Association between orthostatic hypotension and dementia in patients with Parkinson's disease and multiple system atrophy

ABSTRACT

Background and objectives: orthostatic hypotension (OH) increases dementia risk in patients with Parkinson's 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: 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: 132 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 (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, amyloid-β, tau, Alzheimer's 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 to more extensive Lewy, amyloid-β, tau, Alzheimer's or cerebrovascular pathologies. It is likely that OH contributes to cognitive impairment in patients with PD and MSA by hypoxia-induced non-specific neurodegeneration. Further research should evaluate whether improving brain perfusion by treating OH may modify the risk of dementia in these conditions.

INTRODUCTION

Orthostatic hypotension (OH) is one of the most common manifestations of Parkinson's 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 neuropathological 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 to 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- and medio- temporal atrophy on MRI[8] and to increased cerebrospinal fluid neurofilament light chain levels, a non-specific 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 characterised, and whether OH increases the risk of future dementia in patients with MSA as in PD remains to be evaluated.

Lastly, 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 supine hypertension may contribute to cognitive impairment in neurodegenerative disorders although data on PD and MSA patients is 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 pathophysiological explanations, we hypothesized that those with earlier and more severe OH will show more severe neurodegenerative proteinopathies and / or cerebrovascular changes at neuropathological examination. In the present study, we assessed the impact of OH parameters (timing of onset, 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 pathophysiological pathways linking OH with dementia as 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 post-mortem 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 was collated by neurologists with expertise in movement disorders (IRB, YM, EdP-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–mmHg in systolic or > 10–mmHg in diastolic blood pressure on standing or by 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 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; (3) severe intensity / severe distress / poor symptomatic control despite therapeutic interventions. SH was evaluated at the time of diagnosis of OH and graded as mild (140-159/90-99 mmHg), moderate (160-179/100-109 mmHg) or severe (≥180/110 mmHg) 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 categorised 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 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, as incident dementia cases 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's 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 at the time of 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 haematoxylin and eosin, and a panel of immunohistochemistry antibodies for neurodegenerative diseases including α-synuclein, amyloid-β,

3-repeat, 4-repeat and phosphorylated tau. Neuropathologic diagnosis of PD and MSA was made according to current consensus criteria. Severity and distribution of Lewy pathology was evaluated using the Lewy body type classification (brainstem; limbic; diffuse neocortical) and Braak staging system.[24, 25] Patients with MSA were classified into four pathologic subtypes based on previously published criteria.[26, 27]

Only data from the systematic neuropathologic assessment of patients with PD is presented here, as the neuropathologic abnormalities underlying cognitive impairment in patients with MSA have been previously reported elsewhere in detail.[20, 28] For PD cases, amyloid-β deposition, neuritic plaques and neurofibrillary tangles were also evaluated according to Thal phase, the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) 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 (VCING)[33] including semiquantitative grading of multiple vascular changes (arteriosclerosis, arteriolosclerosis, macro/micro infarcts and haemorrhages, 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 chi-square for categorical, independent t-test for continuous and Kruskal-Wallis test for ordinal variables as appropriate. A linear regression model was used to analyse potential associations between OH parameters and the main explanatory variables. Multivariable Cox proportional hazard regression models were used to estimate the risk of dementia for PD cases 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 (as dementia is a rare feature of MSA and the expected low number of incident dementia cases 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 were divided according to time of OH onset in 2 equal size 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 analysis.

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 licence 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

132 patients with PD and 137 patients with MSA were included in the analysis and their demographic data and clinical features are shown in table 1. Patients with MSA had younger age at onset and faster disease progression with shorter survival. In patients with PD, 67 out of 132 (51%) developed OH (confirmed with blood pressure measurements or cardiovascular autonomic test in 91%) whilst 107 out 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 with OH, 22 (35.5%) patients with PD and 30 (29.4%) with MSA had concomitant SH at the time of the diagnosis of OH. The cumulative prevalence for dementia in patients with PD was 57.6% (76 of 132) whilst only 10 patients with MSA out of 134 (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 amyloid-β, tau and cerebrovascular pathologies are shown in the supplementary material (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 (PIGD) 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 PD cases 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, Aβ-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 (figure 1 and 2). Development of OH increased the risk of dementia by 14% per year (HR = 0.86; 95% CI, 0.80 to 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's pathologies increased dementia risk in patients with PD although only the latter remained statistically significant in the multivariate analysis (High Alzheimer's neuropathology NIA score HR 9.58 (2.52 to 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 to 0.83) although severity of OH symptoms or concomitant SH did not show any significant change in cognitive impairment risk (table 5; figure 1 and 2).

