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Autonomic function, as self-reported on the SCOPA-autonomic questionnaire, is normal in essential tremor but not in Parkinson's disease

Anne Damian[a], **Charles H. Adler**[b], **Joseph G. Hentz**[c], **Holly A. Shill**[d], **John N. Caviness**[b], **Marwan N. Sabbagh**[d], **Virgilio G.H. Evidente**[b], **Thomas G. Beach**[d], and **Erika Driver-Dunckley**[b,*]

[a]University of Arizona College of Medicine – Phoenix, Phoenix, AZ, USA

[b]Parkinson's Disease and Movement Disorders Center, Department of Neurology, Mayo Clinic, 13400 East Shea Blvd, Scottsdale, AZ 85259, USA

[c]Biostatistics Section, Mayo Clinic, Scottsdale, AZ, USA

[d]Banner Sun Health Research Institute, Sun City, AZ, USA

Abstract

Objective—To compare autonomic function of subjects with Parkinson's disease (PD) and essential tremor (ET) relative to controls.

Background—It has been reported that patients with PD have autonomic dysfunction while no literature exists regarding autonomic function in ET.

Methods—Subjects with PD, ET, and controls had autonomic function measured using the SCOPA-Autonomic questionnaire, with the total and domain scores transformed to a scale of 0–100 points.

Results—62 subjects with PD, 84 with ET, and 291 controls were included. Women were more prevalent in control (69%) compared to PD (44%) and ET (44%) groups, and mean age was significantly younger in PD (73 yrs) and older in ET (83) compared to controls (81). The mean SCOPA-Aut Total score in PD was significantly higher than controls, with no difference in ET. No autonomic dysfunction was found in any domain in ET but in PD there were significant abnormalities in gastrointestinal, cardiovascular, urinary, and thermoregulatory domains. Individual question data revealed a significantly higher percentage of subjects with dysfunction on 11/23 questions in the PD group but only 1 question (sialorrhea) in the ET group compared with controls.

Conclusion—Autonomic scores, particularly gastrointestinal, cardiovascular, urinary, and thermoregulatory were increased in patients with PD, as assessed by SCOPA-Aut. Patients with ET did not exhibit autonomic dysfunction, with the exception of sialorrhea.

Keywords

Autonomic dysfunction; Parkinson's disease; Essential tremor

*Corresponding author. Tel.: +1 480 301 8100. Driverdunckley.erika@mayo.edu (E. Driver-Dunckley).

1. Introduction

The role of non-motor symptoms in patients with movement disorders is an area gaining increasing recognition. The non-motor symptoms of Parkinson's disease (PD), which include cognitive, psychiatric, autonomic, sleep, and sensory disorders, can be quite significant [1–3]. It has been suggested that the most common non-motor symptoms of PD are autonomic, and that autonomic dysfunction is correlated with poor health related quality of life [4].

Various autonomic symptoms have been described in PD. Gastrointestinal dysfunction positively correlated with increasing disease severity [5]. Cardiovascular autonomic dysfunction, especially orthostatic hypotension, may have a prevalence of up to 58% [6]. Lower urinary tract symptoms have been described [7]. Cutaneous symptoms, such as hypohydrosis or hyperhydrosis, have been reported in PD patients, and correlate with other symptoms of autonomic dysfunction [8]. Sexual dysfunction has also been extensively documented early in the description of the non-motor symptoms of PD [9]. Thus, a large body of literature exits describing autonomic dysfunction in PD.

Despite extensive research on autonomic dysfunction in PD, a thorough literature review did not reveal research regarding autonomic dysfunction in the most common movement disorder, essential tremor (ET). For years, a linkage between PD and ET has been debated [10–12]. In a continued effort to study these disorders comparing non-motor symptoms may be critical. Therefore, the objective of this study is to compare the occurrence of autonomic symptoms in Parkinson's disease, essential tremor, and normal controls, using an autonomic dysfunction questionnaire – the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-Aut).

2. Methods

All subjects were enrolled in the Arizona Parkinson's Disease Consortium's ongoing longitudinal clinicopathological study in the Banner Sun Health Research Institute Brain and Body Donation Program (SHRI BBDP) [13]. All subjects signed written informed consent approved by the Institutional Review Board.

