RESEARCH ARTICLE

Association Between Orthostatic Hypotension and Dementia in Patients With Parkinson Disease and Multiple System Atrophy

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Neurology® 2023;100:e998-e1008. doi:10.1212/WNL.0000000000201659

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Abstract

Background and Objectives
Orthostatic hypotension (OH) increases dementia risk in patients with Parkinson disease (PD), although the underlying mechanisms and whether a similar association between OH and cognitive impairment exists in other synucleinopathies remain unknown. The aim is to evaluate the association between OH and dementia risk in patients with PD, and cognitive impairment risk in patients with multiple system atrophy (MSA), and to explore relevant clinical and neuropathologic factors to understand underlying pathogenic mechanisms.

Methods
This is a retrospective cohort study. Medical records throughout the entire disease course of consecutive patients with neuropathology-confirmed PD and MSA from the Queen Square Brain Bank were systematically reviewed. Time of onset and severity of OH-related symptoms were documented, and their association with other clinical and neuropathologic variables was evaluated. Dementia risk for patients with PD and cognitive impairment risk for patients with MSA were estimated using multivariable hazard regression.

Results
One hundred thirty-two patients with PD and 137 with MSA were included. Patients with MSA developed OH more frequently, earlier in the disease course and with more severe symptoms. Cumulative dementia prevalence was higher in patients with PD. Multivariable adjusted regression models showed that early OH, but not its symptom severity, increased dementia risk in patients with PD by 14% per year (hazard ratio [HR] = 0.86; 95% CI, 0.80–0.93) and cognitive impairment risk in patients with MSA by 41% per year (HR = 0.59; 95% CI, 0.42–0.83). Early OH was not associated with increased α-synuclein, β-amyloid, tau, Alzheimer, or cerebrovascular pathologies. No significant associations were found between severity of OH symptoms and other clinical or neuropathologic variables.

Discussion
Early OH, but not its symptom severity, increases the risk of cognitive impairment in patients with PD and MSA. OH is not associated with more extensive Lewy, β-amyloid, tau, Alzheimer, or cerebrovascular pathologies. It is likely that OH contributes to cognitive impairment in patients with PD and MSA by hypoxia-induced nonspecific neurodegeneration. Further research should evaluate whether improving brain perfusion by treating OH may modify the risk of dementia in these conditions.

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Glossary

HR = hazard ratio; **OH** = orthostatic hypotension; **PD** = Parkinson disease; **MSA** = multiple system atrophy; **SH** = supine hypertension.

Orthostatic hypotension (OH) is one of the most common manifestations of Parkinson disease (PD) and can present at early stages.[1] A growing body of evidence suggests that there is an association between OH and increased dementia risk in patients with PD.[2,3] Therefore, OH could be a potential modifiable risk factor for cognitive impairment in patients with PD.[4] However, the pathogenic mechanisms linking both conditions are complex and remain poorly understood.[3] This association is independent of other autonomic symptoms, and it is present even in asymptomatic OH,[5] suggesting a causative link rather than shared neuroanatomical basis or a more diffuse neuropathologic involvement. OH has shown to cause impairment in cerebral blood supply, and the most accepted hypothesis is that chronic hypoxia secondary to repeated episodes of cerebral hypoperfusion would lead to increased vascular lesions and synergistic neurodegeneration resulting in cognitive impairment.[2,3] OH correlates with severity of white matter hyperintensities on magnetic resonance, which are a presumed imaging marker of small vessel disease independently associated with cognitive impairment in patients with PD.[6,7] Moreover, additional studies have shown that OH can be associated with imaging markers of neurodegeneration, such as anterior temporal and mediotemporal atrophies on MRI,[8] and with increased CSF neurofilament light chain levels, a nonspecific marker of neuronal damage.[9]

OH is one of the diagnostic features of multiple system atrophy (MSA), and its associated symptoms are more prevalent and usually more severe than in patients with PD.[10] OH has been associated with reduced survival in patients with pathologically proven MSA.[11] Despite OH being more prevalent and symptomatic, dementia in patients with MSA is rarer and was initially regarded as a feature to reconsider diagnosis. Recent studies showed that <30% of patients with MSA confirmed neuropathologically showed cognitive impairment with a pattern of frontal executive dysfunction similar to patients with PD and PSP that can be present at early stages.[12,13] Cognitive deficits in patients with MSA remain poorly characterized, and whether OH increases the risk of future dementia in patients with MSA as in PD remains to be evaluated.

Last, up to 50% of patients with PD or MSA and OH may have concomitant supine hypertension (SH), defined as the presence of blood pressure ≥140/90 mmHg measured after at least 5 minutes of rest in the supine position.[14] Emerging evidence suggests that SH may contribute to cognitive impairment in neurodegenerative disorders, although data on patients with PD and MSA are scarce.[15,16]

Our hypothesis is that earlier and more severe OH will be associated with greater risk of dementia in patients with PD and MSA. Based on currently accepted pathophysiologic explanations, we hypothesized that those with earlier and more severe OH will show more severe neurodegenerative proteinopathies and/or cerebrovascular changes at neuropathologic examination. In this study, we assessed the impact of OH parameters (timing of onset and severity of symptoms) on progression to cognitive impairment, evaluated whether the association between OH and cognitive dysfunction differed by the presence of concomitant SH, and correlated these data with the neuropathologic findings in a large cohort of pathology-proven patients with PD and MSA. We explored similarities and differences in OH and cognition in these synucleinopathies to further understand the pathophysiologic pathways linking OH with dementia because this could lead to identification of new therapeutic targets for cognitive impairment in these diseases.