DISCUSSION

This large retrospective clinico-pathologic 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 to OH did not show distinctive features for these conditions although detailed neuropsychometry was only available 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 increased burden of cerebrovascular disease. Repeated cerebral hypoperfusion secondary to OH may induce non-specific 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 cases 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 four 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] whilst others did not find any correlation.[35, 37] Our study represents a large clinico-pathologic 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 pathophysiological 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 to cognitive impairment, as deposition of Aβ-amyloid is associated to age and 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, whilst 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, ischaemic 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 the 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 to 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. Due 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 to 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 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 (as no significant differences were found in cortical Lewy pathology) or secondary to a more diffuse neurodegeneration (as global Lewy pathology did not differ between subgroups). Neuropathologic analysis did not show differences in Aβ-amyloid, tau deposition or Alzheimer's type pathology, which are well-recognised 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 supine hypertension.[15] Interestingly, a large multicentre study did not find an association between OH and white matter hyperintensities, although OH was associated with anterior- and medio- temporal atrophy independent from supine hypertension.[8] Other clinical studies using cerebrospinal fluid biomarkers have demonstrated that OH is associated to increased neurofilament light chain levels, a non-specific marker of neuronal damage.[9] We evaluated the cerebrovascular pathological 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 is 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 non-specific neuronal damage and neurodegeneration.[43]

Lastly, 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 recognised 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 is the pathological confirmation of the diagnosis, the big sample size and the availability of detailed clinical information throughout the entire disease course. Additionally, the detailed neuropathological assessment allowed novel pathophysiological insights to be made. Our results have a few limitations inherent to retrospective clinico-pathologic 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 judgement 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. Lastly, although we reported the effect of concomitant SH on cognition in those with OH at the time of 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 in order to explore the impact of SH and blood pressure variability on cognitive function in patients with PD or MSA.

Conclusions

We found that early development of OH, but not severity of OH symptoms, is independently associated with increased dementia risk in a large cohort of pathology-confirmed PD and MSA cases. Systematic neuropathologic analysis did not show significant differences in the severity of α-synuclein deposition in Braak stages, Aβ-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 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 non-specific hypoxia-related neurodegeneration contributing to cognitive impairment. Further research is required to evaluate whether interventions aimed at improving circulatory abnormalities and brain hypoperfusion associated to OH are able to reduce dementia risk in PD and MSA.

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POTENTIAL CONFLICTS OF INTEREST

Nothing to report.

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FIGURE LEGENDS

Figure 1. Scatterplot showing the association between time of onset of orthostatic hypotension and time to development of cognitive impairment for MSA cases (orange) and dementia for PD cases (blue).

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, C) and severity of symptoms of orthostatic hypotension (B, D).

TABLES

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 (years)	61.4 (11.9)	57.9 (8.7)	0.006
Age at death (years)	77.8 (6.9)	65.6 (7.8)	<0.001
Disease duration – Survival (years)	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 to OH (years)	8.2 (9.1)	3.6 (3.5)	<0.001
Concomitant SH prevalence *	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 (years)	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)	

*data on concomitant supine hypertension were available for 62 out of 67 patients with PD and 102 out of 107 patients with MSA. 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's disease; SH, supine hypertension

Data presented as n (%) for categorical variables or mean (SD) for continuous variables. P values correspond to chi^2 comparisons for categorical variables, t test for continuous variables and Kruskal-Wallis for ordinal data as appropriate.

Table 2. Neuropathologic data of Parkinson disease and multiple system atrophy cases.

Parkinson's 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)
Aβ-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's 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 cases (N=137)	
Neuropathologic subtype	
SND	47 (34.3)
OPCA	46 (33.6)
SND = OPCA	43 (31.4)
Minimal changes	1 (0.7)

Table 3. Association of time of onset of orthostatic hypotension with other variables in PD and MSA cases.

Explanatory variable	Regression coefficient (95% CI)	P value
PD cases		
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 to 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 to 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
MSA cases		
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's Disease; MSA, multiple system atrophy; NIA-AA, National Institute on Aging–Alzheimer's Association; PD, Parkinson's disease; PIGD, postural instability and gait difficulties; VCING, Vascular Cognitive Impairment Neuropathology Guidelines.

Table 4. Association of severity of orthostatic hypotension symptoms with other variables in PD and MSA cases.

Explanatory variable	Regression coefficient (95% CI)	P value
PD cases		
Age at onset	0.01 (0.01 to 0.02)	0.12
Sex (male)	0.40 (0.35 to 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
MSA cases		
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

Table 5. Cox proportional hazard regression models of orthostatic hypotension parameters (time of onset and severity of symptoms) and other significant clinical variables for development of dementia (PD cases) or cognitive impairment (MSA cases).

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