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Autonomic symptoms in early-stage Parkinson's patients and their relationship with cognition and disease parameters

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ABSTRACT

Aims: Autonomic dysfunction is a prevalent feature throughout various stages of the disease and can significantly exacerbate the overall impact of the condition. Moreover, it is linked to accelerated disease advances and diminished vitality rates in individuals with Parkinson's disease (PD). The main goal of this study is to evaluate the prevalence of autonomic symptoms and cognitive findings and investigate their associations with disease-related factors in early-stage PD patients.

Methods: A total of 49 individuals diagnosed with PD were enrolled in this study. Disease severity was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS), and the disease stage was determined through the modified Hoehn & Yahr Rating Scale (mHYRS). By the mH&Y scale, only individuals in the early stages (≤2.5) of the disease were included in this investigation. The evaluation of autonomic symptoms in PD was conducted using the Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms (SCOPA-AUT) scale. The cognitive functions of the patients were assessed utilizing the Turkish version of the Montreal Cognitive Assessment Scale (MOCA-TR).

Results: The study included 44% (n=22) females and 56% (n=27) males as participants. The average age was 61.5±10.1 years. The mean SCOPA-AUT score was 18.9±9.36, with the most prevalent autonomic symptoms related to the gastrointestinal system. A positive correlation was shown with autonomic symptoms and disease stages (p=0.024, r=0.322). However, no significant relationship was found between autonomic symptoms, other disease parameters, and cognition. We observed a notable inverse correlation between the disease stage and cognitive status (p=0.003, r=-0.417).

Conclusion: Our study concluded that autonomic dysfunctions manifest from the early stages of Parkinson's disease and can intensify as the disease progresses. Identifying and addressing these dysfunctions at an early stage would play a pivotal role in lessening the overall impact of the disease.

Keywords: Autonomic dysfunction, Parkinson's disease, SCOPA-AUT, MOCA

INTRODUCTION

Non-motor symptoms in Parkinson's disease (PD) are just as prevalent as motor symptoms, with recent research indicating their presence in nearly all PD patients. Interestingly, non-motor symptoms contribute significantly to morbidity, even in the early stages of PD, surpassing the impact of motor symptoms.[1] In PD, there is evidence of involvement of sympathetic and parasympathetic branches of the autonomous nervous system, with pathology affecting both its peripheral and central components.[2] Dysautonomia, one of the non-motor manifestations, has been found to occur in approximately 50-70% of individuals with PD.[3,4] Autonomic dysfunction can be observed in almost all stages and may increase the burden of the disease. The spectrum of autonomic dysfunction in PD manifests a wide range, including cardiovascular, gastrointestinal, urological, sexual, and thermoregulatory impairments.[5] In a study involving early-stage PD patients, at least one autonomic dysfunction symptom was observed in 71% of them.[6] As previously demonstrated, autonomic dysfunction is linked to an accelerated progression of disease milestones and reduced survival among individuals with PD.[7] There is a limited body of literature evaluating the impact of autonomic dysfunction on cognition in PD, and the results are conflicting.[8,9]

In this study, we aimed to evaluate the prevalence of autonomic symptoms, cognitive findings, and their correlation with disease parameters in early-stage PD patients following up by our movement disorders clinic.

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METHODS

The study was carried out with the permission of the İstanbul Fatih Sultan Mehmet Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.08.2023, Decision No: 2023/121). All procedures were conducted in compliance with ethical guidelines and adherence to the principles of the Declaration of Helsinki.

The study is a cross-sectional study involving 49 individuals admitted to the neurology outpatient clinic of Fatih Sultan Mehmet Training and Research Hospital in August and September 2023. These individuals had been predicted with PD based on the criteria outlined in the clinical diagnostic criteria of the movement disorder association.[10] A brief anamnesis form was created, encompassing the disease stage, clinical motor score, body mass index (BMI), initial motor syptoms (tremor/bradykinesia), medications used, equivalent dose of levodopa, and disease duration for all patients. In addition to levodopa, the levodopa equivalent daily doses (LEDD) of patients using drugs such as rasagiline and pramipexole were calculated according to Tomlison et al.[11] Disease severity was evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), and the disease stage was determined using the modified Hoehn & Yahr Rating Scale (mHYRS). By the mH&Y scale, only individuals in the early stages of the disease (stage ≤ 2.5) were included in this study.[12]

Individuals diagnosed with atypical/secondary parkinsonism, those with mH&Y stage > 2.5, a history of cerebrovascular disease or brain surgery, those had diabetes mellitus, or those unable to comply with tests, as well as individuals diagnosed with psychiatric disorders or those with cardiac arrhythmias or pacemakers, were not included in the study.