Methods

Participants and Study Design

This retrospective cohort study included consecutive pathology-confirmed patients with brain donation to the Queen Square Brain Bank in London, United Kingdom, between 2009 and 2019 for patients with PD and between 2002 and 2018 for patients with MSA. Patients were excluded if an additional diagnosis of a neuropathologic condition was found on postmortem examination or comorbidities known to affect autonomic function (e.g., diabetic neuropathy) were present.

Clinical Assessment

A systematic review of all available medical records was retrospectively performed. All patients were regularly reviewed by experienced hospital specialists (neurologists and geriatricians) in the United Kingdom throughout their disease course and by primary care professionals according to clinical needs. Medical records included primary care medical notes, National Hospital for Neurology and Neurosurgery medical records, correspondence from hospital specialists, Queen Square Brain Bank reports, and self-assessment forms to the time of death. Clinical data were collated by neurologists with expertise in movement disorders (I.R.B., Y.M., and E.d.P.-F.), and all clinical data were obtained from routine clinical information. Patients without detailed clinical information sufficient to accurately document the main variables of the study throughout the disease were not included. OH was defined by a documented decrease >20 mm Hg in systolic or >10 mm Hg in diastolic blood pressure on standing or by the presence of orthostatic symptoms suggesting OH persistent over at least 6 months and after therapeutic measures to address non-neurogenic OH had been implemented based on the clinical impression of the treating physician. Patients with suspected non-neurogenic OH were not included in the study. Severity of OH symptoms was graded using a 4-point semiquantitative scale based on the impact and necessity of therapeutic intervention as previously described[17]: (0) absent; (1) mild severity/mild distress to patient/no therapeutic intervention required; (2) moderate severity/moderate distress/good symptomatic control with therapeutic intervention; and (3) severe intensity/severe distress/poor symptomatic control despite therapeutic interventions. SH was evaluated during the diagnosis of OH and graded as mild (140–159/90-99 mm Hg), moderate (160–179/100-109 mm Hg) or severe (≥180/110 mm Hg) as per consensus definition.[14] Dementia was defined as cognitive dysfunction documented by a clinician or neuropsychological test severe enough to significantly affect tasks of daily living not attributable to motor impairment. When objective documented cognitive deficits were insufficient to interfere with functional independence, they were categorized as mild cognitive impairment.[12,18] Subjective patient's or caregiver's cognitive complaints were excluded from these categories unless confirmed by a clinician or documented neuropsychological test. In patients with PD with a detailed cognitive examination, cognitive impairment was classified into "frontal executive" or "posterior cortical" according to the pattern of deficits.[19] Similarly, patients with MSA and cognitive impairment were classified as fronto-subcortical or memory impairment predominant as previously described.[20] Progression of cognitive deficits was evaluated using the time from diagnosis to dementia for patients with PD or to any type of cognitive impairment (including mild cognitive impairment and dementia) in patients with MSA because cases with incident dementia were expected to be low in this group. Response to initial levodopa treatment was measured using a 4-point semiquantitative scale (nil to mild; moderate; good; and excellent) derived from the UK Parkinson Brain Bank criteria response to levodopa therapy based on the clinical impression documented by the treating physician.[11,21] Maximum levodopa equivalent daily dose in mg was estimated for patients with PD.[22] Additional clinical variables were collected for the PD group. Patients were classified according to PD motor subtype into tremor predominant, akinetic rigid or postural instability, and gait difficulty. Severity of motor and cognitive symptoms during diagnosis was graded using the similar 4-point semiquantitative score used for OH symptoms based on symptom severity, functional impairment, and/or therapeutic need and response as previously published.[17,23]

Neuropathologic Assessment

Neuropathologic evaluation followed standard Queen Square Brain Bank protocols. Brain tissue was fixed in 10% formalin buffer for 3 weeks, and paraffin-embedded 8-μm sections were sampled from representative regions. Sections were stained with hematoxylin and eosin and a panel of immunohistochemistry antibodies for neurodegenerative diseases including α-synuclein, β-amyloid, 3-repeat tau, 4-repeat tau, and phosphorylated tau. Neuropathologic diagnosis of PD and MSA was performed according to current consensus criteria. Severity and distribution of Lewy pathology was evaluated using the Lewy body–type classification (brainstem; limbic; and diffuse neocortical) and Braak staging system.[24,25] Patients with MSA were classified into 4 pathologic subtypes based on previously published criteria.[26,27]

Only data from the systematic neuropathologic assessment of patients with PD is presented in this study because the neuropathologic abnormalities underlying cognitive impairment in patients with MSA have been previously reported elsewhere in detail.[20,28] For those with PD, β-amyloid deposition, neuritic plaques, and neurofibrillary tangles were also evaluated according to Thal phase, the Consortium to Establish a Registry for Alzheimer Disease scheme, and Braak and Braak stage, respectively.[29-31] Alzheimer disease neuropathologic changes were assessed using the ABC scoring system proposed by the National Institute on Aging (absent, low, intermediate, and high).[32] Assessment of cerebrovascular pathology following the Vascular Cognitive Impairment Neuropathology Guidelines[33] including semiquantitative grading of multiple vascular changes (arteriosclerosis, arteriolosclerosis, macroinfarcts/microinfarcts and hemorrhages, and cortical, capillary and leptomeningeal cerebral amyloid angiopathy changes) in representative brain regions was available in a subgroup of patients.

