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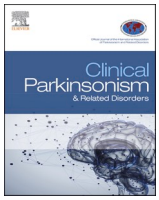

Autonomic dysfunction in progressive supranuclear Palsy: A retrospective study

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ABSTRACT

Objectives: This study aims to investigate the characteristics of autonomic dysfunction in progressive supranuclear palsy (PSP) compared to Parkinson's disease (PD) and multiple system atrophy-parkinsonian type (MSA-P).

Methods: We retrospectively reviewed 128 patients who underwent multidisciplinary team (MDT) intervention at Peking Union Medical College Hospital between March 31, 2021, and November 22, 2023. A total of 16 PSP, 27 MSA-P, and 11 PD patients were included. Autonomic dysfunction was assessed using the SCOPA-AUT scale and medical record data, analyzed with IBM SPSS Statistics 26.

Results: SCOPA-AUT revealed varying degrees of autonomic dysfunction across all groups. The total SCOPA-AUT score was lower in PSP (16.88 ± 6.70) than in MSA-P (23.33 ± 8.80) ($p = 0.019$), but not significantly different from PD (18.64 ± 9.80). All five SCOPA-AUT subscales were affected in PSP, though significant differences were found only in urinary control ($p = 0.006$) and urinary storage ($p = 0.008$) scores between PSP and MSA-P. Orthostatic hypotension was clinically identified in 7.7 % of PSP, 66.7 % of MSA-P, and 27.3 % of PD patients, with a significant difference between PSP and MSA-P ($p < 0.001$). Residual urine volume in MSA-P (137.5 [75.5–190.25] mL) was significantly higher than in PD (34.5 [1.50–60.00] mL, $p < 0.001$) and PSP (9.95 [1.13–56.25] mL, $p < 0.001$).

Conclusions: Our findings indicate that PSP presents with various forms of autonomic dysfunction, as assessed by SCOPA-AUT, with similarities to both MSA-P and PD. Objective measures, such as orthostatic blood pressure assessments and residual urine ultrasound, can provide additional insights into autonomic dysfunction in PSP.

1. Introduction

Patients with Parkinsonian syndrome often have considerable overlap in terms of clinical presentation, leading to difficulties in differential diagnosis. The lack of biomarkers also reflects our insufficient understanding of the pathophysiological mechanisms of the diseases. Progressive supranuclear palsy (PSP) is a sporadic neurodegenerative disease characterized by the accumulation of abnormal tau protein in the brain. The prevalence of PSP in Japan, Europe, and the United States ranges from 2 to 17 cases per 100,000 individuals, with Japan exhibiting a notably higher prevalence [1,2]. The typical manifestations of PSP include walking instability with early falls and vertical ocular movement disorders, which is named as Richardson's syndrome. In fact, a variety of symptoms could be present in PSP, including dystonia, bradykinesia, and cognitive dysfunction, indicating strong clinical heterogeneity. Early prominent autonomic involvement has been traditionally considered an exclusion criterion in the MDS-PSP, as it is typically associated with multiple system atrophy (MSA). However, recent findings have revealed that PSP can also exhibit autonomic involvement [3,4,5,23], leading to a complex situation in clinical differentiation. Therefore, clinical research is necessitated due to the scarcity of literature. This study aims to characterize the autonomic involvement in PSP patients at our center in order to enhance the understanding of PSP.

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2. Data and methods

We retrospectively reviewed the clinical data of 128 patients with Parkinsonian syndrome who underwent multidisciplinary consultation at Peking Union Medical College Hospital from March 31, 2021, to November 22, 2023. A total of 120 patients with SCOPA-AUT score has been screened and 54 patients who met the following inclusion and exclusion criteria has been finally included. (1) Sixteen cases (10 males, 6 females) met the criteria for probable PSP and possible PSP according to the 2017 MDS-PSP[6]; (2)Eleven cases (7 males, 4 females) met the criteria for clinically established or probable PD according to the 2015 MDS criteria[7]; (3) Twenty-seven cases (12 males, 15 females) met the criteria for clinically established or probable MSA-P according to the 2022 MDS criteria[8,9]; (4) All patients were excluded based on clinical manifestations, medical history, and auxiliary examinations for chronic diabetes, cardiac dysfunction, insufficient blood volume, peripheral neuropathy, immune diseases, and autonomic hypotension. Additional exclusion criteria included infection, urinary calculi, urinary system tumors, and organic digestive system diseases.

