# In patients with Parkinson's disease, autonomic symptoms are frequent and associated with other non-motor symptoms

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**OBJECTIVES:** To assess frequency of **autonomic symptoms** in a consecutive series of PD patients and to correlate them **to motor** and **non-motor symptoms**.

**INTRODUCTION:** Several studies have reported on the clinical burden of non-motor symptoms in Parkinson's disease (PD) [1]. These include cognitive-psychiatric, autonomic, sleep, sense disorders and fatigue. Autonomic symptoms (AS) are common, correlated with poor quality of life, and with great financial burden [2]. Sleep disorders (SD) are common non-motor symptoms, affecting up to 60–95 % of PD patients [3]. Scales for Out-comes in Parkinson's disease-Autonomic (**SCOPA-AUT**) and Parkinson Disease Sleep Scale/Epworth Sleepiness Scale (**PDSS/ESS**) have been developed to measure AS and SD in PD. Both AS and SD begin in the early stages of the disease [4] and they might recognize similar pathogenesis being the clinical manifestation of pathological changes within common subcortical structures [5].We estimated the frequency of AS in a consecutive series of non-demented PD patients and we explored their association with other non-motor symptoms, like SD.

## CLINICAL EVALUATION:

We enrolled all consecutive PD patients, according to the UK Society PD Brain Bank criteria, seen in our department from January 2010 to July 2014. Patients with cerebellar signs, early dementia with disturbances of memory, language and praxis or other symptoms suggestive for atypical parkinsonism were excluded.

**We administered a questionnaire investigating the following variables:**

- Age.
- Birth place.
- Gender
- Area of residence
- Education
- Tobacco, alcohol and coffee consumption.
- Information about PD:

age at onset, duration of disease, type of onset and pharmacological treatments.

**Patients were assessed by movement disorder trained neurologists with:**

Hoehn and Yahr Stagin and Unified Parkinson's Disease Rating Scale (UPDRS).
Mini Mental State Exam (MMSE), Beck's Depression Inventory (BDI), Neuropsychiatric Inventory (NPI).
SCOPA-AUT scale.
Cumulative Illness Rating Scale (CIRS).
Parkinson's diseases Sleep Scale (PDSS), the Epworth Sleepiness Scale (ES).
PDQ-39 scale.
Orthostatic hypotension, defined as a drop in systolic blood pressure [20 mmHg upon adopting the standing position] according to the recommendations of EFNS for orthostatic hypotension in Parkinson's disease.
The L-Dopa Equivalent Dose (LED) for daily levodopa and dopamine agonist has been calculated fot PD patients. therapy.

Table 1. Demographic and clinical data (means ± SD) and univariate analysis (t-test) according to mean SCOPA-AUT scale scores (above and below the mean)

