Cognition and transcranial sonography in Parkinson’s disease patients with or without orthostatic hypotension

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Abstract

Background: Orthostatic hypotension (OH) is a common nonmotor symptom in patients with Parkinson’s disease (PD), with an incidence ranging from 14% to 54%.

Aims: This study explored changes in cognition and transcranial sonography (TCS) findings in patients with PD and OH.

Methods: We enrolled PD patients who visited the outpatient or inpatient department from 2017 to 2020. Blood pressure was measured in different positions, and demographic data were collected. Motor and nonmotor symptoms were evaluated using standard scales. A subset of 107 patients underwent TCS.

Results: We enrolled 66 PD-OH patients and 92 PD-no orthostatic hypotension (NOH) patients. There were no significant differences in gender, age, disease duration, or Hoehn and Yahr stage between groups. Binary logistic regression revealed age as an independent risk factor for OH in PD patients. There were statistically significant group differences in visuospatial and executive function and Unified Parkinson’s Disease Rating Scale (UPDRS) I and II scores (p < .05). Among PD-OH patients, there was a statistically significant difference in UPDRS II and III scores between patients with or without clinical symptoms (p < .05). The substantia nigra (SN) area was significantly larger in PD-NOH patients (0.45 ± 0.18 cm²) than PD-OH patients (0.34 ± 0.16 cm²) (p < .05).

Conclusions: PD-OH patients had poorer visuospatial and executive function and lower UPDRS I and II scores compared with PD-NOH patients. Within the PD-OH group, there was no significant difference in cognition between patients with or without clinical symptoms. The difference in the SN area may indicate different subtypes of PD or a tendency to develop parkinsonism syndrome.

KEYWORDS
Cognition, orthostatic hypotension, Parkinson’s disease, transcranial sonography
Orthostatic hypotension (OH) is a nonmotor symptom in Parkinson’s disease (PD) that is more common in advanced stages of the disease. OH reflects autonomic nervous system dysfunction, and the prevalence in PD is about 53% (Zhang et al., 2019). This condition is associated with many other nonmotor symptoms such as lightheadedness and fatigue (Xin et al., 2016). Lewy bodies are a pathologic biomarker of PD, and alpha-synuclein is an important component of these proteinaceous aggregates. Alpha-synuclein is deposited in both the central nervous system and peripheral autonomic nervous system. Central and peripheral baroreflex mechanisms are damaged in PD-OH patients (Freeman et al., 2018; Goldstein et al., 2005). Levodopa, dopamine and peripheral baroreflex mechanisms are damaged in PD-OH patients. We excluded PD patients who were taking the other chronic medications. This study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University.

2 | METHODS

2.1 | Participants

A total of 158 PD patients treated at the Second Affiliated Hospital of Soochow University from 2017 to 2020 were included in the study. All patients were diagnosed with PD according to the diagnostic criteria of the UK Parkinson’s Disease Society Brain Bank by at least two neurologists (Hughes et al., 1992). Of these, 107 patients underwent TCS. We excluded PD patients who were taking the other chronic medications. This study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University.

2.2 | Study design

This was a cross-sectional study. We used a corrected electronic sphygmomanometer to measure BP. Measurements were taken after 5 min in a supine position and 3 min in an orthostatic position. OH was defined as a decrease of at least 20 mm Hg in systolic BP (SBP) and/or 10 mm Hg in diastolic BP (DBP) within 3 min from shifting from the supine to upright position. Upright mean blood pressure (MBP) < 75 mm Hg is highly specific and sensitive for identifying symptomatic OH (Palma et al., 2015). According to OH and MBP, we divided patients into three groups: including PD patients without OH (PD-[neurogenic orthostatic hypotension] NOH), asymptomatic PD-OH, and symptomatic PD-OH. Demographic data were collected for all patients.

PD-related symptoms were evaluated by trained clinicians. Cognition was evaluated with the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA) including visuospatial/executive functions, naming, attention, learning, abstraction, delayed verbal memory, and orientation. Motor symptoms were assessed with the Unified Parkinson’s Disease Rating Scale (UPDRS III). Nonmotor symptoms were evaluated by nonmotor symptom questionnaire (NMSQ). Emotional problems were measured with the Hamilton Depression Scale (HAMD)–24 items and the Hamilton Anxiety Scale (HAMA)–14 items. Daily life was assessed with the UPDRS II and Parkinson’s Disease Quality of Life Questionnaire (PDQL)–39. Fatigue was measured with the Fatigue severity scale (FSS).