Statistical Analysis

Comparisons between groups were performed using the χ^2 test for categorical variables, independent *t* test for continuous variables, and Kruskal-Wallis test for ordinal variables, as appropriate. A linear regression model was used to analyze potential associations between OH parameters and the main explanatory variables. Multivariable Cox proportional hazards regression models were used to estimate the risk of dementia for patients with PD and the risk of cognitive impairment (including mild cognitive impairment and dementia) for patients with MSA. The decision to focus the regression analysis on patients with MSA and any type of cognitive impairment was made for statistical purposes (because dementia is a rare feature of MSA and the expected low number of cases with incident dementia in the MSA group was unlikely to have enough statistical power to confidently evaluate the association), based on the methodology used in previous research evaluating cognitive function in patients with MSA[13,20,34-37] and the fact that dementia is an exclusion feature in the diagnostic criteria.[38] Grouping patients with MSA with cognitive impairment was also felt to be more relevant for the identification of potential pathogenic mechanisms. Other potential confounders in the association, including age at diagnosis, sex, pattern of cognitive impairment, and PD clinical features, were included in the model as explanatory variables. Only those with a relevant association in the adjusted multivariate analysis were included in the final model. Adjusted hazard ratios (HRs) and 95% confidence intervals were calculated to estimate effect size. Patients with PD and MSA

Table 1 Demographic and Clinical Characteristics

Variable	PD (n = 132)	MSA (n = 137)	*p* Value
Sex, male	80 (60.6)	69 (50.4)	0.09
Age at onset (y)	61.4 (11.9)	57.9 (8.7)	0.006
Age at death (y)	77.8 (6.9)	65.6 (7.8)	<0.001
Disease duration–Survival (y)	16.4 (8.8)	7.7 (3.5)	<0.001
PD motor subtype		NA	
Tremor predominant	21 (15.9)		
Akinetic rigid	84 (63.6)		
PIGD	27 (20.5)		
MSA subtype	NA		
MSA-P		91 (66.4)	
MSA-C		46 (33.6)	
Levodopa response		NA	
Nil to mild	6 (4.6)		
Moderate	9 (6.9)		
Good	30 (23.1)		
Excellent	85 (65.4)		
Maximum levodopa equivalent dose (mg)	887 (425)	684 (358)	<0.001
OH cumulative prevalence	67 (50.8)	107 (78.1)	<0.001
Severity of symptoms of OH			<0.001
Absent	65 (49.2)	30 (21.9)	
Mild	27 (20.5)	45 (32.9)	
Moderate	26 (19.7)	35 (25.6)	
Severe	14 (10.6)	27 (19.7)	
Time from onset to OH (y)	8.2 (9.1)	3.6 (3.5)	<0.001
Concomitant SH prevalence[a]	22 (35.5)	30 (29.4)	0.418
SH severity			0.424
Absent	40 (64.5)	72 (70.6)	
Mild	14 (22.6)	22 (21.6)	
Moderate	6 (9.7)	8 (7.8)	
Severe	2 (3.2)	0	
Dementia cumulative incidence	76 (57.6)	10 (7.3)	<0.001
Time to dementia (y)	12.5 (8.3)	5.1 (5.0)	0.002
MCI cumulative incidence	NA	10 (7.3)	
Time to MCI	NA	5.6 (4.1)	
Pattern of cognitive impairment	n = 42	n = 14	0.073
Frontal subcortical	25 (59.5)	12 (85.7)	
Posterior cortical	17 (40.5)	2 (14.3)	

Abbreviations: MCI = mild cognitive impairment; MSA-C = multiple system atrophy–cerebellar subtype; MSA-P = multiple system atrophy–parkinsonian subtype; NA = not applicable/not available; OH = orthostatic hypotension; PIGD = postural instability and gait difficulties; PD = Parkinson disease; SH = supine hypertension.
Data presented as n (%) for categorical variables or mean (SD) for continuous variables. *p* values correspond to χ^2 comparisons for categorical variables, *t* test for continuous variables, and the Kruskal-Wallis test for ordinal data as appropriate.
[a] Data on concomitant supine hypertension were available for 62 of 67 patients with PD and 102 of 107 patients with MSA.

were divided according to the time of OH onset into 2 equal-sized groups by the median value (early OH and late OH) for visual representation purposes. Kaplan-Meier curves of dementia and survival were plotted and their visual inspection and plots of scaled Schoenfeld residuals against time were used to assess the proportional hazards assumption. Censoring was considered uninformative. Results were considered statistically significant at 2-tailed $p < 0.05$. Stata statistical software version 17 (StataCorp) was used to perform all statistical analyses.

Standard Protocol Approvals, Registrations, and Patient Consents

The brain donor program and protocol were approved by the London-Central Research Ethics Committee (18/LO/0721), all donors provided written informed consent, and brain tissue is stored for research under a license issued by the Human Tissue Authority (12198).

Data Availability

Data not provided in the article because of space limitations may be shared (anonymized) at the request of any qualified investigator, if in compliance with regulatory ethical approvals, for purposes of replicating procedures and results.

