Published Ahead of Print on June 7, 2021 as 10.1212/WNL.0000000000012342

Neurology®

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The Official Journal of the American Academy of Neurology

AMERICAN ACADEMY OF NEUROLOGY®

Neurology Publish Ahead of Print
DOI: 10.1212/WNL.0000000000012342

Association of Orthostatic Hypotension With Cerebral Atrophy in Patients With Lewy Body Disorders

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Statistical analysis:

Dr. Andrea Pilotto and Dr. Alok K. Dwivedi conducted the statistical analysis and sample size calculation.

Word Count (text): 3147 words

Word Count (Abstract): 246 words

Title characters count: 97

Number of Tables: 5

Number of Supplementary Tables: 1, available on Dryad

Number of Figures: 2

Number of References: 50

Keywords: α-synucleinopathies; orthostatic hypotension; MRI; atrophy, supine hypertension

STUDY FUNDING

Nothing to declare.

DISCLOSURE

Andrea Pilotto received speaker honoraria and travel grants from AbbVie Pharmaceuticals BioMarin Pharmaceutical, Chiesi Pharmaceuticals, Nutricia Pharmaceuticals, UCB Pharma and Zambon Pharmaceuticals.

Alberto Romagnolo has received grant support and speaker honoraria from AbbVie, speaker honoraria from Chiesi Farmaceutici and travel grants from Lusofarmaco, Chiesi Farmaceutici, Medtronic, and UCB Pharma.

Andrea Scalvini has no financial conflict to disclose.

Mario Masellis receives salary support from the Department of Medicine at Sunnybrook Health Sciences Centre and the University of Toronto, as well as the Sunnybrook Research Institute. He has received grants/research Support from: Parkinson Canada, Canadian Institutes of Health Research, Teva, Early Researcher Award - Ministry of Economic Development and Innovation, C5R, Weston Brain Institute, Ontario Brain Institute, Sunnybrook AFP Innovation Fund, Novartis, Washington University, Roche, Alzheimer's Drug Discovery Foundation (ADDF), Brain Canada, Heart and Stroke Foundation Centre for Stroke Recovery. He has received consulting fees from Ionis, Wave Life Sciences, Alector and Arkuda Therapeutics, as well as royalties from Henry Stewart Talks Ltd.

Yasushi Shimo was funded by grants from the Japan Society for the Promotion of Science, Grant-in-Aid for Scientific Research and received speaker honoraria from Medtronic, Boston Scientific, Otsuka Pharmaceutical, Takeda Pharmaceutical CO, Sumitomo Dainippon Pharma, Novartis Pharma, MSD, FP Pharmaceutical Corporation, Kyowa Hakko Kirin, and AbbVie, Inc.

Laura Bonanni has no financial conflict to disclose.

Richard Camicioli acknowledges funding from CIHR, Brain Canada, the Michael J Fox Foundation, the University of Alberta Hospital Foundation, and Parkinson Canada. Data included in the current study were obtained through a CIHR operating grant. He is funded by the Canadian Consortium on Neurodegeneration in Aging (CCNA) as lead of the Lewy Body Team.

Lily Wang: no financial conflict to disclose.

Alok K. Dwivedi is supported as a co-investigator by the NIH (1R01HL125016-01), (1 R21 HL143030-01) and (1R21 AI133207) grants and as a collaborator in NIH R21 AI118228 grant. He has been also serving as a statistician in CPRIT grants (PP180003, PP170068, PP170004, PP140164, 140211, PP110156, PP150031, and PP130083), CCTST K12 (consultant) award, Coldwell (co-investigator) and TMF (co-investigator). He is a director of Biostatistics & Epidemiology Consulting Lab at the TTUHSC EP.

Katherine Longardner has no financial conflict to disclose.

Federico Rodriguez-Porcel has no financial conflict to disclose.

Mark DiFrancesco has no financial conflict to disclose.

Joaquin A Vizcarra has no financial conflict to disclose.

Elisa Montanaro has no financial conflict to disclose.

Simona Maule has no financial conflict to disclose.

Alessandro Lupini has no financial conflict to disclose.

Carmen Ojeda-Lopez has no financial conflict to disclose.