All subjects received standardized movement disorder examinations, including the UPDRS, Hoehn & Yahr staging and tremor rating scales [14–16], and cognitive examinations as previously described [17]. Subjects with dementia were excluded from this analysis as accurate completion of the SCOPA-Aut could not be guaranteed. Clinically probable PD (PD) was diagnosed if the subject had 2 of the 3 cardinal signs (rest tremor, bradykinesia, cogwheel rigidity), no symptomatic cause, and a response to dopaminergic medications. Essential tremor was diagnosed if the subject had the presence of a grade 2 postural and/or kinetic tremor of the hands or forearms without identifiable secondary cause or other exclusion criteria (e.g. prominent unilateral tremor, rigidity or bradykinesia). Subjects were examined with arms outstretched (postural tremor) and on finger-to-nose-to-finger testing (kinetic tremor). Subjects with a tremor score between .5 and 2 were also considered ET if the research evaluations found the tremor was present for at least 3 years, with similar exclusion criteria, or medical records supported longstanding ET. Subjects with Parkinson's disease or other movement disorders were excluded from the ET group [18]. The control group was defined as subjects without evidence for a neurodegenerative disorders such as progressive supranuclear palsy, dementia with Lewy bodies, other forms of parkinsonism or dementia. Categories of medications were recorded for each subject at each visit. Subjects did not complete any additional imaging studies.

Autonomic function was measured using the SCOPA-Aut questionnaire [19], a 23 question questionnaire divided into six domains. We selected each subject's most recent valid SCOPA-Aut result (valid response on >75% of the questions) and linked them to the closest movement and cognitive examination within 1 year. The SCOPA-Aut total score and domain scores were transformed to a scale from 0 to 100 points.

Participants were selected from the SHRI BBDP if they had completed the SCOPA-Aut questionnaire and did not have restless legs syndrome or a neurodegenerative disease other than PD. Subjects with PD and ET were each compared to the Control group. Comparisons of mean SCOPA-Aut scores were made by using the two-sample t test. Means adjusted for use of medication were compared by using a general linear model. The proportions of subjects with a score greater than zero were compared by using the Pearson chi-square test. The sample had 80% power (α .05) if the prevalence of a characteristic were 60% for PD versus 40% for controls, and had 90% power if the prevalence of a characteristic were 60% for ET versus 40% for controls.

3. Results

There were 2760 subjects in the database and of these 642 had a SCOPA-Aut score. 120 subjects were excluded due to a neurodegenerative disorder other than PD, 83 were excluded due to RLS, and 2 were excluded due to having both ET and PD. Therefore, 62 subjects with PD, 84 with ET, and 291 Controls included in the analysis. Women were less prevalent in both the PD (44%) and ET (44%) groups compared to the Control group (69%) (Table 1). The mean (+SD) age was lower in the PD group (72.9 ± 8.8 yrs) but higher in the ET group (82.8 ± 6.6) compared to the Control group (80.5 ± 7.9) (P <.001) (Table 1). The SCOPA-Aut Total score was not associated with sex or age in the Control group and therefore it was not necessary to adjust for these when comparing groups. The mean SCOPA-Aut Total score was 15.8 ± 8.6 for women and 16.7 ± 7.2 for men (95% CI − 3.2 to 1.4, P = .43). The correlation between the SCOPA-Aut Total score and age was only − .03 (95% CI −.15 to .08, P = .59).

3.1. Parkinson's disease

The mean SCOPA-Aut Total score in subjects with PD was higher than Control subjects (Table 1). Individual question data revealed a significantly higher percentage of subjects with autonomic symptoms on 11/23 questions in the PD group. The greatest difference between PD and Control was in the GI domain (Tables 1 and 2). Other categories with greater autonomic symptoms in PD included urinary, cardiovascular and thermoregulatory complaints (Tables 1 and 2). There were significant correlations between PD severity based on Hoehn and Yahr staging and urinary urgency, urinary incontinence, and sensitivity to bright light (Table 3). The SCOPA-Aut Total score and Gastrointestinal subscale score also had correlations of at least .25 with Hoehn and Yahr stage. Using the Unified Parkinson's Disease Rating Scale (UPDRS) motor score there was a significant correlation between disease severity and constipation, heat and cold intolerance. Urinary incontinence, syncope, and hyperhidrosis also had correlations of at least .25 with UPDRS motor score (data not shown).