Results

One hundred thirty-two patients with PD and 137 patients with MSA were included in the analysis, and their demographic data and clinical features are summarized in Table 1. Patients with MSA had younger age at onset and faster disease progression with shorter survival. In patients with PD, 67 of 132 (51%) developed OH (confirmed with blood pressure measurements or cardiovascular autonomic test in 91%) while 107 of 137 (78%) patients with MSA had OH (confirmed with blood pressure measurements or cardiovascular autonomic test in 98%). Patients with MSA developed OH earlier in the disease course and with more severe symptoms than patients with PD (Table 1). Among those

Table 2 Neuropathologic Data of Cases With Parkinson Disease and Multiple System Atrophy

Parkinson disease (N = 132)	
α-Synuclein (Braak) stage	
Stage 4	2 (1.5)
Stage 5	15 (11.4)
Stage 6	115 (87.1)
Lewy pathology subtype	
Brainstem	1 (0.8)
Limbic	20 (15.2)
Cortical	111 (84.1)
β-amyloid (Thal)	
0	30 (22.7)
1	25 (18.9)
2	10 (7.6)
3	42 (31.8)
4	15 (11.4)
5	10 (7.6)
Neurofibrillary tangle (Braak and Braak)	
0	8 (6.1)
1	31 (23.5)
2	61 (46.2)
3	21 (15.9)
4	7 (5.3)
5	3 (2.3)
6	1 (0.8)
Neuritic plaque (CERAD)	
None	56 (42.4)
Sparse	46 (34.9)
Moderate	27 (20.5)
Frequent	3 (2.3)
Alzheimer disease (NIA)	
Not	34 (25.8)
Low	74 (56.1)
Intermediate	21 (15.9)
High	3 (2.3)
Cerebrovascular pathology (VCING score); n = 40	4.1 (2.8)
Multiple system atrophy (N = 137)	
Neuropathologic subtype	
SND	47 (34.3)
OPCA	46 (33.6)
SND = OPCA	43 (31.4)
Minimal changes	1 (0.7)

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer Disease; NIA = National Institute on Aging; VCING = Vascular Cognitive Impairment Neuropathology Guidelines.

with OH, 22 (35.5%) patients with PD and 30 (29.4%) with MSA had concomitant SH during the diagnosis of OH. The cumulative prevalence for dementia in patients with PD was 57.6% (76 of 132) while only 10 patients with MSA of 137 (7.3%) developed frank dementia ($\chi^2 = 39.043$; $p < 0.001$) with 10 more additional patients with MSA with mild cognitive impairment. A frontal-subcortical cognitive syndrome was the predominant pattern of cognitive impairment in both conditions. Dementia was a late feature in patients with PD and occurred at earlier stages of disease in patients with MSA (Table 1). Neuropathologic assessment showed that patients with PD had advanced α-synuclein pathology with 115 of 132 (87.1%) cases with Braak stage 6 and 111 of 132 (84.1%) cases with diffuse neocortical Lewy pathology. Further details on β-amyloid, tau, and cerebrovascular pathologies are shown in Table 2.

Association of Time of Onset of OH With Other Clinical and Pathologic Variables

Patients with PD and early OH showed a distinctive clinical phenotype, with older age at diagnosis, postural instability and gait difficulty motor subtype, poorer response to levodopa, and poorer cognitive performance at diagnosis, although there was no association with severity of motor symptoms (see Table 3 for effect size estimates). In patients with MSA, development of OH was associated with older age. The pattern of cognitive impairment in patients with PD with early OH tended to have a posterior cortical pattern, although this association did not reach statistical significance. Early OH in patients with PD was associated with limbic distribution of α-synuclein pathology (limbic subtype), although there were no other significant associations with Braak stages of α-synuclein deposition, β-amyloid, tau, or vascular pathologies (Table 3).

Association of Severity of OH Symptoms With Other Clinical and Pathologic Variables

Analysis of the severity of OH symptoms did not show any significant association with demographic, clinical, or pathologic variables in patients with PD or MSA (Table 4).

OH and Risk of Cognitive Impairment and Dementia

Earlier development of OH was associated with developing dementia in patients with PD (Figures 1 and 2). Development

Table 3 Association of Time of Onset of Orthostatic Hypotension With Other Variables in Cases With PD and MSA

Explanatory variable	Regression coefficient (95% CI)	*p* Value
Patients with PD		
Age at onset	−0.58 (−0.70 to −0.46)	<0.001
Sex (male)	−1.21 (−5.93 to 3.50)	0.61
PIGD motor subtype (vs tremor predominant)	−11.13 (−17.59 to −4.67)	0.001
Levodopa response	5.33 (2.78–7.88)	<0.001
Initial motor score	−1.09 (−2.57 to 0.38)	0.14
Initial cognition score	−5.43 (−8.77 to −2.10)	0.002
Pattern of cognitive impairment	−6.50 (−14.01 to 1.00)	0.09
Lewy pathology type—neocortical (vs limbic)	6.39 (0.56–12.21)	0.03
Synuclein staging (Braak)	4.20 (−1.57 to 9.98)	0.15
Neurofibrillary tangle tau (Braak and Braak)	−1.60 (−3.68 to 0.49)	0.13
Aβ plaque (Thal)	0.30 (−1.19 to 1.80)	0.69
Neuritic plaque (CERAD)	−1.50 (−4.58 to 1.58)	0.33
Level of AD neuropathology (NIA-AA score)	0.43 (−2.98 to 3.85)	0.80
Vascular pathology (VCING score)	−0.65 (−2.05 to 0.74)	0.34
Patients with MSA		
Age at onset	−0.13 (−0.20 to −0.06)	<0.001
Sex (male)	−0.72 (−2.06 to 0.61)	0.29
Pattern of cognitive impairment	−0.70 (−6.06 to 4.67)	0.783
Pathology subtype	−0.11 (−0.93 to 0.70)	0.78