The assessment of autonomic symptoms in Parkinson's patients was performed using the SCOPA-AUT (Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms) scale.[13] The SCOPA-AUT scale consists of 25 items covering various domains of dysfunction, including the gastrointestinal system (7 items), urinary (6 items), cardiovascular (3 items), thermoregulatory (4 items), pupillomotor (1 item), and sexual (2 items for males, 2 items for females). Respondents select from options "never, sometimes, often, and frequently" to answer the questions, and a scoring system ranging from 0 (never) to 3 (frequently) is applied based on these choices. The highest possible total score is 69, with a higher score indicating a more pronounced degree of autonomic dysfunction.

To evaluate patients' cognitive functions, we employed the Turkish version of the Montreal Cognitive Assessment Scale (MOCA-TR). The MOCA-TR assesses various cognitive domains, including visuospatial and executive functions, abstraction, naming, delayed recall, attention, language, and orientation.[14]

Statistical analysis was carried out using IBM SPSS Statistics 23 software, which was provided by IBM SPSS Turkey. To summarize the data, we utilized descriptive methods such as mean, standard deviation, median, frequency, ratio, minimum, and maximum. The normality of data distribution was evaluated using the Shapiro-Wilk Test. In the case of two-group comparisons involving quantitative data with a normal distribution, we employed Student's t-test. We used the Mann-Whitney U Test to compare qualitative data between the two groups. Categorical data were compared using Pearson's Chi-Square test. To examine the relationship between variables, Pearson's correlation was applied. Statistical significance was determined at a significance level of $p<0.05$.

RESULTS

The research encompassed 49 patients, comprising 44% (n=22) females and 56% (n=27) males. The participants' ages ranged from 32 to 84 years, with an average age of 61.5±10.1 years. Comprehensive demographic and clinical findings, including disease duration, LEDD, UPDRS, and mHYRS scores, initial motor syptoms, BMI, MOCA-TR, and SCOPA-AUT scores are detailed in **Table 1**.

Table 1. Clinical characteristics of the patients

	Mean±SD	Median (min-max)
Age	61.5±10.1	62 (32-84)
Sex (F/M)	22 (44%)/27 (56%)	
Duration of disease (years)	5.43±5.04	4 (1-20)
Initial motor syptoms (B/T)	B: 22 (44%)/T: 27 (56%)	
LEDD	550±245	525 (200-1200)
UPDRS	28.4±14.4	23 (8-69)
m H&Y	1.65±0.5	1.50 (1-2.5)
BMI	26.3±3.89	26 (20.8-37.3)
MOCA-TR	21.2±4.9	22 ((9-28)
SCOPA-AUT	18.9±9.36	17 (5-44)

SD: standard deviation, F: female, M: male, LEDD: Levodopa equivalent daily dose,, BMI: Body mass index, B: Bradykinesia, T: tremor, UPDRS: Unified Parkinson's disease rating scale, m H&Y: modified Hoehn and Yahr scale, MOCA-TR: Turkısh version of Montreal Cognitive Assessment scale, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms

The Mean SCOPA-AUT scores were 18.9±9.36, and the most common autonomic symptoms were about the gastrointestinal system. This was followed by the urinary and thermoregulatory systems, respectively. The occurrence of autonomic symptoms is displayed in **Table 2**.