Multiple medications were more prevalent in the PD group than the Control group including dopaminergic drugs, cholinesterase inhibitors, antidepressants, and sedatives (Table 4). With the exception of dopaminergic drugs, none of these medications substantially altered the comparison of autonomic symptoms between PD and Controls. It is not possible to determine, with the current data, the overall effect of dopaminergic medications on the difference in autonomic scores between groups.

3.2. Essential tremor

The mean SCOPA-Aut Total score in subjects with ET was not higher than Control subjects (Table 1). There were also no differences between groups for any of the subscores (Table 1). Individual question data revealed a significantly higher percentage of subjects with autonomic symptoms in only 1/23 questions (sialorrhea) in the ET group compared with controls (Table 2). While there were more females with orgasm problems by percentage, only four responded in the ET group making comparison unclear. There were no significant differences in the medications taken between ET and Control subjects. Only an additional 6% of subjects used antidepressant medication in the ET group than in the Control group (PD 27%, ET 22%, Controls 16%). Adjustment for use of antidepressant medication did not increase the difference between the ET and Control groups.

4. Discussion

This study confirms the presence of increased autonomic symptoms in Parkinson's disease and is the first to establish that autonomic symptoms are essentially not present in subjects with essential tremor. A strength of this study was the standardized method used to collect autonomic symptom data amongst the groups of PD, ET, and control subjects. Autonomic symptoms were assessed using a validated questionnaire of autonomic dysfunction, the SCOPA-Aut [19]. The SCOPA-Aut was developed in 2004 by Visser and colleagues, as a questionnaire tool designed to assess autonomic symptoms in patients with PD [19]. This group subsequently used the SCOPA-Aut to evaluate a large cohort of PD patients for autonomic findings, demonstrating increased symptoms in patients with PD in all autonomic domains assessed by the SCOPA-Aut, namely gastrointestinal, urinary, cardiovascular, thermoregulatory, pupillomotor, as well as sexual. These authors further reported that increased age, increased disease severity, as well as higher doses of dopaminergic medications were associated with more symptoms of autonomic dysfunction [20]. This instrument has since been independently validated, and found to be an acceptable, consistent, valid and precise scale in patients with Parkinson's disease [21]. However, there has been criticism of this instrument, reporting a lack of concordance of both overall score and item scores of cardiovascular and thermoregulatory domains of the SCOPA-AUT with cardiovascular and skin autonomic function testing by sympathetic skin response and *R–R* interval variation test [22]. Additionally, Rasch analysis of this instrument has suggested that a shorter version and a simpler response scheme would optimize this test [23]. Nonetheless, the SCOPA-AUT is a simple, valid, reliable tool for assessing for the presence of autonomic symptoms.

Our results confirm that compared to a group of control subjects, PD patients experience increased symptoms in multiple domains, namely: gastrointestinal, urinary, cardiovascular, and thermoregulatory. Pupillomotor findings of oversensitivity to bright light, as well as sexual symptoms in men, were not significantly different in our sample of PD patients relative to controls. In our sample of PD patients gastrointestinal dysfunction (swallowing/choking, sialorrhea, dysphagia, constipation, straining for defecation, and fecal incontinence) are the most prevalent of the autonomic systems affected. This finding supports prior data suggesting that gastrointestinal symptoms are the most common of the symptoms of autonomic dysfunction in PD patients [20]. Not all individual symptoms assessed by the SCOPA-Aut were found to be significantly different between PD patients and controls. Symptoms of fecal incontinence, incomplete emptying of urine, frequency of urination, nocturia, hyperhydrosis during the day and cold intolerance were not significantly different in our PD group. This is in contrast to data previously reported by Verbaan et al., which suggests that all these individual symptoms within the overall autonomic domains were significantly different in PD patients as compared to controls, with the exception of vaginal lubrication and problem with orgasm in women [20]. While the significance of the

specific symptoms is challenged by this study, our data suggests, as does prior literature, that PD patients experience autonomic dysfunction pervasive to multiple autonomic domains.

Other than sialorrhea, our data found that subjects with ET did not have significant autonomic symptoms. None of the overall systems measured by the SCOPA-Aut exhibited a statistically significant difference from controls. There have been no previous reports of autonomic function in ET for comparison. Certain non-motor manifestations of ET have been reported including respiratory disorders [24], cognitive decline [25,26], depression [3], and anxiety [3]. In a small group of 10 ET patients a cinefluorographic study found slight slowing in esophageal transit and vocal tremor during speech without evidence of progressive deterioration [27]. This was contrasted with 100 PD patients who showed severely disordered swallowing and speech function [27]. However, there is no literature systematically documenting the presence or absence of other autonomic symptoms in patients with ET.