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer Disease; MSA = multiple system atrophy; NIA-AA = National Institute on Aging–Alzheimer Association; PD = Parkinson disease; PIGD = postural instability and gait difficulties; VCING = Vascular Cognitive Impairment Neuropathology Guidelines.

of OH increased the risk of dementia by 14% per year (HR = 0.86; 95% CI, 0.80–0.93) after adjusting for other potential confounding variables (Table 5). In the univariate analysis, severity of OH symptoms was not associated with increased dementia risk in patients with PD (Figure 2). The risk of severity of different proteinopathies and dementia was also evaluated. In the univariate analysis, severity of tau pathology and Alzheimer pathologies increased dementia risk in patients with PD, although only the latter remained statistically significant in the multivariate analysis (high Alzheimer neuropathology NIA score HR 9.58 (2.52–36.41); $p = 0.001$). The presence of concomitant SH was associated with an increased risk of dementia in patients with PD in the univariate analysis, although it did not remain significant after adjusting for other relevant factors in the multivariate analysis. In addition to early OH, older age, poor cognitive performance at diagnosis, and poor response to levodopa were other independent variables associated with dementia in PD in the multivariate model (Table 5).

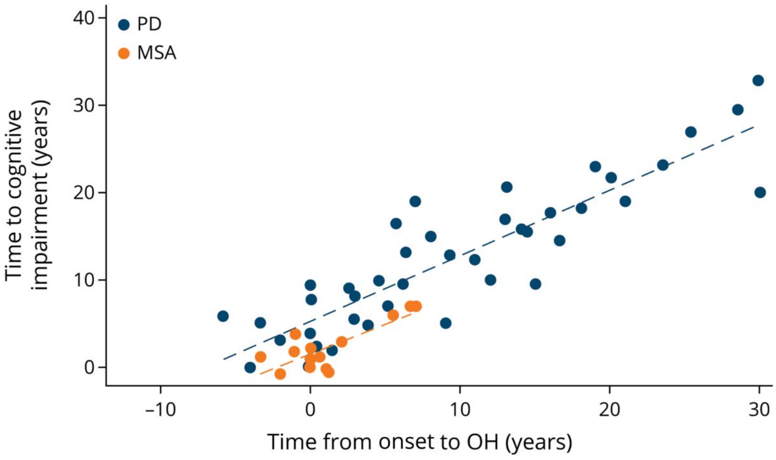
Similar results were found in patients with MSA. Early OH was associated with an increase of 41% risk of future cognitive impairment per year (HR = 0.59; 95% CI, 0.42–0.83), although severity of OH symptoms or concomitant SH did not show any significant change in cognitive impairment risk (Table 5 and Figures 1 and 2).

Table 4 Association of Severity of Orthostatic Hypotension Symptoms With Other Variables in Cases With PD and MSA

Explanatory variable	Regression coefficient (95% CI)	*p* Value
Patients with PD		
Age at onset	0.01 (0.01–0.02)	0.12
Sex (male)	0.40 (0.35–0.77)	0.03
PIGD motor subtype (vs tremor predominant)	0.02 (−0.59 to 0.62)	0.96
Levodopa response	−0.07 (−0.29 to 0.15)	0.533
Initial motor score	0.02 (−0.09 to 0.14)	0.71
Initial cognition score	−0.03 (−0.30 to 0.24)	0.83
Pattern of cognitive impairment	−0.28 (−0.91 to 0.36)	0.39
Lewy pathology type—neocortical (vs limbic)	−0.29 (−0.75 to 0.18)	0.22
Synuclein staging (Braak)	0.02 (−0.45 to 0.49)	0.93
Neurofibrillary tangle tau (Braak and Braak)	−0.07 (−0.24 to 0.10)	0.41
Aβ plaque (Thal)	−0.001 (−0.12 to 0.11)	0.98
Neuritic plaque (CERAD)	−0.05 (−0.27 to 0.17)	0.63
Level of AD neuropathology (NIA-AA score)	−0.04 (−0.30 to 0.22)	0.77
Vascular pathology (VCING score)	−0.07 (−0.19 to 0.06)	0.29
Patients with MSA		
Age at onset	−0.01 (−0.03 to 0.01)	0.26
Sex (male)	0.30 (−0.05 to 0.65)	0.09
Pattern of cognitive impairment	0.35 (−0.18 to 0.89)	0.18
Pathology subtype	−0.03 (−0.24 to 0.19)	0.81

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer Disease; MSA = multiple system atrophy; NIA-AA = National Institute on Aging–Alzheimer Association; PD = Parkinson disease; PIGD = postural instability and gait difficulties; VCING = Vascular Cognitive Impairment Neuropathology Guidelines.