Table 2. Frequency of autonomic symptoms in patients

	Patients (N:49) Mean±SD	Frequency (%)
SCOPA-AUT-Total	18.9±9.36	100%
Gastrointestinal system	5.49±3.37	29%
Urinary	5.18±3.92	27%
Cardiovascular	1.27±1.37	6%
Thermoregulatory	4.69±3.44	24%
Pupillomotor	1.06±1.25	5%
Sexual	1.20±1.66	6%

N: number, SD: standard deviation, SCOPA-AUT: Scales for Outcomes in Parkinson's Diseas for Autonomic Symptoms

The study did not find a statistically significant rate of difference in autonomic symptoms between male and female patients. See in **Table 3**.

Table 3. Comparison of autonomic symptoms in female and male patients

	Female (N:22)	Male (N:27)	p value
SCOPA-AUT-Total	19.73±9.84	18.26±9.09	0.590
Gastrointestinal system	6.05±3.17	5.04±3.51	0.302
Urinary	5.14±4.07	5.22±3.88	0.940
Cardiovascular	1.59±1.30	1.0±1.39	0.133
Thermoregulatory	4.86±3.52	4.56±3.42	0.758
Pupillomotor	1.0±1.23	1.11±1.28	0.760
Sexual	1.0±1.38	1.37±1.86	0.443

*T- test, N: Number, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms

Autonomic symptoms were positively correlated with disease stages (p=.024 r=.322). However, we did not find a relationship between autonomic symptoms and other disease parameters and cognition. See in **Table 4**. We also did not find any relationship between autonomic symptoms and the following areas: visuospatial and executive functions, naming, attention, language, abstraction, delayed recall, and orientation (p>0.05).

While a weak positive correlation was observed between cognition and LEDD, a significant moderate negative relationship was detected between disease stage and cognitive status (p<0.05). This is shown in **Table 5**.

DISCUSSION

We examined autonomic symptoms among early-stage PD patients and explored their connections with disease-related factors and cognitive function. The gastrointestinal system exhibited the highest prevalence of autonomic symptoms. Additionally, a positive correlation was found between the severity of autonomic symptoms and disease stages. No significant relationship was found between autonomic symptoms, other disease parameters, and cognition. However, we did observe a noteworthy inverse correlation between disease stage and cognitive status.

Autonomic dysfunctions, first described by James Parkinson, present with symptoms of constipation, excessive salivation, and urinary incontinence.[15] Histopathological examinations have indicated the presence of Lewy bodies (LB), which are pathological protein aggregates, in various areas of the disease's pathology, including the brainstem, hypothalamus, sympathetic system (thoracic inter mediolateral column and sympathetic ganglia), and parasympathetic system (dorsal, vagal, and sacral parasympathetic nuclei). Additionally, LB has been observed in neural plexuses innervating the adrenal medulla, intestines, heart, and pelvic region.[16] Furthermore, if synuclein pathology impacts the cardiac sympathetic fibers, it may lead to conditions like orthostatic hypotension and postural hypotension. Conversely, exposure to parasympathetic fibers can induce variations in heart rate.[17]

PD patients experience a range of dysautonomia: gastrointestinal issues, cardiovascular irregularities, urinary problems, sexual dysfunction, thermoregulation abnormalities, and pupillomotor abnormalities.[5] Gastrointestinal symptoms are remarkably prevalent in PD, even in the early stages of the condition. Studies indicate that a significant 88.9% of individuals with PD experience gastrointestinal symptoms before the emergence of classic Parkinsonian motor symptoms.[18]

Table 4. Correlation of autonomic symptoms with disease parameters and cognition

	Correlation of SCOPA-AUT						
SCOPA-AUT Total	**Age**	**Duration of disease**	**BMI**	**LEDD**	**UPDRS**	**m H&Y**	**MOCA-TR**
Pearson's r	0.138	0.244	0.205	0.020	0.264	0.322*	0.037
p-value	0.343	0.091	0.158	0.890	0.066	0.024	0.801
N	49	49	49	49	49	49	49

* p < 0.05, LEDD: Levodopa equivalent daily dose, BMI: Body mass index, UPDRS: Unified Parkinson's disease rating scale, m H&Y: modified Hoehn and Yahr scale, MOCA-TR: Turkish version of Montreal Cognitive Assessment scale, SCOPA-AUT: Scales for Outcomes in Parkinson's Disease for Autonomic Symptoms, N: Number

