years) and disease duration (≤ / > 10 years). Because of this selection process, the results cannot be generalized to the general PD population. For instance, compared to other studies, this cohort has a relatively young mean age and a large number of patients using dopamine agonists.

AS were evaluated using a reliable and valid instrument that includes items that were considered relevant by patients and specialists.[3] Our results show that compared to a group of control subjects with a similar overall age and sex distribution, patients with PD experience significantly more problems with gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, and sexual functioning, indicating that virtually no autonomic domain remains unaffected in this disease. As such, the results are in line with studies that have focused on specific autonomic impairments in PD.[5,30]

Most prominent differences in severity of symptoms between patients and control subjects emerged in the gastrointestinal domain with the largest frequency differences for sialorrhea, constipation, straining for defecation, and problems related to swallowing. Compared to control subjects, patients also reported substantially more urinary problems with the largest frequency differences for urgency and incontinence. A substantial proportion of patients using laxatives or medication for urinary urgency never or sometimes experienced problems with these AS. Assuming that these patients experienced benefit from the medication, our findings may underestimate the true frequency of these symptoms in PD.

Half of the patients experienced problems (item score ≥1) with urinary incontinence and 11% of the patients experienced problems with fecal incontinence. Sialorrhea was reported by 73% of the patients and occurred regularly or often in 22%. These AS are all embarrassing and have a severe impact on social life. Sialorrhea is generally noticed during follow-up visits, but patients may hesitate to report incontinence. Consequently, increased clinical awareness is important and may prevent undertreatment of AS in PD. Although several therapeutic treatment options for the various areas of autonomic dysfunction in PD are available, there is a lack of evidence from randomized trials regarding their efficacy.[31] The high frequency of AS in PD found in this study clearly indicates the need for good randomized controlled studies. Compared to other AS, cardiovascular symptoms were least frequent in patients with PD. In view of the often reported cardiac sympathetic denervation, this finding may come as a surprise.[6,10,17] This discrepancy may have emerged because of the different applied methods of assessment, that is, objective vs subjective evaluations. Comparisons between subjective assessment of symptoms and objective assessment of a particular autonomic function may reveal low to moderate relations.[32]

In the current study, AS increased with higher age in both control subjects and patients. Additionally, in PD disease severity and DRT contribute to AS. To unravel the effects of disease severity and DRT, the influence of each of the factors was assessed while controlling for age and the other factor. Cardiovascular and pupillomotor functioning were negatively affected by disease severity, whereas gastrointestinal, urinary, and thermoregulatory functioning were negatively affected by both disease severity and DRT. Interestingly, most other studies have described relations between DRT and worsening of cardiovascular function.[8,13,16,18,19] These differences are probably caused by the aforementioned use of different assessment methodology. In contrast to a study that used a structured interview to evaluate sexual functioning in PD, we found no relation between sexual functioning and disease severity.[33] We also did not find a relation between sexual functioning and DRT. The conclusions from studies on the influence of DRT on sexual functioning are inconsistent.[33-37] The differences between our results and the results of other studies could be due to the high occurrence of

participants who answered "non-applicable" to one or both of the sexual items in our study. "Non-applicable" response options were excluded from the analyses, which may have resulted in bias. It is difficult to determine in which direction this potential bias may have influenced the results.

In PD, the progressive loss of nigral neurons is associated with classical motor symptoms and signs. Recent studies, however, indicate that the disease process is much more extensive, involving projection neurons of both the peripheral and central nervous systems.[38,39] Lewy body pathology is thought to start in neuronal circuits involved in autonomic function, but whether the pathological process begins in the brain or in the peripheral nervous system is unknown.[39] For instance, constipation may occur as an early manifestation reflecting involvement of neuronal circuits of the gastrointestinal system or arise as a consequence of other factors, such as a reduced water intake secondary to diminished thirst sensation.[40] Two studies have supported the notion that PD may start with autonomic involvement. One study found that infrequent bowel movements were associated with an elevated risk of future PD in men while another study reported that constipation preceded the onset of motor symptoms in the majority of patients with PD.[40] In our study, de novo patients had significantly more gastrointestinal and cardiovascular problems compared to control subjects, which could also support the notion that PD may begin with autonomic involvement.[41]

This cross-sectional study shows that, at group level, more severe AS are associated with more severe impairments in other domains of PD, including motor function, depressive symptoms, cognition, psychiatric complications, nighttime sleep, and EDS, indicating advancing disease. This finding may suggest that one general disease process underlies the progressive involvement of different impairment domains in PD. Whether this process is primarily spatially (simultaneous involvement of different brain areas) or temporally (sequential involvement of different brain areas) organized remains unclear. In both cases differential cell type vulnerability may result in differences in phenotypic expression. Since this cannot be determined in the context of a cross-sectional design, we are currently performing a longitudinal study which evaluates all relevant PD impairment domains.

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