Figure 1 Scatterplot Showing the Association Between Time of Onset of Orthostatic Hypotension and Time to Development of Cognitive Impairment for Cases With MSA (Orange) and Dementia for PD Cases (Blue)



Discussion

This large retrospective clinicopathologic study demonstrates an association between early development of OH—but not severity of OH symptoms—and future dementia in PD and cognitive impairment in MSA despite clinical differences in OH and cognitive deficits between these conditions. The pattern of cognitive impairment associated with OH did not

Figure 2 Kaplan-Meier of Cumulative Risk of Dementia in PD and Risk of Cognitive Impairment in MSA by Time of Onset of Orthostatic Hypotension (A) and (C) and Severity of Symptoms of Orthostatic Hypotension (B) and (D)

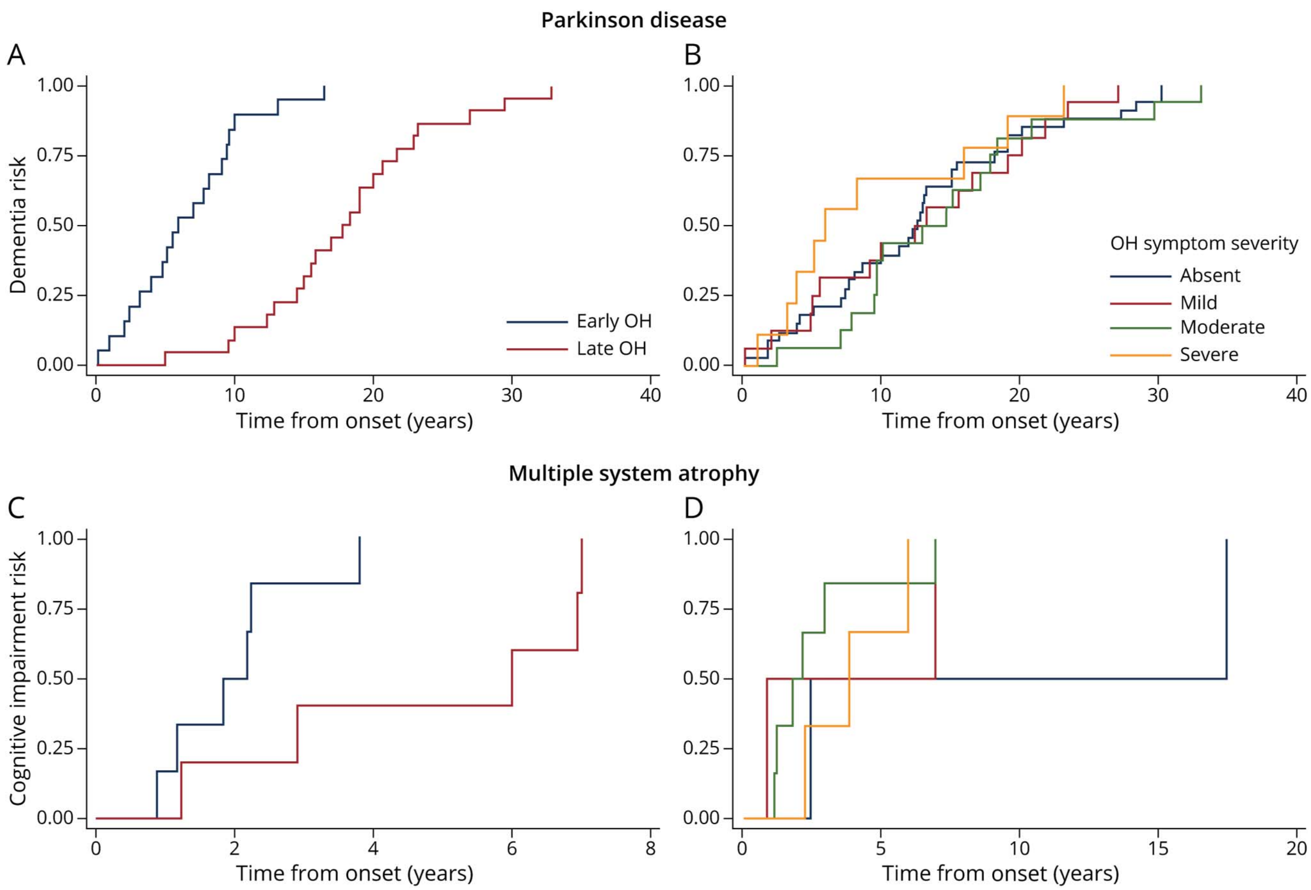


Table 5 Cox Proportional Hazard Regression Models of Orthostatic Hypotension Parameters (Time of Onset and Severity of Symptoms) and Other Significant Clinical Variables for The Development of Dementia (Cases With PD) or Cognitive Impairment (Cases With MSA)

Variable	Crude HR (95% CI)	*p* Value	Adjusted HR (95% CI)	*p* Value
Patients with PD–dementia risk				
Age at onset (y)	1.10 (1.07–1.13)	<0.001	1.08 (1.02–1.13)	0.003
Sex	1.32 (0.82–2.13)	0.25	NA	NA
Initial cognition	5.12 (3.32–7.87)	<0.001	2.24 (1.12–4.50)	0.02
Initial motor score	1.52 (1.22–1.90)	<0.001	1.20 (0.75–1.93)	0.444
PD motor phenotype	2.78 (1.26–6.14)	0.01	3.76 (0.80–17.79)	0.09
Levodopa response	0.02 (0.01–0.22)	0.001	0.46 (0.26–0.81)	0.007
Maximum levodopa equivalent dose	0.998 (0.998–0.999)	<0.001	1 (0.999–1.002)	0.525
Time from onset to OH	0.83 (0.78–0.88)	<0.001	0.86 (0.80–0.93)	<0.001
OH severity	1.04 (0.83–1.30)	0.74	NA	NA
Concomitant SH	4.20 (1.91–9.24)	<0.001	2.10 (0.49–8.93)	0.317
Cases with MSA–cognitive impairment risk				
Age at diagnosis onset (y)	1.12 (0.98–1.27)	0.09	NA	NA
Sex	1.66 (0.64–4.35)	0.62	NA	NA
MSA subtype	1.74 (0.55–5.50)	0.34	NA	NA
Maximum levodopa equivalent dose	1.0 (0.99–1.00)	0.91	NA	NA
Time from onset to OH	0.59 (0.42–0.83)	0.002	0.59 (0.42–0.83)	0.002
OH severity	1.52 (0.32–7.21)	0.60	NA	NA
Concomitant SH	1.90 (0.50–7.23)	0.35	NA	NA