Sandra E. Black has no financial conflict to disclose.

Stefano Delli Pizzi has no financial conflict to disclose.

Myrlene Gee has no financial conflict to disclose.

Ryota Tanaka received honoraria from Takeda Pharmaceutical, CO., Ltd., Nippon Behringer Ingelheim, CO., Ltd., Dai-Nippon Sumitomo Pharma, Co., Ltd., Otsuka Pharmaceutical, Co., Ltd.

Kazuo Yamashiro has no financial conflict to disclose.

Taku Hatano received grant support from the AMED under grant number 19dm0107156 and the Setsuro Fujii Memorial Osaka Foundation for Promotion of Fundamental Medical Research; and speaker honoraria from Takeda Pharmaceutical, CO., Lid., Dai-Nippon Sumitomo Pharma, Co., Ltd., Otsuka Pharmaceutical, Co., Ltd, Eisai Co., Ltd., Abbvie Inc., and Ono pharmaceutical, CO., Ltd.; and publishing royalties from Nankodo.

Barbara Borroni has no financial conflict to disclose.

Roberto Gasparotti has no financial conflict to disclose.

Maria Cristina Rizzetti has no financial conflict to disclose.

Nobutaka Hattori has received speaker honoraria from Dai-Nippon Sumitomo, Otsuka, Takeda, Kyowa-Kirin, GSK, Nippon, Boehringer Ingelheim, FP, Eisai, Kissei, Nihon Medi-physics, Novartis, Biogen Idec Japan, AbbVie, Astellas, Boston Scientific Japan, Sanofi, Pfizer Japan, Alexion, Mylan N.V, MSD, Daiichi Sankyo and MDS. And he has received consultancies and subcontracting from Dai-Nippon Sumitomo, Biogen Idec, Otsuka, Takeda, Kyowa-Kirin, Meiji Seika, Hisamitsu and Kao.

Leonardo Lopiano Lopiano has received honoraria for lecturing and travel grants from Medtronic, UCB Pharma, and AbbVie.

Irene Litvan research is supported by the National Institutes of Health grants: 2R01AG038791-06A, U01NS090259, U01NS100610, U01NS80818, R25NS098999, P20GM109025; U19 AG063911-1; 1R21NS114764-01A1; Parkinson Study Group, Michael J Fox Foundation, Parkinson Foundation, Lewy Body Association, Roche, Abbvie, Biogen, EIP-Pharma and Biohaven Pharmaceuticals. She was member of the Scientific Advisory Board of a Lundbeck and Corticobasal Degeneration Solutions. She receives her salary from the University of California San Diego and as Chief Editor of *Frontiers in Neurology*.

Alberto Espay has received grant support from the Michael J Fox Foundation and the NIH, personal compensation as a consultant/advisory board member for Abbvie, Neuroderm, Neurocrine, Amneal, Acadia, Acorda, Kyowa Kirin, Sunovion, Lundbeck, and USWorldMeds;

publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer; and honoraria from USWorldMeds, Acadia, and Sunovion.

Alessandro Padovani received grant support from Ministry of Health and Ministry of Education, Research and University, from CARIPLO Foundation; personal compensation as a consultant/ advisory board member for Avanir, Lundbeck, Eli-Lilly, Biogen, Neuraxpharma, GE Health.

Aristide Merola is supported by NIH (KL2 TR001426) and has received speaker honoraria from Theravance BioPharma, Medtronic, CSL Behring, Cynapsus Therapeutics, Lundbeck, AbbVie, and Abbott. He has received grant support from Lundbeck and Abbott.

ABSTRACT

Objective: To evaluate whether orthostatic hypotension (OH) or supine hypertension (SH) is associated with brain atrophy and white matter hyperintensities (WMH), we analyzed clinical and radiological data from a large multicenter consortium of patients with Parkinson's disease (PD) and dementia with Lewy bodies (DLB).

Methods: Supine and orthostatic blood pressure and structural magnetic resonance imaging data were extracted from PD and DLB patients evaluated at eight tertiary-referral centers in the USA, Canada, Italy, and Japan. OH was defined as a systolic/diastolic BP fall ≥20/10 mm/Hg within 3 minutes of standing from the supine position (severe, ≥30/15 mm/Hg) and SH as a BP ≥140/90 mmHg with normal sitting blood pressure. Diagnosis-, age-, sex-, and disease duration-adjusted differences in global and regional cerebral atrophy, as well as WMH were appraised using validated semi-quantitative rating scales.