SCOPA-Aut total score in both our PD and ET patients were not correlated with age or sex of the patient, which is inconsistent with prior data suggesting a correlation with age in PD patients [20,21]. In our study, symptoms of urinary urgency, urinary incontinence, and oversensitivity to bright light were positively correlated with increasing Hoehn and Yahr stage of PD and some questions correlated with UPDRS motor severity scores. However, one weakness of this study is that our sample was too small to rule out a correlation between the other domains tested and greater disease severity. Prior data has indicated that total SCOPA-Aut scores increased with increasing disease severity [20,21], and all domain scores, with the exception of pupillomotor and sexual domains, also increased with increasing disease severity [20].

The finding that autonomic dysfunction based on self-report was not common in ET yet was in PD may add to the discussion of whether there is a link between ET and PD. One of the earliest non-motor symptoms in PD is hyposmia/anosmia [28]. Data regarding hyposmia in ET has been inconsistent with the majority of studies finding no association [29–31]. Further studies have evaluated sleep [32,33], cognitive function [26,34], and other non-motor features in ET. These studies are conflicting regarding non-motor abnormalities in ET (see recent review paper Ref. [11]). This study presents another piece of evidence showing a lack of association of non-motor symptomatology between PD and ET. Our findings confirmed the presence of autonomic symptoms in PD, and with the exception of sialorrhea, found no autonomic symptoms in ET.

It is unclear what causes the autonomic symptoms in PD. It has been demonstrated in PD patients that phosphorylated alpha-synuclein histopathology is present in the regions of the spinal cord containing preganglionic autonomic neurons, as well as within sympathetic ganglia. It has therefore been suggested that alpha-synuclein histopathology is likely present within end organ targets of the autonomic nervous system as well [35]. This study did in fact also document phosphorylated alpha-synuclein histopathology in the vagus nerve, gastrointestinal system, sciatic nerve and endocrine system [35]. While to date the histopathology of the autonomic nervous system has not been studied in ET patients, the lack of autonomic symptoms suggests a lack of underlying pathology. Thus this suggests that the primary autonomic pathology demonstrated histopathologically in PD patients does not exist in patients with ET.

In addition to previously mentioned limitations, this study was small. Yet the numbers were large enough to find significant differences between groups. Another limitation is that the data is subjective in nature with no objective testing performed and depression was not assessed.

In summary, these data demonstrate the presence of autonomic dysfunction in subjects with Parkinson's disease but not with essential tremor. Further study of this population, larger groups of subjects, and objective measurements of autonomic function are needed.

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Table 1

Demographics and SCOPA-autonomic total and domain scores transformed to a 0–100 scale.

	PD	ET	Control
N	62	84	291
Female	44%[a]	44%[a]	69%
Age (yrs); mean ± SD	72.9 ± 8.8[a]	82.8 ± 6.6[b]	80.5 ± 7.9
SCOPA-Aut (0–100); mean			
Total	25[a]	17	16
Gastrointestinal	24[a]	12	10
Urinary	34[b]	30	28
Cardiovascular	9[b]	4	5
Thermoregulatory	16[b]	13	12
Pupillomotor	21	17	21
Sexual – Men	61	57	49
Sexual – Women	32	21	25

[a] $P < .001$ vs Control.

[b] $P < .05$ vs Control.

Table 2

SCOPA-Aut score greater than zero.