Abbreviations: HR = hazard ratio; CERAD = Consortium to Establish a Registry for Alzheimer Disease; MSA = multiple system atrophy; NIA-AA = National Institute on Aging–Alzheimer Association; OH = orthostatic hypotension; PD = Parkinson disease; PIGD = postural instability and gait difficulties; SH = supine hypertension; VCING = Vascular Cognitive Impairment Neuropathology Guidelines.

show distinctive features for these conditions, although detailed neuropsychometry was available only in a proportion of cases. Our clinical and neuropathologic data demonstrated that the association between OH and cognitive impairment is not due to shared neuroanatomical basis, more extensive specific neurodegenerative proteinopathies, or an increased burden of cerebrovascular disease. Repeated cerebral hypoperfusion secondary to OH may induce nonspecific neurodegeneration contributing to cognitive impairment.

Our results demonstrated that OH is associated with an increased risk of dementia of 14% per year in patients with PD and 41% risk of cognitive impairment per year in patients with MSA over the entire course of the disease. The increased risk is independent of the presence of concomitant SH and other factors associated with cognitive impairment. These results are consistent with previous prospective cohort studies showing a 3-fold increased risk of dementia in patients with PD and OH over a mean 4 years of follow-up.[4,39] Data from literature evaluating this association in patients with MSA are scarce and derive mainly from relatively small series, with short follow-up periods and without neuropathologic confirmation. Results are less conclusive than for patients with PD, with some studies showing a positive association,[34,36] whereas others did not find any correlation.[35,37] Our study represents a large clinicopathologic series of patients with pathology-confirmed MSA with clinical information on OH and cognition throughout the entire disease course providing robust data demonstrating an increased risk of cognitive impairment in patients with MSA with OH. Although OH seems to independently increase the risk of cognitive impairment in both synucleinopathies, there are additional factors contributing to cognitive deterioration that could modify effect size of this association, explaining the paradoxical finding that patients with MSA have lower rates of cognitive impairment despite more frequent and earlier development of OH than patients with PD. The most obvious factors that may explain these pathophysiologic differences are disease duration and age at death. Assuming a cumulative damage from early development of OH, patients with MSA have shorter survival and therefore may not have sufficient exposure to OH-related chronic hypoxia to develop cognitive difficulties. Younger age at death means that they are less likely to have aging-related changes or additional proteinopathies contributing to neurodegenerative changes associated with cognitive impairment because deposition of β-amyloid is associated with age and is more common in patients with PD.[40] Growing evidence suggest that differences in neuronal vulnerability and molecular characteristics of α-synuclein between these diseases may additionally contribute to the distinct phenotypes between synucleinopathies[41,42] and, potentially, they could also have an influence on the development and effect of OH on cognitive function.

In both patients with PD and patients with MSA, time of onset of OH was the relevant factor in association with cognitive dysfunction, while the severity of OH symptoms did not increase the risk of cognitive impairment in either condition. These findings suggest that the deleterious effect of OH causes cumulative damage leading to cognitive deficits and dementia, even when asymptomatic or mildly symptomatic. Repeat bouts of OH compromising brain perfusion and inducing chronic hypoxia is the most likely pathogenic mechanism. Both ischemic and neurodegenerative changes secondary to chronic hypoxia have been demonstrated in animal models and human studies.[2,3,43]

In our study, 35.5% patients with PD and 29.4% patients with MSA had concomitant SH at the time of diagnosis of OH. The deleterious effects of OH on cognitive function were independent of the presence of hypertension, and concomitant SH was not associated with cognitive dysfunction in patients with PD or MSA in our cohort. Our results are in contrast with recent research showing that SH may contribute to the development of cognitive impairment in patients with PD by increasing the burden of white matter hyperintensities (a surrogate biomarker of brain damage associated with cognitive impairment).[15] Both OH and SH may be different manifestations of the blood pressure dysregulation present in patients with PD or MSA and autonomic dysfunction. Based on emerging evidence from studies on the general population,[44] the concept of blood pressure variability has attracted increasing interest as an independent additional factor contributing to cognitive impairment, and further research is warranted to evaluate the contribution of SH and blood pressure variability in patients with PD and MSA as potential modifiable factors.

Our findings have important clinical implications and raise questions about the current management of OH in patients with PD and MSA. Current treatment recommendations are guided by symptom severity and aimed at reducing the symptomatic burden and improving functional capacity. Owing to the chronicity of OH in patients with PD and MSA, cerebral blood flow regulatory mechanisms in these patients develop adaptive changes. Therefore, OH symptoms may not be an accurate indicator of cerebral hypoperfusion, and some authors propose the incorporation of vasodynamic parameters (standing mean blood pressure) in therapeutic decision-making.[45] Regular blood pressure measurements were not available in all our patients, although previous studies suggested that the dementia risk associated with OH may correlate with vasodynamic and neurocirculatory abnormalities.[46,47] Therefore, OH could be one of the very few potential modifiable factors contributing to cognitive impairment,[4] although it is likely that any potential benefit obtained would require therapeutic interventions aimed at improving these circulatory abnormalities rather than guided by symptomatic severity.