Table 1 displayed the characteristics of demographic characteristics and disease duration at visit of multidisciplinary consultation, subjective motor scores, and medication. Among the 16 patients, 13 were diagnosed with PSP-RS and 3 with PSP-P. Due to the small sample size, subgroup analysis was not conducted. The MDS-UPDRS Part II (Motor Experiences of Daily Living, M−EDL) and the SCOPA-AUT score were extracted from medical record. Both scales were self-assessed by patients with the presence of family members during multidisciplinary consultations. The M−EDL was utilized to assess motor symptom-related quality of life. The levodopa equivalent dose (LED) of patients was recorded. Given the advanced age of the patients in this group, issues related to sexual function were not assessed.

Table 2 showed the total SCOPA-AUT score, along with individual scores for its five subscales for urinary control, gastrointestinal symptoms, temperature regulation, cardiovascular disease and pupil regulation, were recorded. We further delineated the urinary control function into urine storage and voiding function. Orthostatic hypotension (OH) was confirmed based on typical OH definition [2011Consensus], which a decrease of at least 20 mmHg in systolic and/or 10 mmHg in diastolic blood pressure was detecting on active standing. Fifty patients underwent residual urine volume ultrasound, including 14 patients of PSP, 26 patients of MSA, and 10 patients of PD.

Statistical Analysis: For data following a normal distribution, mean and standard deviation were used for description, otherwise, median and interquartile range were used. Categorical data were described using counts and percentages. ANOVA or Kruskal-Wallis tests were employed for comparing numerical variables, while Chi-square or Fisher's exact tests were used for comparing categorical variables. Bonferroni correction was applied for pairwise comparisons of categorical variables. The significance level was set at 0.05. Data analysis was performed using IBM SPSS Statistics 26.

3. Results

The basic clinical data was present in Table 1. The age, gender, M−EDL were not statistically different among groups. Significant difference could be observed in disease duration on examination(DDE)and LED, which PD patients had longer DDE and higher LED than other groups..

The SCOPA-AUT score of three groups was shown in Table 2 and the proportion was present in attached table. The total SCOPA-AUT scores, as well as sub-score of urinary function were statistically different among groups. SCOPA-AUT score suggested that all patients of three groups exhibited urinary and gastrointestinal involvement. In terms of specific urinary dysfunction, the urinary storage items showed significant difference among groups rather than voiding items. There were no statistical differences in other sub-scale scores. PSP patients exhibited involvement in all five subdomains of SCOPA-AUT, with proportions as follows: urinary dysfunction 100 % (urinary storage 100 %, voiding 87.5 %), gastrointestinal symptoms 100 %, temperature regulation (81.25 %), cardiovascular disease (56.25 %), and pupil regulation (56.25 %). In the MSA group, 100 % of patients experienced urinary dysfunction, with 100 % having storage issues and 96.30 % having voiding problems. Additionally, 100 % reported gastrointestinal symptoms, and 77.78 % had issues with temperature regulation. Cardiovascular problems were present in 74.10 %, while 51.85 % experienced pupil regulation dysfunction. In the PD group, 100 % of patients had urinary dysfunction, with 100 % experiencing storage issues and 72.73 % having voiding problems. Gastrointestinal symptoms were reported by 100 %, while 72.73 % had issues with temperature regulation, 54.55 % had cardiovascular problems, and 54.55 % experienced pupil regulation dysfunction. No significant difference was revealed in the involved proportions among groups.