Results: A total of 384 patients (310 with PD, 74 with DLB) met eligibility criteria, of whom 44.3% (n= 170) had OH, including 24.7% (n= 42) with severe OH, and 41.7% (n= 71) with SH. OH was associated with global brain atrophy (p=0.004) and regional atrophy involving the anterior-temporal (p= 0.001) and medio-temporal (p=0.001) regions, greater in severe vs. non-severe OH (p=0.001). The WMH burden was similar in those with and without OH (p=0.49). SH was not associated with brain atrophy (p=0.59) or WMH (p=0.72).

Conclusions: OH, but not SH, was associated with cerebral atrophy in Lewy body disorders, with prominent temporal region involvement. Neither OH nor SH were associated with WMH.

INTRODUCTION

Orthostatic hypotension (OH), defined as blood pressure (BP) drop ≥ 20/10 mmHg (systolic/diastolic) within 3 minutes of standing[1], and supine hypertension (SH), defined as supine BP ≥140/90 mmHg with normal sitting BP[2], are hemodynamic manifestations of cardiovascular dysautonomia, commonly associated with Lewy body disorders. It has been estimated that 30% of patients with Parkinson's disease (PD) and 30-70% with dementia with Lewy bodies (DLB) are affected by OH and that approximately 40-70% of OH cases are complicated by SH[3].

Multiple studies have documented an association between OH and cognitive impairment, suggesting that common pathogenic mechanisms might be involved in cognitive and autonomic dysfunction or that recurrent episodes of cerebral hypo- and hyper-perfusion might negatively impact the cognitive function of patients with Lewy body disorders[3–7]. These hypotheses are supported by small imaging studies showing regional brain atrophy in the insula[8] and the cholinergic pathways[5] and by the assumption that hemodynamic dysfunction might result in transient cognitive impairment or chronic cerebrovascular damage reflected by white matter hyperintensities (WMH)[9–11].

Using a large multicenter repository of imaging and clinical data, we sought to analyze the association of OH and SH with global and regional brain atrophy and with WMH.

METHODS

We searched the clinical and imaging repositories of a large multicenter consortium constituted by eight specialized Movement Disorder and Dementia Centers in the USA (University of Cincinnati), Canada (University of Toronto, University of Alberta), Italy (University of Brescia, University of Torino, University of Chieti-Pescara, Parkinson's disease Rehabilitation Centre Trescore Balneario), and Japan (Juntendo University, Tokyo).

Inclusion and exclusion criteria

PD and DLB patients meeting all of the inclusion and none of the exclusion criteria listed below were enrolled in the study:

Inclusion criteria were 1) clinical diagnosis of idiopathic PD, as per the Movement Disorders Society (MDS) criteria[12] or DLB, as per the International DLB consortium criteria[13]; 2) standardized orthostatic BP assessment (patient lying supine for at least 5 minutes and then standing for 3 minutes); 3) stable dosage of dopaminergic and vasopressor medications for at least 4 weeks prior to the orthostatic BP assessment; 4) brain MRI, including T1-weighted and T2-weighted sequences acquired at $\geq$ 1.5 Tesla; 5) availability of MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) section III (motor symptoms)[14] or UPDRS score at the time of BP assessment; and 6) availability of Montreal Cognitive Assessment (MoCA)[15] or Mini Mental State Examination (MMSE)[16] scores at the time of BP assessment.

Exclusion criteria were 1) non-neurogenic OH, defined as Δheart rate (HR)/Δsystolic BP ratio $\geq$ 0.5 bpm/mmHg[17]; 2) comorbid diabetic neuropathy or other disorders associated with deficits within the autonomic nervous system[18]; 3) non-neurogenic OH due to treatment with antihypertensive drugs or any therapy with an effect on BP, such as alpha-adrenergic antagonists for prostate disorders; 4) clinical history of acute cerebrovascular disease (ischemic/hemorrhagic stroke and/or transient ischemic attack); 5) other neurologic disorders or medical conditions potentially associated with cognitive deficits including kidney and liver metabolic diseases[19]; 6) any atypical clinical features lowering the diagnostic certainty of PD or DLB; 7) major psychiatric diseases requiring chronic use of typical antipsychotic medications; and 8) history of drug or alcohol abuse.