Early OH was associated with more severe α-synuclein deposition in limbic structures in people with PD according to the Lewy-related pathology subtypes. Early and more severe Lewy pathology deposition in interconnected neuroanatomical structures of the limbic system involved in autonomic regulatory control such as the anterior cingulate, amygdala or insula, may explain the early development of OH in these patients. Our results go against the hypotheses that OH and dementia may be associated due to shared neuroanatomical basis (because no significant differences were found in cortical Lewy pathology) or secondary to a more diffuse neurodegeneration (because global Lewy pathology did not differ between subgroups). Neuropathologic analysis did not show differences in β-amyloid, tau deposition, or Alzheimer-type pathology, which are well-recognized factors contributing to cognitive impairment in patients with PD[48] or increased global cerebrovascular pathology in a subgroup of patients (n = 40). Imaging studies have explored the association between OH and white matter hyperintensities as a marker of small vessel disease with inconsistent results. While some studies have shown that OH correlates with white matter hyperintensities on magnetic resonance imaging and cognitive outcomes in patients with PD,[6,7,49] it is unclear whether these changes are related to concomitant SH.[15] Of interest, a large multicenter study did not find an association between OH and white matter hyperintensities, although OH was associated with anterior temporal and mediotemporal atrophies independent from SH.[8] Other clinical studies using CSF biomarkers have demonstrated that OH is associated with increased neurofilament light chain levels, a nonspecific marker of neuronal damage.[9] We evaluated the cerebrovascular pathologic changes of OH in patients with PD, and our results showed that cerebral hypoperfusion secondary to OH did not translate into more severe cerebrovascular burden. Taken together, these data suggest that the deleterious effects of OH on cognition are not mediated by an increased burden of cerebrovascular disease and that repeated cerebral hypoperfusion may lead to chronic hypoxic changes activating molecular pathways leading to nonspecific neuronal damage and neurodegeneration.[43]

Last, although the effect of OH on cognition was independent from other confounders, early OH in patients with PD was associated with other clinical variables such as older age at diagnosis, suboptimal response to levodopa, and more severe postural and gait difficulties at diagnosis. These clinical features commonly present together and have become increasingly recognized as defining features of the so-called "diffuse or malignant" PD subtype, with more rapid disease progression and reduced survival.[17]

The main strengths of our study are the pathologic confirmation of the diagnosis, the big sample size, and the availability of detailed clinical information throughout the entire disease course. In addition, the detailed neuropathologic assessment allowed novel pathophysiologic insights to be made. Our results have a few limitations inherent to retrospective clinicopathologic studies. The assessment by different professionals without clear methodologic homogeneity may potentially account for some limitations in the accuracy of the recording and interpretation of the symptoms. To limit this potential bias, only cases with detailed clinical information and regular assessments throughout the disease course were included. The clinical assessment of OH in the study did not allow a confirmation of the neurogenic origin of OH in all patients, although we restricted participants to those with persistent OH >6 months and excluded those with suspected non-neurogenic OH. Moreover, clinical parameters evaluated in the study were selected based on their relevance in clinical practice and are more likely to be confidently documented in medical records. Our study mostly relied on the clinical judgment of the treating specialists for the diagnosis and symptom evaluation of OH. We acknowledge that the lack of regular blood pressure measurements during orthostatism and the potential underreporting of atypical or mild OH–associated symptoms without relevant effect on clinical practice may have delayed the detection of OH in some patients. The lack of use of validated quantitative scales for OH symptoms (such as the Orthostatic Hypotension Questionnaire[50]) and cognitive assessments prevented a more detailed evaluation of the potential pathogenic mechanisms. Last, although we reported the effect of concomitant SH on cognition in those with OH during diagnosis, our data did not allow the assessment of SH without OH or a longitudinal assessment of incident SH throughout the disease course. Further research is warranted to explore the impact of SH and blood pressure variability on cognitive function in patients with PD or MSA.

We found that early development of OH, but not severity of OH symptoms, is independently associated with an increased dementia risk in a large cohort of patients with pathology-confirmed PD and MSA. Systematic neuropathologic analysis did not show significant differences in the severity of α-synuclein deposition in Braak stages and β-amyloid, tau, or cerebrovascular pathologies, suggesting that the association between OH and cognitive impairment is not due to shared neuroanatomical basis, more extensive neuronal damage secondary to specific neurodegenerative proteinopathies, or an increased burden of cerebrovascular disease. Taking our results and evidence from previous clinical studies together, it is likely that repeated cerebral hypoperfusion events secondary to OH may induce nonspecific hypoxia-related neurodegeneration contributing to cognitive impairment. Further research is required to evaluate whether interventions aimed at improving circulatory abnormalities and brain hypoperfusion associated with OH are able to reduce dementia risk in PD and MSA.

Acknowledgment
The authors thank the patients and their families, without whose generous donation and support none of this research would have been possible.

Study Funding
The authors report no targeted funding.

Disclosure
The authors report no relevant disclosures. Go to Neurology.org/N for full disclosures.

Publication History
Received by *Neurology* May 5, 2022. Accepted in final form October 21, 2022. Submitted and externally peer reviewed. The handling editor was Associate Editor Peter Hedera, MD, PhD.

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