13 PSP, 27 MSA, and 11 PD patients underwent blood pressure measurements on active standing. There are statistical differences between PSP and MSA, and no statistically difference was found between PSP and PD (Table 3). The median PVR of the three groups were 34.5 (1.50–60.00), 137.5(75.5–190.25) and 9.95 (1.13–56.25), respectively. Significant difference was detected between PSP and MSA ($p < 0.001$), but not observed between PSP and PD.

After adjusting for gender, age, disease duration, LED, and m-EDL, the average SCOPA-AUT scores for PSP, MSA, and PD were 16.52, 23.19, and 18.85, respectively. PSP was significantly lower than MSA ($p = 0.002$), but no significant differences were found between the other two groups. In urinary function, MSA had the highest scores, significantly higher than PSP and PD ($p < 0.001$, $p < 0.05$). MSA also scored higher than PSP in urinary storage ($p < 0.001$) and higher than both groups in voiding ($p < 0.05$). PSP scored lower than MSA and PD in gastrointestinal function ($p < 0.05$, $p < 0.01$). There were no significant differences in cardiovascular, temperature regulation, or pupillary responses. MSA had significantly higher residual urine volume than PSP and PD ($p < 0.001$, $p = 0.002$). Logistic regression showed that the proportion of orthostatic hypotension (OH) in PSP was significantly lower than in MSA ($p = 0.005$), with no significant differences between the other two groups.

Table 1
Basic information of the patients in this group.

	PSP	MSA −P	PD	F / Z / X^2	P
Number of cases (%)	16(29.60)	27(50.00)	11(20.40)		
Age(year)	69(64.50–72.00)	63(59.00–68.00)	72(57.00–77.00)	5.734	0.057
Male cases (%)	10(62.50)	12(44.40)	7(63.60)	1.865	0.393
DDE (year)	4(2.60–5.40)	3(2.00–4.50)	6.0(5.00–8.00)	14.411	0.001*
M−EDL	21.00(15.25–26.00)	23.00(14.00–40.00)	17.00(11.00–32.00)	1.462	0.482
LED(mg)	412.50(336.25–668.75)	400.00(225.00–612.50)	650.00(500.00–807.00)	6.788	0.034*

Note: The findings are reported as median (interquartile range) for continuous variables and as counts (%) for categorical variables. *$p < 0.05$, **$p \leq 0.001$. M−EDL: Motor Experiences of Daily Living; LED: Levodopa equivalent dose; PSP: progressive supranuclear palsy; PD: Parkinson's disease; MSA-P: multiple system atrophy-parkinsonian type; DDE:Disease duration on examination.

Table 2
Scale scoring and objective examination.

	PSP	MSA-P	PD	F / Z / X 2 values	P
SCOPA-AUT Total score	16.88 ± 6.70	23.33 ± 8.80	18.64 ± 9.80	3.253	0.047*
Cardiovascular	1.00(0.00–1.75)	1.00(0.00–2.00)	1.00(0.00–3.00)	2.099	0.350
Urine control function	5.50(3.00–9.00)	11.00(7.00–15.00)	4.00(3.00–11.00)	12.494	0.002**
Urinary storage items	4.00(2.25–5.00)	7.00(4.00–10.00)	3.00(1.00–7.00)	12.005	0.002**
Urinary voiding items	2.00(1.00–4.00)	3.00(2.00–5.00)	2.00(1.00–4.00)	5.604	0.061
Gastrointestinal	3.00(2.00–5.00)	4.00(3.00–7.00)	6.00(2.00–7.00)	5.501	0.064
Temperature regulation	3.00(2.00–5.75)	2.00(1.00–4.00)	2.00(0.00–3.00)	1.889	0.389
Pupils	1.00(0.00–1.75)	1.00(0.00–1.00)	1.00(0.00–1.00)	0.264	0.876
OH (%)	1(7.70)	18(66.70)	3(27.30)	13.881	0.001**
PVR(ml)	34.5(1.50–60.00)	137.5(75.5–190.25)	9.95(1.13–56.25)	22.770	<0.001***

Note: Results are expressed as mean ± standard deviation, median (interquartile spacing), example (%).*p < 0.05, **p < 0.01, ***p < 0.001.OH: orthostatic hypotension; PVR: post-void residual urine volume.