Definition of orthostatic hypotension and supine hypertension

BP and HR were evaluated in the sitting, supine (after at least 5 minutes of rest), and standing positions. OH was defined as a BP fall ≥ 20 mm/Hg systolic or 10 mm/Hg diastolic within 3 minutes of standing[20] from the supine position, and rated as severe OH if the BP fall was ≥ 30 mm/Hg systolic or 15 mm/Hg diastolic BP[21]. SH was defined as supine systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg; severe SH as supine systolic BP values of ≥ 180 mmHg or diastolic BP values of ≥ 110 mmHg in patients with normal sitting BP[2].

Imaging data

T1-weighted and T2-weighted images were exported in a DICOM format and analyzed in a centralized fashion by four independent raters as detailed in the statistical methods.

Brain atrophy was evaluated in 6 distinct regions (anterior-cingulate; orbito-frontal; anterior-temporal; fronto-insular; medio-temporal; posterior) on T1-weighted images according to the semi-quantitative approach described by Harper and colleagues[22] and rated as follows: 0= closed sulcus; 1= sulcal opening ; 2= sulcal widening; 3= severe sulcal widening with volume loss; 4 = profound volume loss (score 4 applicable only for medial and anterior temporal lobe atrophy)[22].

WMH was assessed in 4 distinct regions (periventricular white matter; deep white matter; basal ganglia plus internal capsule; and infratentorial white matter) on T2-weighted images and rated, according to Scheltens and colleagues[23], as follows: 0=no WM lesion; 1=punctiform WM lesions; 2=early confluent WM lesions; 3=confluent WM lesions. The final analyses were performed by adding the separate scores recorded for regions in left and right hemispheres, resulting in scores between 0 and 6 (0 to 8 for temporal atrophy).

Based on Harper et al., the inter-rater reliability of scales of atrophy ranged from 0.5 to 0.79 for different regions with average rater scores for all scales (>=0.73)22. A random sample of 36 MRIs were preliminary evaluated by the four raters to estimate the intraclass correlation

coefficient (ICC), which was deemed acceptable if greater than 0.70 (eTable 1, Data available form Dryad, https://doi.org/10.5061/dryad.6q573n5zd).

Clinical data

The medical records were searched for the following demographic/clinical information within a time frame of 3 months from MRI: sex, age, age at disease onset, ethnicity, family history of neurological or psychiatric disorders, diabetic neuropathy, hypertension, hypercholesterolemia, previous history of hemorrhagic/ischemic stroke or transient ischemic attack, myocardial infarction, coronary artery bypass graft, angioplasty or stenting, atrial fibrillation, and valvulopathy[19]. The MDS-UPDRS-III or UPDRS-III score, Hoehn & Yahr (H&Y) stage, and MoCA or MMSE score were also collected. A conversion from MMSE to MoCA was applied as needed using the Lawton formula[24], and the MoCA total score was used as a measure of global cognition. A conversion from UPDRS-III to MDS-UPDRS-III was applied using the formula developed by Goetz and coauthors[25], when needed.

Dopaminergic therapies, including levodopa, dopamine agonists, monoamine-oxidase-B inhibitors (IMAO-B), catechol-O-methyltransferase inhibitors (I-COMT) were recorded and used to calculate the total levodopa equivalent daily dose (LEDD) as per the conversion table proposed by Tomlinson and colleagues[26]. The use of medications for diabetes, hypertension, hyperlipidemia, depression, and psychosis was also recorded.