| Variables | All PD patients (135) | Patients with SCOPA-AUT >13.1 (60) | Patients with SCOPA-AUT ≤13.1 (75) | p |
|---|---|---|---|---|
| Age at interview (years) | 67.2 ± 10 | 70.4 ± 7.5 | 64.6 ± 11.0 | 0.0006 |
| Disease duration (years) | 5.3 ± 4.5 | 7.1 ± 4.2 | 3.7 ± 3.2 | <0.0001 |
| UPDRS TOT (score) | 31.05 ±19.5 | 39.9 ± 20.1 | 23.9 ± 15.9 | <0.0001 |
| UPDRS motor section | 19.3 ± 12.7 | 24.15 ±13.5 | 15.3 ± 10.6 | <0.0001 |
| Levodopa (mgs) | 278.7 ±266.3 | 379.2 ±285.7 | 198.3 ± 220.6 | 0.0001 |
| Dopa agonists (mgs) | 211.8 ± 266 | 248.7 ±191 | 182.3 ± 148.1 | 0.03 |
| LED | 489.6 ± 367.5 | 624.3 ± 400.3 | 381.9 ± 300.6 | 0.0002 |
| PDSS | 108.9 ± 26.7 | 102.3 ± 24.3 | 114 ± 27.5 | 0.01 |
| ESS | 6.3 ± 4.3 | 7.1 ± 4.2 | 5.7 ± 4.3 | 0.06 |
| BDI | 6.9 ± 5.9 | 7.9 ± 5.6 | 6.1 ± 6.1 | 0.09 |
| NPI | 9.1 ±8.9 | 10.5 ± 9.4 | 7.9 ± 8.4 | 0.09 |
| MMSE | 28.15 ± 1.9 | 27.9 ± 1.8 | 28.3 ± 1.9 | 0.21 |
| Quality of life (PDQ-39) | | | | |
| Stigma | 13.9 ± 22.7 | 13.7 ± 23.4 | 14.1 ± 22.3 | 0.93 |
| Mobility | 35.6 ± 35 | 44.6 ± 36.5 | 28.5 ± 32.3 | 0.009 |
| Social supp | 5.6 ±13.3 | 7.5 ± 16.9 | 4.2 ± 9.5 | 0.2 |
| Daily activity | 31.3 ± 32.4 | 40.7 ± 35 | 23.8 ± 28.4 | 0.003 |
| Well-being | 25.5 ± 20 | 28.2 ± 22.3 | 23.3 ± 17.8 | 0.2 |
| Comunication | 7.05 ± 14.7 | 7.3 ± 15.9 | 6.8 ± 13.7 | 0.9 |
| Cognition | 23.05 ± 21.4 | 27.5 ± 20.5 | 19.5 ± 21.5 | 0.03 |
| Bodily discomfort | 24.6 ± 22.2 | 28.4 ± 24.1 | 21.6 ± 20.3 | 0.08 |

A total of 135 patients (79 males, 58.5%) with PD were seen during the study period and they were included in the study. Most of the patients. (85 %) were on HY stage 1–2 (49.6 % stage 1, 34.8 % stage 2, 9.6 % stage 3, 6 % stage 4 and none stage 5.

The most frequently involved domains of SCOPA-AUT scale were the urinary (83 %) and the gastrointestinal (84 %), followed by the cardiovascular (51 %),the thermoregulatory (43 %), the sexual (30 %), and the pupillomotor dysfunction (26.2 %). Orthostatic hypotension was twice as common in patients with higher score of SCOPA-AUT scale (8.3 %, 5/60) as compared to those with lower scores (4 %, 3/75).

Table 2. Association between SCOPA-AUT scale scores and PD related variables, univariate analyse ($\chi 2$ test)