4. Discussion

It is generally believed that autonomic dysfunction is a common feature of α-synucleinopathy. However, recent studies reported that autonomic involvement could be observed in PSP patients [3]. Therefore, we retrospectively analysis the data of parkinsonian patients who underwent MDT consultation in our center. We found that autonomic involvement with varying degrees could be recognized through autonomic spectrums both subjectively and objectively. To our best knowledge, this is the first retrospective study on autonomic involvement in PSP in China.

Regarding the possible mechanisms of autonomic involvement in PSP, previous neuropathological studies provided evidence of preganglionic involvement, including severe involvement of the reticular formation in the brainstem and the giant cell reticular nucleus neuron cell skeleton [9], as well as severe cell loss, presence of neurofibrillary tangles, neuropil threads, and glial inclusions in Onuf's nucleus of the sacral cord [10]. Hidetomo Tanaka and his colleagues found that peripheral nerves, particularly in PSP, exhibit 4R and p-tau deposits with seeding capacity, which may explain the autonomic dysfunction in PSP [11]. Additionally, postganglionic neurons and factors such as age, medications, and diet may also play a role [3]. Autonomic involvement in PSP can manifest in various aspects of the autonomic nervous system, but previous studies have drawn different conclusions regarding the proportion and extent of autonomic involvement in PSP [3]. Subjective symptoms do not always match objective examination results [12,13], possibly due to differences in assessment methods, inclusion criteria, medication therapy, etc. SCOPA-AUT [13,14] is a useful tool for quantitatively analyzing autonomic symptoms in various types of Parkinsonian syndromes, comprehensively assessing cardiovascular, gastrointestinal, genitourinary, pupillary, and thermoregulatory aspects. Both the SCOPA-AUT scale and objective examinations were collected to evaluate the autonomic impairment of our patients.

Our results showed that the SCOPA-AUT total score in PSP was significantly lower than in MSA-P patients, but similar to that of PD. Previous study applied SCOPA-AUT in different stages of PD and found that the scores increased with the severity of the disease, which were 16.5, 19.8, and 21.4 in H-Y I-II, H-Y III and H-Y IV-V [14]. The mean score of our PD patients (18.6) was close to that of advanced stage mentioned above (H-Y III), which was in accord with the fact that patients with more severe condition would enter MDT procedure in our center. Therefore, although there was no significant difference in SCOPA-AUT total scores between PSP and PD, our results suggested the degree of autonomic manifestation in PSP was generally comparable to that of advanced stage of PD. A few studies have assessed the SCOPA-AUT scale among patients with PD, MSA and PSP. Berganzo K and his colleagues [13] similarly assessed three groups of patients with SCOPA-AUT, and suggested that the score of PSP was not significantly different from the other two groups. Dubbioso R and his colleagues found that PSP patients had higher SCOPA-AUT total scores than PD [12]. Our results were in consistent with previous studies which demonstrate that the autonomic dysfunction was not rare in PSP.