Sample size calculation

Applying the adjusted difference of 0.53 units of atrophy (95% CI, 0.05–1.02) in subjects with and without OH in WMH (15.6 ± 9.6 vs 11±8.2 for total score) reported in previous studies[27,28], and assuming an equal variance between groups, a sample size of at least 90 OH+ and 90 OH- (total=180) was estimated to achieve 80% power for WMH assessment with 1% level of significance using a multiple linear regression analysis. The combined coefficient of covariation

R^2 was assumed to be 20% with covariates. The level of significance was adjusted to 1% due to multiple comparisons. Assuming a prevalence of OH as 40% in Lewy body disorders (95% CI: 23% to 38%) with similar effect sizes as considered for WMH, it was estimated that 350 cases would be needed to have more than 80% power to evaluate the effects of OH groups after adjusting for diagnosis (PD vs. DLB) on MRI using multiple linear regression analysis. The sample size was explored for different OH prevalence scenarios (30% to 60%) using PASS (PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.).

Statistical analyses

Demographic variables, clinical characteristics, and vascular risk factors were compared in patients with and without OH (subdivided further into OH and severe OH) using ANOVA/multiple linear analysis, with study group as main factor, and the $\chi 2$ test for continuous and dichotomous variables, respectively. Quantitative data were presented as mean +/- standard deviation. ANCOVA was used to estimate differences in semi-quantitative scales for the assessment of regional cerebral atrophy and WMH (dependent variables) between the three OH groups (without OH, OH, and severe OH – independent variables) adjusting for diagnosis (PD vs. DLB), age, sex, years of education, and disease duration (covariates). The effect size (mean difference and 95% confidence interval) of OH groups on each region of cerebral atrophy and WMH was determined using multiple linear regression analysis. In addition, Cohen's effect size was estimated for each outcome in relation with OH groups using multiple ordinary linear regression analysis using STATA 15.1 codes.

The same analysis using t-test and chi square for demographics and ANCOVA for atrophy and WMH rating were performed using SH as an independent variable in the group of OH patients only. Multiple comparison adjustment using Bonferroni's correction was applied to the significance level (α) for single atrophy regions (α=0.05/6=0.008) and WMH (α=0.05/5=0.01).

ANCOVA assumption of homogeneity of regression slopes was verified. Statistical tests were performed using Statistical Package for the Social Sciences (SPSS 21.0 for Macintosh, Chicago, Illinois, USA). The two-tailed significance threshold was set at 0.016 in post-hoc analyses of within group comparisons.

Standard Protocol Approvals, Registrations, and Patient Consents

This study received Institutional Review Board (IRB)/ethics committee approval at all participating centers and was conducted in accordance with Good Clinical Practice and any applicable national and local regulations. The General Data Protection Regulation requirements for data collection were met. Written informed consent was obtained from all participants.

Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

RESULTS

Patients

A total of 410 patients were initially included in the study. Of these, 6 were excluded due to MRI motion artifacts, 8 due to subcortical ischemic strokes (4 without OH, 3 with OH, and 1 with severe OH), and 12 due to low imaging quality, insufficient for accurate brain atrophy rating (Figure 1). Out of the remaining 384 patients (310 PD and 74 DLB), 44.3% (n= 170) had OH. Among OH patients, 24.7% (n=42) had severe OH and 41.7% SH (n= 71). PD patients were younger (65.8 ± 10.3 vs. 79.1 ± 7.2) and had longer disease duration (9.2 ± 5.3 vs. 6.6 ± 4.5) and better cognitive scores (MoCA 24.3 ± 2.9 vs. 16.1 ± 5.1) than those with DLB. No differences were observed in the OH distribution between PD and DLB (Table 1).

Patients with OH had longer disease duration (p=0.02) and higher MDS-UPDRS-III scores (p=0.02) compared to patients without OH, with no differences in age, sex distribution, and vascular risk factors (Table 2). Patients with SH had more vascular risk factors (hypertension, diabetes, dyslipidemia, cardiovascular disease) but similar age, sex distribution, disease duration, motor performance, and cognitive impairment than those without SH (Table 2).

OH-associated imaging data

Age, sex, diagnosis, education, and disease duration adjusted data showed an association of OH with both global cerebral atrophy (p=0.004) and regional atrophy involving the anterior-temporal (p=0.001), and medio-temporal (p=0.001) regions (Table 3 and Figure 2). Post-hoc analyses showed greater global atrophy in patients with severe OH vs. patients without OH (p=0.006); patients with severe OH showed greater anterior temporal atrophy compared to both patients with OH (p<0.001) and patients without OH (p<0.001), and greater medial temporal atrophy compared to patients without OH (p=0.002) (Table 4). No differences were observed in the global and regional scoring of WMH between patients with OH and those without OH (Table 3 and Figure 2).