Table 5. Correlation of cognition with disease parameters

Correlation of MOCA-TR						
MOCA-TR	**Age**	**Duration of disease**	**BMI**	**LEDD**	**UPDRS**	**m H&Y**
Pearson's r	-0.092	- 0.157	0.186	0.283*	-0.265	- 0.417*
p-value	0.527	0.281	0.201	0.049	0.066	0.003
N	49	49	49	49	49	49

* p < 0.05, LEDD: Levodopa equivalent daily dose, BMI: Body mass index, UPDRS: Unified Parkinson's disease rating scale, m H&Y: modified Hoehn and Yahr scale, MOCA-TR: Turkish version of Montreal Cognitive Assessment scale, N: Number

The frequency of gastrointestinal symptoms in our study was lower, and this difference may be related to the use of different measurement scales. Two independent research studies, which utilized the same measurement tool as our study (SCOPA-AUT), consistently reported high gastrointestinal and urinary symptoms. Our research results corroborate and support the findings from these studies.[19,20]

A recent study has uncovered a distinct progression of dysautonomia symptoms that appears to be independent of motor disability. In addition, this study included only stage one patients and observed them for three years, yet they associated dysautonomia findings with non-motor symptoms and age.[6] However, we did not find a relationship between autonomic symptoms and parameters such as age, disease severity, disease duration, medication doses, and cognition. We speculate that this discrepancy could be attributed to the cross-sectional design of our research. In a retrospective study of 100 PD patients with autopsy-confirmed diagnoses, researchers found that autonomic dysfunction was linked to certain factors.[7] These factors included older age at the time of PD diagnosis, being male, having a poor initial response to levodopa treatment, and belonging to the motor PD subtype characterized by postural instability and gait difficulty. Additionally, the study revealed that the onset of autonomic dysfunction at an earlier stage of PD was associated with a faster disease progression and reduced survival.[7] Nevertheless, we observed that autonomic symptoms were exclusively linked to the disease stage.

The available literature on the influence of autonomic dysfunction on cognitive function in Parkinson's disease is limited, and the findings are inconclusive.[8,9] In one study, participants were evaluated for postprandial hypotension (PPH), heart rate responses during deep breathing (HR (DB)) and orthostatic hypotension (OH) in addition to the SCOPA-AUT scale.[8] The presence of orthostatic OH or PHP did not show a crucial association with cognition. However, although PD patients with dementia experience more cardiovascular symptoms, no significant association between autonomic manifestations and cognitive decline could be found.[8] In a similar research performed in our country, no relationship was found between autonomic symptoms and cognitive tests.[9] In both studies, Mini-Mental State Exams (MMSE) were utilized for cognitive assessment. However, a comparative investigation suggests that the Montreal Cognitive Assessment Scale (MoCA) is a more effective tool than the MMSE within the PD population.[21] Turkish-validated MOCA scale was used in our study, and although we compared all cognitive domains and autonomic symptoms, we did not find any relation between them. This indicates that the progression of cognitive and autonomic symtoms in PD occurs independently of each other and varies between individual PD. Furthermore, in our study, the degree of cognitive impairment was found to be associated with the disease stage, and our results supported the existing literature.[8,9]

Among the limitations of our study are the absence of a control group, the presentation of cross-sectional data, and the assessment of autonomic symptoms solely based on subjective patient responses.

Its strengths include the investigation of early-stage PD and the use of cognitive assessments with the MOCA-TR test. Particularly, future research would benefit from longitudinal designs that include patients in premotor stages or those who are treatment-naive, incorporate objective data like orthostatic hypotension and PPH, and involve a larger number of participants.

CONCLUSION

Based on our current knowledge, no study has been conducted in our country, particularly in the early stages and newly diagnosed PD patients, that incorporates the frequency of autonomic dysfunction. Detecting and managing these dysfunctions in the early stages would be instrumental in reducing the overall impact of the disease.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the İstanbul Fatih Sultan Mehmet Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.08.2023, Decision No: 2023/121).

Informed Consent: Written informed consent form was obtained from participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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