TCS was performed as previously described (Sheng et al., 2017). It is according to the standardized procedure of TCS in neurodegenerative diseases established on the Ninth Meeting of the European Society of Neurosonology and Cerebral Hemodynamics (Berg et al., 2008; Walter, Behnke, et al., 2007). A 2.5-MHz sonographic device (Sequoia 512, Siemens Medical Solutions USA, Inc. 4V1C transducer) was used to detect both temporal bone windows. Poor temporal bone windows prevented us from detecting the image. As a result, patients with poor temporal bone windows were excluded. Reports were finished and confirmed by sonologists who received uniform training. They were blinded to the clinical diagnosis and assessment. We recorded middle cerebral artery velocity and resistance of the artery, third ventricle (V3) width, and level and area of the SN.
### Table 1  
Basic statistics and motor and non-motor symptom evaluation of the Parkinson’s disease-orthostatic hypotension (PD-OH) and PD-no orthostatic hypotension (NOH) groups

|                          | PD-OH (n = 66) | PD-NOH (n = 92) | p value |
|--------------------------|----------------|----------------|---------|
| Male (%)                 | 46/66 (69.7%)  | 59/92 (64.1%)  | .465    |
| Age (years)              | 67.18 ± 7.95   | 63.20 ± 12.07  | .063    |
| Duration (years)         | 7.41 ± 4.21    | 6.27 ± 3.98    | .102    |
| H-Y stage                | 2.42 ± 0.73    | 2.27 ± 0.96    | .072    |
| Recumbent systolic pressure (mm Hg) | 140.26 ± 18.07 | 123.40 ± 12.33 | .000*   |
| Recumbent diastolic pressure (mm Hg) | 75.18 ± 12.38 | 75.20 ± 10.18  | .540    |
| Orthostatic systolic pressure (mm Hg) | 106.02 ± 21.53 | 128.37 ± 15.08 | .000*   |
| Orthostatic diastolic pressure (mm Hg) | 64.79 ± 12.60 | 79.85 ± 9.72   | .000*   |
| Orthostatic mean arterial pressure (mm Hg) | 78.45 ± 13.33 | 95.07 ± 10.21  | .000*   |
| MMSE                     | 25.98 ± 4.03   | 26.12 ± 3.69   | .838    |
| MoCA                     | 20.61 ± 5.33   | 21.91 ± 4.84   | .126    |
| Visuospatial/executive functions | 2.61 ± 1.54   | 3.21 ± 1.47    | .018*   |
| Naming                   | 4.92 ± 1.30    | 2.58 ± 0.67    | .961    |
| Attention                | 4.92 ± 1.30    | 5.04 ± 1.15    | .700    |
| Learning                 | 1.74 ± 0.92    | 1.87 ± 0.99    | .334    |
| Abstraction              | 1.02 ± 0.64    | 1.16 ± 0.80    | .169    |
| 5-Minute delayed verbal memory | 2.18 ± 1.80   | 2.29 ± 1.71    | .664    |
| Orientation              | 5.62 ± 0.91    | 5.76 ± 0.52    | .811    |
| UPDRS I                  | 4.36 ± 2.26    | 3.5 ± 2.16     | .240    |
| UPDRS II                 | 14.26 ± 6.91   | 12.03 ± 6.23   | .047*   |
| UPDRS III                | 27.08 ± 14.74  | 25.37 ± 12.26  | .543    |
| NMSQ                     | 10.59 ± 5.42   | 9.24 ± 6.07    | .061    |
| FSS                      | 3.16 ± 1.80    | 3.16 ± 2.41    | .616    |
| HAMA                     | 10.42 ± 7.87   | 9.51 ± 7.32    | .455    |
| HRSD                     | 11.03 ± 8.44   | 11.62 ± 9.88   | .913    |
| PDQ-39                   | 37.16 ± 22.77  | 31.51 ± 23.49  | .091    |

*Note: Values are reported as the mean ± standard deviation (SD).

*p < .05 was considered statistically significant.

Abbreviations: FSS, Fatigue Severity Scale; H-Y, Hoehn and Yahr; HAMA, Hamilton Anxiety Scale; HRSD, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NMSQ, Non-Motor Symptoms Questionnaire; PDQ-39, Parkinson’s Disease Questionnaire; UPDRS, Unified Parkinson’s Disease Rating Scale.

### 2.3 Statistical analysis

We used SPSS IBM SPSS Statistics (Version 25.0. Armonk, NY: IBM Corp) for all statistical analyses. If continuous variables were normally distributed, independent sample t-tests were used; Mann–Whitney U tests were performed to analyze continuous variables, and these were not normally distributed. Binary logistic regression analysis was carried out to identify independent risk factors. Differences were considered significant at p < .05.