SH-associated imaging data

Age, sex, diagnosis, education, and disease duration adjusted data showed no associations between SH or severe SH and global cerebral atrophy (p=0.59 and p=0.74, respectively), regional atrophy (p≥0.07, or WMH (p≥0.57) (Table 5).

DISCUSSION

Clinical and neuroimaging data from 384 patients with Lewy body disorders demonstrated that OH is associated with global and regional brain atrophy involving the anterior-temporal, and medio-temporal regions, more pronounced in those with severe OH. No differences in WMH

burden were detected in patients with and without OH or SH. Also, SH was not associated with global or regional brain atrophy.

A growing number of studies have reported OH as one of the strongest predictors of cognitive outcomes in PD and DLB[3,29]. Small single-center studies documented increased alpha-synuclein cortical and subcortical pathology in patients with OH[30], suggesting the association with a malignant disease phenotype, potentially worsened by acute and chronic cerebral hypoperfusion[4,10]. Others proposed that the hemodynamic stress due to OH and SH might cause chronic damage to the small brain vessels, resulting in WMH, which can contribute to dementia in Lewy body disorders[11,31]. To date, however, no studies have adequately addressed the impact of OH and SH on brain structural changes.

Whether repetitive hypotensive episodes contribute to these adverse outcomes through direct hypoxic damage of vulnerable areas or are merely associated with a more aggressive clinical subtype of Lewy body pathology remains unclear. The possibility exists that chronic hypoxia might trigger or accelerate the progression of neurodegenerative mechanisms. Experimental studies from aging animals showed that chronic brain hypoperfusion yields synaptic changes, metabolic dysregulation, cholinergic receptor loss, protein synthesis abnormalities, and visuospatial deficits[32,33]. In addition, aging animals kept for prolonged periods of time after chronic brain hypoperfusion showed a tendency to develop neuronal damage in the hippocampal region and temporo-parietal cortex[34]. In a rat model of Alzheimer disease, chronic hypoxia was associated with increased deposition of amyloid β in the frontal cortex and hippocampus, and hyperphosphorylated tau in the temporal cortex[35]. Overall, these findings support the hypothesis that chronic hypoxia might interfere with the cellular metabolic pathways already impaired by the ongoing neurodegenerative processes, ultimately leading to a faster progression of the

neurodegenerative damage. However, the extent to which these pathogenic mechanisms apply to PD and DLB remains to be clarified.

The results of our study, adjusted for age, sex, disease duration, education, and vascular comorbidities, showed that OH is independently associated with global brain atrophy, more prominently in the temporal regions. The involvement of the anterior- and medio-temporal lobes is critical, as these regions have been directly associated with the progression of dementia in Lewy body disorders[36,37]. Also, we found that OH has no effect on subcortical WMH burden. This finding clarifies a highly controversial point in the literature. A study of 44 PD patients evaluated with cardiovascular autonomic testing and brain imaging found a similar WMH burden in patients with and without OH, suggesting that OH-associated cognitive deficits could not be explained by subcortical vascular disease[38]. Yet, three other studies based on simple bedside BP measurements yielded opposite results[28,39,40]. These conflicting findings might be partly related to the inclusion of patients with non-neurogenic OH, wherein there may be a greater role for vascular risk factors[19]. In this study, we included only patients with neurogenic OH and stratified for OH severity and concomitant presence of SH to analyze subcategories of patients at potentially higher risk of microvascular damage. Interestingly, we found that neither OH nor SH were associated with a significantly higher burden of WMH, which can be explained by the fact that WMH require years of chronic vascular shear stress, whereas OH and SH are paroxysmal by definition, with acute episodic complications, such as falls[21,41,42] and cognitive fluctuations[43].