OH is a common symptom of autonomic cardiovascular impairment. Clinical manifestations include a variety of symptoms of, such as dizziness, blurred vision, syncope, and coat-hanger sign, depending on the hypoperfusion of specific location. The involvement in PSP was inconsistent due to different measurement previously. Orthostatic symptoms investigated by questionnaires were reported by 20–50 % of PSP patients and by 13 % on structured interview [3]. Van Gerpen [15] JA did not find OH in 14 cases of PSP assessed by formal autonomic testing. Data from a pathologically confirmed PSP cohort (104 patients) reported the prevalence of symptomatic OH or recorded data was only 9 % [16]. Our study found that the autonomic cardiovascular symptoms could be revealed in 56.25 % of PSP, 74.1 % of MSA-P and 54.55 % of PD by SCOPA-AUT. However, OH was detected in only 7.7 % of PSP, 66.7 % of MSA-P and 27.3 % of PD when evaluating at office. Thus, we postulated that SCOPA-AUT might overestimate the presence of OH, which has been suspected by previous study [3]. OH could also be induced by dopaminergic medication [17]. Therefore, we evaluated the LED and found the median LED was 412.50 mg for PSP, 400.00 mg for MSA-P and 650.00 mg for PD, which was not in parallel to the proportion of OH, making drug-induced OH unlikely. In addition to orthostatic hypotension, studies [3,18–20] have investigated objective parameters such as blood pressure drop after postural changes, blood pressure response to Valsalva maneuver and isometric exercise, heart rate variability during Valsalva maneuver and deep breathing test, plasma catecholamine levels, and cardiac sympathetic nerve imaging in PSP, with inconsistent conclusions, but severe sympathetic and parasympathetic function test results have not been reported.

In contrast to the uncertainty of autonomic cardiovascular symptoms, all the PSP patients in our study had symptoms of urinary dysfunction, including storage problems such as frequency, urgency, urinary incontinence, nocturia, and voiding problems such as difficulty urinating and thinning of urine flow, in different combinations. Previous urodynamic studies in patients with PSP suggested hyperactive detrusor reflex, which may explain the prevalent impairment of storage function in our study [21,22]. Nojszewska M, Vichayanrat E found some evidence suggesting bladder dysfunction particularly in the storage phase [23,24]. In our study, the median score for storage function in PSP patients was higher than that for voiding function, suggesting that storage problems were more impaired than voiding difficulties, consistent with previous research results. Significant differences were found in total scores of urinary control function and storage function items among the groups, rather than voiding function items, indicating that subjective symptoms of voiding dysfunction were similar among the three groups, but storage dysfunction symptoms were more prominent in MSA-P. Our results was inconsistent with previous study, which suggested that voiding dysfunction in PSP appears to be closer to MSA but more severe than PD; storage dysfunction among the three is similar [25]. Among the three groups, MSA had the highest residual urine volume, which was

Table 3
Statistical values of pairwise comparisons.

	OH		PVR		Urine control function		Urinary storage items		Age		DDE		SCOPA-AUT Total score		LED	
	X2	P	H	P	H	P	H	P	H	P	H	P	P		H	P
PSP vs MSA	12.238	< 0.001***	−18.780	< 0.001***	−15.193	0.006**	−14.87	0.008**	12.879	0.033*	6.167	0.213	0.019*		5.549	0.790
PSP vs PD	0.537	0.300	2.043	0.735	−0.293	1.000	−0.318	1.000	4.227	1.000	−15.136	0.014*	0.597		−9.017	0.429
PD vs MSA	3.442	0.064	20.835	< 0.001***	14.901	0.024*	14.552	0.028*	−8.652	0.401	−21.303	< 0.001***	0.127		−14.566	0.029*

*p < 0.05, **p < 0.01, ***p < 0.001. LED: Levodopa equivalent dose; PSP: progressive supranuclear palsy; PD: Parkinson's disease; MSA-P: multiple system atrophy-parkinsonian type; DDE:Disease duration on examination. OH: orthostatic hypotension; PVR: post-void residual urine volume.

statistically different from PD and PSP, but there was no significant difference between PSP and PD, suggesting that the severity of residual urine in PSP may be similar to that in PD. Additionally, a large amount of residual urine was only observed in MSA.

About 40–89 % PSP patients would have digestive system involvement [26,27], manifesting as dysphagia, esophageal motility disorders, gastric emptying slowness (gastric palsy, bloating, nausea, and vomiting), and intestinal problems (constipation, diarrhea), among which constipation and dysphagia being the most frequent [3,16]. The subscore of digestive system involvement among the three groups in this study showed no statistically significant difference. There were few studies on the digestive system involvement in PSP. Warnecke T et al. studied swallowing disorders in PSP patients using swallow video fluoroscopy and found that oral phase disorders were more pronounced than pharyngeal phase, suggesting a possible association with the control of complex voluntary movements rather than autonomic nerves [22]. The pathological mechanism of digestive system involvement is currently unclear, as pathological studies have not found tau accumulation in the enteric nervous system, unlike α-synucleinopathies such as PD [28].