### 3 RESULTS

Among the 158 PD patients in the study, 66 (41.8%) had OH and 92 (58.2%) patients did not. The PD-OH group had significantly higher supine systolic pressure (SSP), orthostatic systolic pressure (OSP), orthostatic diastolic pressure (ODP), and orthostatic mean arterial pressure (OMAP) (all p < .05). The PD-OH and PD-NOH groups did not differ in gender, age, duration, or disease stage (all p > .05, Table 1).

Patients with OH tended to have lower scores in visuospatial/executive functions and UPDRS II compared with the PD-NOH group (p < .05). There were no significant differences in other evaluations of motor and nonmotor symptoms including MMSE, MoCA (naming, attention, learning, abstraction, 5-minute delayed verbal memory), UPDRS I, UPDRS III, NMSQ, FSS, HAMA, Hamilton Rating Scale for Depression (HRSD), and PDQ-39 (all p > .05, Table 1). We performed binary logistic regression to identify independent variables associated with the presence of OH. The results showed that age was an independent risk factor for OH (p = .04, odds ratio = .963; Table 2).
was no correlation between the extent of BP difference and cognitive function.

In the PD-OH group, 12 (18.18%) patients had symptomatic OH. There were no differences in age, gender, duration, or H-Y stage between subjects with asymptomatic and symptomatic OH (p > .05). However, patients with symptomatic OH tended to have lower level of SN. This result partially overlaps with our conclusion. Another study found that executive function was reduced in the upright position (Sforza et al., 2018), which is consistent with our results.

The reasons underlying cognitive decline in PD-OH patients is currently unclear. One hypothesis is that central and peripheral noradrenergic dysfunction may lead to cognitive deficits. Hypothalamus damage has been reported in PD patients (Langston & Forno, 1978). This structure is the integration center of the autonomic nervous system and is under the influence of the limbic system (Blessing, 1997). This may explain why executive functions were impaired in PD-OH patients.

Other studies have shown that hyperperfusion and hypotension may cause ischemic damage to subcortical structures (McDonald et al., 2016). Another group reported that cognitive impairment is associated with more white matter hyperintensities on magnetic resonance imaging (Kim et al., 2012). This is consistent with our findings: PD-OH patients had higher SSP and lower OSP and ODP, and ischemic damage may affect executive function.

SN hyperechogenicity >0.20 cm² is considered as a cut-off point to detect PD (Chitsaz et al., 2013), but we found higher values in both groups in our study (PD-OH: 0.34 cm², PD-NOH: 0.45 cm²). PD-OH patients showed smaller SN hyperechogenic areas. This may indicate that different clinical subtypes of PD are associated with different SN patterns (Walter, Dressler, et al., 2007). Patients with postural instability and gait difficulty have larger SN hyperechogenicity areas on TCS (Sheng et al., 2017), so it is possible that PD patients with OH have smaller SN hyperechogenicity areas. TCS can also be used to diagnose Parkinsonism. It is reported that the frequency of SN hyperechogenicity in nontremor dominant PD patients was significantly higher than in patients with multiple system atrophy (MSA) with predominant parkinsonism (Zhou et al., 2018). PD-OH may be more likely to convert to MSA. The early presence of OH is a Movement Disorder Society clinical diagnostic criterion for PD (Postuma et al., 2015). Measuring the SN area may help us distinguish Parkinson’s disease from PD. However, it is not clear why the SN becomes hyperechogenic. Two studies reported that increased cellular iron and neuromelanin contents and microglia are associated with SN hyperechogenicity (Berg et al., 2010; Tribl et al., 2009). This may suggest different mechanisms underlying PD and PDS.

Our results should be considered in the context of its limitations. First, this was a cross-sectional study, so when OH develops in patients with PD is not clear. Since we did not follow up for patient outcomes,
### TABLE 3  Basic statistics and motor and non-motor symptoms evaluation of symptomatic orthostatic hypotension (OH) and asymptomatic OH