| | SCOPA-AUT ≤13.1(%) | SCOPA-AUT >13.1(%) | OR, 95% CI | p |
|---|---|---|---|---|
| Sex | | | | |
| Males | 45 (57) | 34 (43) | | |
| Females | 30 (53.6) | 26 (46.4) | 1.1, 0.6-2.3 | 0.7 |
| Age | | | | |
| ≤ 67.2 | 42 (70) | 18 (30) | | |
| > 67.2 | 33 (44) | 42 (56) | 3.0, 1.4-6.1 | 0.003 |
| Disease duration | | | | |
| ≤ 5.3 | 56 (68.3) | 26 (31.7) | | |
| > 5.3 | 19 (35.8) | 34 (64.2) | 3.9, 1.9-8.0 | 0.0002 |
| Onset | | | | |
| Tremor | 49 (55) | 40 (45) | | |
| Akinetic-rigid | 26 (56.5) | 20 (43.5) | 1.1, 0.5-2.2 | 0.9 |
| HY | | | | |
| ≤ 2 | 68 (59.7) | 46 (40.3) | | |
| > 2 | 7 (33.3) | 14 (66.7) | 3.0, 1.1-7.9 | 0.03 |
| UPDRS | | | | |
| ≤ 31.05 | 59 (72) | 23 (28) | | |
| > 31.05 | 16(30.2) | 37(69.8) | 5.9, 2.8-12.7 | <0.0001 |
| UPDRS motor examination | | | | |
| ≤19.3 | 55 (67) | 27 (33) | | |
| >19.3 | 20 (37.7) | 33 (62.3) | 3.4, 1.6-6.9 | 0.0008 |
| Levodopa | | | | |
| ≤ 278.7 | 53 (68.8) | 24 (31.2) | | |
| > 278.7 | 22(38) | 36 (62) | 3.6, 1.8-7.4 | 0.0003 |
| Dopa agonists | | | | |
| ≤ 211.8 | 50 (61.7) | 31 (38.3) | | |
| > 211.8 | 25 (46.3) | 29 (53.7) | 1.9, 0.9-3.8 | 0.08 |
| LED | | | | |
| ≤ 489.6 | 56 (66.7) | 28 (33.2) | | |
| > 489.6 | 19 (37.25) | 32 (62.75) | 3.4, 1.6-7.0 | 0.0009 |
| PDSS | | | | |
| ≥ 108.9 | 49 (66.2) | 25 (33.8) | | |
| < 108.9 | 26 (42.6) | 35 (57.4) | 2.6, 1.3-5.3 | 0.006 |
| ESS | | | | |
| ≤ 6.3 | 49 (61.3) | 31 (38.7) | | |
| > 6.3 | 26 (47.3) | 29 (52.7) | 1.8, 0.5-3.5 | 0.1 |
| NPI | | | | |
| ≤ 9.1 | 51 (56.8) | 35 (43.2) | | |
| > 9.1 | 24 (49) | 25 (51) | 1.5, 0.7-3.1 | 0.2 |
| BECK | | | | |
| ≤14 | 67 (56.5) | 51 (43.5) | | |
| >14 | 8 (47.1) | 9 (52.9) | 1.5, 0.4-5.4 | 0.5 |
| **Quality of life (PDQ-39)** | | | | |
| Stigma | | | | |
| ≤13.9 | 53 (54.6) | 44(45.4) | | |
| >13.9 | 22 (57.9) | 16(42.1) | | 0.7 |
| Mobility | | | | |
| ≤35.6 | 54 (62.8) | 32 (37.2) | | |
| >35.6 | 21 (57.1) | 28 (42.9) | | 0.02 |
| Social support | | | | |
| ≤5.6 | 59 (55.7) | 47 (44.3) | | |
| >5.6 | 16 (55.2) | 13 (44.8) | | 0.9 |
| Daily activity | | | | |
| ≤31.3 | 55 (65.5) | 29 (34.5) | | |
| >31.3 | 20 (39.2) | 31 (60.8) | | 0.003 |
| Well-being | | | | |
| ≤25.5 | 45 ( 57.7) | 33 (42.3) | | |
| >25.5 | 30 (52.6) | 27 (47.4) | | 0.6 |
| Comunication | | | | |
| ≤7.05 | 57 (56.4) | 44 (43.6) | | |
| >7.05 | 18 (52.9) | 16 (47.1) | | 0.7 |
| Cognition | | | | |
| ≤23.05 | 49 (63.6) | 28 (36.4) | | |
| >23.05 | 26 (44.8) | 32 (55.2) | | 0.03 |
| Bodily discomfort | | | | |
| ≤24.6 | 42 (60) | 28 (40) | | |
| >24.6 | 33 (50.8) | 32 (49.2) | | 0.3 |

Table 3. Comorbidities in patients with Parkinson's disease across SCOPA-AUT strata

| | SCOPA-AUT ≤13.1 | SCOPA-AUT >13.1 | p |
|---|---|---|---|
| **Urinary** | | | |
| No | 69 (92) | 47 (78.3) | 0.02 |
| Yes | 6 (8) | 13 (21.7) | |
| **Diabetes** | | | |
| No | 66 (88) | 53 (88.3) | 0.95 |
| Yes | 9 (23) | 7 (11.7) | |
| **Hypertension** | | | |
| No | 40 (53.3) | 26 (43.3) | 0.25 |
| Yes | 35 (46.7) | 34 (56.7) | |
| **Heart** | | | |
| No | 71 (94.7) | 53 (88.3) | 0.2 |
| Yes | 4 (5.3) | 7 (11.7) | |