	PD	ET	Control
Swallowing/Choking	32/60 (53%)[a]	21/84 (25%)	63/290 (22%)
Sialorrhea	50/62 (81%) [a]	36/84 (43%)[b]	72/287 (25%)
Dysphagia	25/61 (41%) [a]	13/84 (15%)	56/289 (19%)
Early abdominal fullness	24/58 (41%) [b]	17/78 (22%)	63/284 (22%)
Constipation	39/62 (63%) [a]	27/83 (33%)	90/286 (31%)
Straining for defecation	43/58 (74%) [b]	42/83 (51%)	151/284 (53%)
Fecal incontinence	8/60 (13%)	19/84 (23%)	44/285 (15%)
Urinary urgency	41/62 (66%) [c]	43/83 (52%)	150/288 (52%)
Urinary incontinence	37/62 (60%)	40/83 (48%)	143/288 (50%)
Incomplete emptying	33/61 (54%)	37/84 (44%)	121/290 (42%)
Weak stream of urine	33/61 (54%)	48/84 (57%)	138/291 (47%)
Frequency	50/61 (82%)	66/83 (80%)	221/289 (76%)
Nocturia	61/62 (98%)	79/83 (95%)	271/290 (93%)
Lightheaded standing up	24/61 (39%) [a]	14/84 (17%)	56/287 (20%)
Lightheaded standing for some time	17/62 (27%) [b]	8/84 (10%)	42/290 (14%)
Syncope	3/61 (5%)	1/84 (1%)	5/285 (2%)
Hyperhidrosis during the day	21/62 (34%) [c]	15/84 (18%)	64/287 (22%)
Hyperhidrosis during the night	21/61 (34%) [c]	25/84 (30%)	66/291 (23%)
Cold intolerance	22/59 (37%)	26/83 (31%)	95/287 (33%)
Heat intolerance	27/59 (46%)	24/81 (30%)	95/285 (33%)
Oversensitive to bright light	31/61 (51%)	31/84 (37%)	132/289 (46%)
Erection problem – Male	30/32 (94%)	27/32 (84%)	56/70 (80%)
Ejaculation problem – Male	26/31 (84%)	24/30 (80%)	42/58 (72%)
Vaginal lubrication – Female	9/11 (82%)	1/4 (25%)	24/45 (53%)
Problem with orgasm – Female	7/11 (64%)	4/4 (100%)[c]	18/40 (45%)

[a] $P \leq .001$.

[b] $P < .01$.

[c] $P \leq .05$ vs Control.

Table 3

Relationship between Hoehn and Yahr stage and SCOPA-Aut score among subjects with PD.

	N	*r*	*P*
Total (0–100)	56	.25	.06
Gastrointestinal (0–100)	54	.25	.07
Swallowing/Choking	54	.22	.11
Sialorrhea	56	.16	.25
Dysphagia	55	.26	.06
Early abdominal fullness	52	.07	.61
Constipation	56	.16	.25
Straining for defecation	52	.06	.65
Fecal incontinence	54	.13	.36
Urinary (0–100)	55	.30	.03
Urinary urgency	56	.29	.03
Urinary incontinence	56	.42	.001
Incomplete emptying	55	.25	.06
Weak stream of urine	55	.11	.40
Frequency	55	.07	.62
Nocturia	56	.05	.74
Cardiovascular (0–100)	54	.03	.82
Lightheaded standing up	55	−.01	.95
Lightheaded standing for some time	56	.05	.73
Syncope	55	.18	.18
Thermoregulatory (0–100)	55	.13	.33
Hyperhidrosis during the day	56	.09	.51
Hyperhidrosis during the night	55	.06	.68
Cold intolerance	53	−.03	.82
Heat intolerance	53	.26	.06
Pupillomotor (0–100)	55	.29	.03
Oversensitive to bright light	55	.29	.03
Sexual – Men (0–100)	29	.00	.99
Erection problem	31	.11	.55
Ejaculation problem	30	−.12	.52
Sexual – Women (0–100)	9	.05	.91
Vaginal lubrication	9	.19	.63
Problem with orgasm	9	−.14	.72

Table 4

Medications.

	PD	ET	Control
Cholinesterase inhibitor	6/51 (12%)	1/65 (2%)	8/186 (4%)
SSRI	4/51 (8%)	6/65 (9%)	15/186 (8%)
Other antidepressant	7/51 (14%)	7/65 (11%)	16/186 (9%)
Atypical antipsychotic	1/51 (2%)	0/65 (0%)	1/185 (1%)
Typical antipsychotic	1/51 (0%)	0/65 (0%)	0/185 (0%)
Anxiolytic	9/51 (18%)	9/65 (14%)	14/185 (8%)
Sedative hypnotic	3/51 (6%)	11/65 (17%)	13/185 (7%)
Dopaminergic agent	50/51 (98%)	1/65 (2%)	4/186 (2%)
Statin	13/51 (25%)	24/65 (37%)	67/186 (36%)
Vitamin E	8/51 (16%)	7/65 (11%)	25/186 (13%)
NSAID	9/51 (18%)	11/65 (17%)	36/186 (19%)
Estrogen	2/51 (4%)	4/65 (6%)	20/185 (11%)