|                     | Symptomatic OH (n = 12) | Asymptomatic OH (n = 53) | p value |
|---------------------|-------------------------|--------------------------|---------|
| Male (%)            | 3/12 (25.0%)            | 17/53 (32.1%)            | .894    |
| Age (years)         | 68.42 ± 2.76            | 66.91 ± 1.04             | .556    |
| Duration (years)    | 7.66 ± 1.01             | 7.35 ± 0.59              | .641    |
| H-Y stage           | 2.75 ± 0.23             | 2.35 ± 0.09              | .098    |
| Recumbent systolic pressure (mm Hg) | 140.33 ± 3.55          | 140.24 ± 2.61            | .987    |
| Recumbent diastolic pressure (mm Hg) | 67.33 ± 3.32          | 76.92 ± 1.63             | .010*   |
| Orthostatic systolic pressure (mm Hg) | 75.25 ± 2.01           | 112.85 ± 2.34            | .000*   |
| Orthostatic diastolic pressure (mm Hg) | 48.25 ± 2.70          | 68.46 ± 1.37             | .000*   |
| MMSE                | 24.41 ± 1.73            | 26.33 ± 0.47             | .225    |
| MoCA                | 18.25 ± 1.36            | 21.12 ± 0.73             | .056    |
| Visuospatial/executive functions | 2.41 ± 0.43           | 2.64 ± 0.21              | .615    |
| Naming              | 2.50 ± 0.19             | 2.51 ± 0.11              | .599    |
| Attention           | 4.41 ± 0.36             | 5.03 ± 1.77              | .051    |
| Learning            | 1.33 ± 0.22             | 1.83 ± 0.12              | .072    |
| Abstraction         | 1.00 ± 0.21             | 1.02 ± 0.86              | .932    |
| Delayed verbal memory | 1.50 ± 0.50            | 2.33 ± 0.24              | .132    |
| Orientation         | 5.08 ± 0.45             | 5.74 ± 0.09              | .131    |
| UPDRS1              | 5.08 ± 0.60             | 4.20 ± 0.31              | .211    |
| UPDRSII             | 19.08 ± 1.65            | 13.19 ± 0.91             | .003*   |
| UPDRSIII            | 33.91 ± 3.10            | 25.56 ± 2.06             | .016*   |
| NMSQ                | 12.33 ± 1.47            | 10.20 ± 0.74             | .205    |
| FSS                 | 3.49 ± 0.59             | 3.08 ± 0.23              | .538    |
| HAMA                | 12.58 ± 2.78            | 9.94 ± 1.01              | .449    |
| HRSD                | 13.58 ± 3.63            | 10.46 ± 0.99             | .532    |
| PDQ-39              | 40.00 ± 6.91            | 36.54 ± 3.08             | .594    |

Note: Values are reported as the mean ± standard deviation (SD).
Abbreviations: FSS, Fatigue Severity Scale; H-Y, Hoehn and Yahr; HAMA, Hamilton Anxiety Scale; HRSD, Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NMSQ, Non-Motor Symptoms Questionnaire; OH, orthostatic hypotension; PDQ-39, Parkinson’s Disease Questionnaire; UPDRS, Unified Parkinson’s Disease Rating Scale.

*p < .05 was considered statistically significant.

### TABLE 4  Transcranial sonography results in the Parkinson’s disease-orthostatic hypotension (PD-OH) and PD-neurogenic orthostatic hypotension (NOH) groups

|                     | PD-OH (n = 33) | PD-NOH (n = 40) | p value |
|---------------------|---------------|----------------|---------|
| Middle cerebral artery velocity (cm/s) | 68.93 ± 18.90 | 77.17 ± 20.15 | .540    |
| Resistance          | 0.58 ± 0.08   | 0.61 ± 0.06    | .119    |
| Third ventricle width (cm) | 0.63 ± 0.19    | 0.60 ± 0.20    | 1.000   |
| Level of the substantia nigra | 3.00 ± 0.00    | 3.00 ± 0.00    | -       |
| Area of the substantia nigra (cm²) | 0.34 ± 0.16    | 0.45 ± 0.18    | .009*   |

Values are reported as the mean ± standard deviation (SD).

*p < .05 was considered statistically significant.
the long-term evolution of OH in PD remains unknown. Second, we did not adjust for dopaminergic therapy, which may influence cognitive function (McDonald et al., 2016). These therapies may also impact the presence and severity of OH, although one study reported that levodopa use was not significantly different between PD-OH and PD-NOH patients (McDonald et al., 2016).

5 | CONCLUSION

In this study, age was an independent risk factor for OH in PD. The presence of OH had no influence on cognition. Only 31% of PD patients who meet OH diagnostic criteria are symptomatic (Palma et al., 2015). As a result, symptoms cannot be the only indicators to screen for OH. We often ignore asymptomatic OH in our clinical work, underscoring the need to test for OH in PD patients without symptoms. Treatment of neurogenic OH remains challenging because of the lack of clinical studies. Interventions must be applied in early stages of disease to improve cognition. TCS results were different between the PD-OH and PD-NOH groups, and the presence of OH may help distinguish different subtypes of PD or PDS. Further studies are necessary to confirm these findings.

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CONFLICT OF INTEREST

There is no conflict of interest to be disclosed.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

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