Association between higher SCOPA-AUT scores and some PD related variables

| | Adjusted OR | p |
|---|---|---|
| PDSS <108.9 vs ≥108.9 | 2.5 (1.1-5.5) | 0.02 |
| Age >67.2 vs ≤ 67.2 years | 3.5 (1.6-7.7) | 0.002 |
| Duration >5.3 vs ≤ 5.3 years | 3.1 (1.4-6.9) | 0.004 |

Adjusted for Hoen and Yahr, age, duration, PDSS and Levodopa

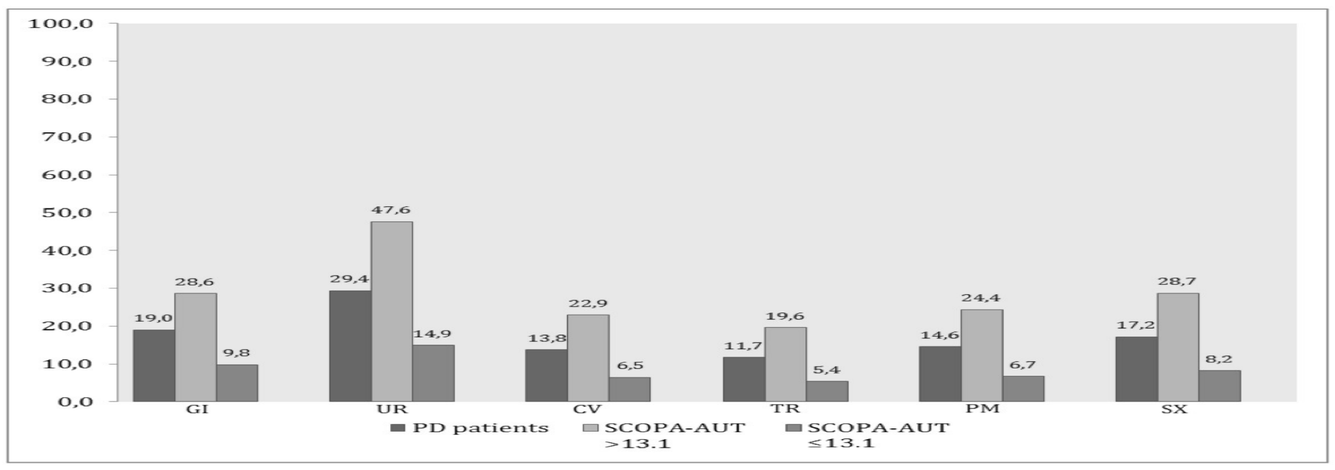


Figure 1: Relative mean and standard deviation scores of SCOPA-AUT scale domains: GI: gastro-intestinal; UR: urinary; CV: cardio-vascular; TR: themo-regulatory; PM: pupillomotor; SX: sexual.

## DISCUSSION AND CONCLUSIONS

- In our study, nearly 84 % of patient complained of autonomic symptoms. PD patients, according to SCOPA-AUT scale, suffered from clinically relevant dysautonomia.
- Patients with more severe involvement of autonomic system were significantly older, had a longer disease duration and complained of worst quality of sleep.
- Our results remark the role of autonomic dysfunction in PD. In our population characterized by mild to moderate disease severity, most of the patients had autonomic system involved.
- According to Braak theory, neuropathological changes progressing to the brainstem regions (pedunculopontine nucleus, locus coeruleus, tegmental area and nucleus magnus cellularis) would be the rationale for the association between autonomic symptoms and sleep disorders.
- Urinary and gastrointestinal domains were the most frequently involved. However, analysis from CIRS data showed that, though urinary disorders were significantly more common in patients with higher scores of SCOPA-AUT scale compared to those with lower scores, 80 % of patients with autonomic dysfunction did not report any disease of the genitourinary system.
- Our study, in agreement with previous studies, support the view of Parkinson's disease as a complex disorder, highlighting the frequency of autonomic symptoms and their association with other non-motor symptoms, in particular with sleep disorders.

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