The sweat glands of the skin are innervated by cholinergic sympathetic nerve fibers, mainly responsible for temperature regulation. The subjective scale scores in this study indicated that 13/16 (81.3 %) PSP patients had temperature regulation disorders, higher than the results of previous studies (59 % of PSP patients had sweating disorders[29]). There was no statistically significant difference in the severity between the three groups, consistent with most previous studies [13,29]. In previous studies, sweat secretion function tests commonly used quantitative sudomotor axon reflex test (QSART) and thermoregulatory sweat test (TST) to evaluate sweat function. The composite autonomic symptom scale (CASS), age, and sex corrected, is more commonly used in the assessment of sweat function. Through tests and scales, approximately half of PSP patients reported symptoms of sweat dysfunction [15,30], indicating the need for more attention to temperature regulation function in PSP patients.

Pupillary light reflex reflects autonomic function and is the response of pupillary constriction to light, which is mainly controlled by parasympathetic nerves and can occur in various diseases with autonomic involvement. In this study, 1/2 of PSP patients had symptoms of light sensitivity to strong light, with no significant difference in severity between the three groups. Photophobia is more common in PSP patients and is also supportive of the diagnosis of MDS-PSP. This symptom seems to be more common in PSP-RS [3] and less common in other phenotypes. Dubbioso R and his colleague [12] found that about half (41 %) of PSP patients had pupillary motor dysfunction, with a higher incidence of PSP pupillary motor dysfunction than PD (41 % vs. 9 %). There have been few experiments measuring pupil diameter in the past, and studies have suggested that 70 % of PSP patients have pathological pupil diameters in at least one eye after dark adaptation, significantly higher than PD and MSA [31]. Habibi M et al. observed changes in pupil constriction or dilation by adjusting screen brightness in PSP patients and found that the magnitude of pupil changes in PSP patients was smaller than that in the normal control group, while MSA patients was the opposite [32]. It is clinically necessary to pay more attention to patient pupils and light responses, and more experiments are needed to evaluate the value of pupil response in the classification of PSP.

There were some limitations of this study. Firstly, patients participating MDT consultation may have more severe or complicated diseases, leading to a less representative of the PSP patient. Secondly, sexual function items were neglected, due to the advanced age of the patients, which made the assessment incomplete. Third, there were certain differences in the age and disease duration among the three groups, and although M−EDL compensated to some extent, this may still have an impact on the results of the study. Lastly, the sample size of this study was small, so clinical classification of PSP was not performed. In addition, there is an absence of pathological validation and few objective examinations had been applied except for residual urine amount. More

assessment would be suggested, such as urodynamic study, swallow video fluoroscopy, et al. to quantitatively evaluate the autonomic dysfunction in PSP. While the sample size and the limited use of objective assessments are acknowledged as potential limitations, these aspects also present opportunities for future research to build upon these findings and further explore this important area.

In conclusion, this study is the first in China to compare the autonomic involvement of PSP, MSA-P, and PD, suggesting that various forms of autonomic dysfunction could be detected in patients with PSP by SCOPA-AUT scale. Some of the subscales were not significantly different from MSA-P and PD, suggesting the autonomic dysfunction in PSP might be as common as PD. Urinary dysfunction could offer valuable information for enhancing our understanding of PSP and merits further research in the future.

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CRediT authorship contribution statement

Yichun Wang: Validation, Supervision, Methodology. **Manqing Xie:** Writing – review & editing, Supervision, Formal analysis. **Dan Xu:** Writing – review & editing, Supervision, Formal analysis. **Yanhong Wang:** Validation, Supervision, Methodology. **Han Wang:** Validation, Supervision, Methodology.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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