Taking advantage of our large dataset, we also explored the impact of SH, which was not possible in prior smaller cohorts. Data from patients with chronic essential hypertension suggest that SH increases the risk of cardiovascular comorbidities[44] and a recent study found an association between SH and multi-organ damage in patients with pure autonomic failure,

multiple system atrophy, and some cases of PD[45]. However, in our analysis of 170 Lewy body disorders patients with OH, 71 of whom had concomitant SH, we did not find an association between SH and brain atrophy or subcortical WMH burden. While we cannot exclude that a long-term follow-up analysis of SH patients might reveal signs of cerebrovascular organ damage, our findings suggest that SH may have a lower impact on brain parenchyma than essential hypertension, possibly because of its paroxysmal rather than chronic nature[44]. This outcome can inform therapeutic protocols for the management of hemodynamic autonomic dysfunction in patients with PD and DLB, as the successful treatment of OH often requires accepting a higher frequency of SH. Our data seem to suggest that this can be achieved with minimal impact on the vulnerable cortical and subcortical structures.

Several limitations should be acknowledged. First, we used semi-quantitative scales for the assessment of brain atrophy. Despite extensive validation, these scales remain less sensitive than voxel-based morphometry analyses or fully quantitative region of interest analyses, especially for the posterior cortical regions. However, this would not be feasible for a retrospective study as most clinical brain MRIs do not include a volumetric T1 sequence for such purpose. A systematic and prospective acquisition of clinical, hemodynamic, and imaging data has already been initiated in selected centers and will be critical to confirm these results. Similarly, the collection of biological samples, such as cerebrospinal fluid, will allow for the evaluation of biomarkers, which may identify the underlying pathological processes associated with the observed neuroimaging findings and evaluate the relationship with Alzheimer's disease copathology[46]. Second, our observational study design is inevitably prone to selection biases, which might have played a role in the observed outcomes. It is possible that the inclusion of patients with availability of standardized BP assessments in the supine and standing position may have introduced a biased toward the selection of those reporting orthostatic symptoms. In fact, the OH prevalence observed in our study (44%) is slightly higher than the average reported

in the literature (~30%)[47]. Third, the lack of extensive cognitive assessments limited our analyses to measures of global cognition. More comprehensive cognitive testing and prospective follow-up assessments are required to evaluate the impact of OH/SH on specific neuropsychological deficits. Fourth, the cardiovascular autonomic assessment was limited to the study of BP and heart rate. A more extensive battery of cardiovagal, adrenergic, and sudomotor testing will allow distinguishing pathogenic mechanisms involving different components of the autonomic nervous system. Finally, the lack of longitudinal assessments precluded the possibility of studying the effect of vasopressor treatments on the rate of brain atrophy progression[48]. Clarifying this point will be critical to ascertain the extent to which brain atrophy represents a consequence rather than a cause of OH, a question of critical importance to inform the development of therapeutic protocols for the management of OH and SH.

Despite the limitations associated with an observational study, our findings support the association between OH and not SH with cerebral atrophy, with a more pronounced effect on the anterior- and medio-temporal regions. These results are consistent with the known vulnerability of the medio-temporal lobe and hippocampus to acute and chronic hypoxia due to cerebral hypoperfusion[49], and suggest that there may be a direct hemodynamic impact of OH on these selected cortical areas[3,30,50]. Alternatively, the observed atrophy might represent a specific phenotype of patients with OH, characterized by widespread progression of Lewy body pathology. Future research endeavors will be needed to clarify whether an aggressive treatment with vasopressor agents, even at the expense of greater prevalence of SH, may reduce the extent of brain atrophy and result in better short- and long-term outcomes.

APPENDIX 1 - AUTHORS

Name	Location	Contribution
Andrea Pilotto	Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy	Conception and design of the study; acquisition, analysis and interpretation of data; writing of the first draft
Alberto Romagnolo	Department of Neuroscience "Rita Levi Montalcini", University of Turin, Turin, Italy	Conception and design of the study; acquisition and interpretation of data; critical revision for important intellectual content
Andrea Scalvini	Neurology Unit, Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy	Acquisition, analysis and interpretation of data; critical revision for important intellectual content
Mario Masellis	Department of Medicine (Neurology), University of Toronto; Hurvitz Brain Sciences Program, Sunnybrook Research Institute, Sunnybrook Health Sciences Centre, Toronto, Canada	Acquisition and interpretation of data; critical revision for important intellectual content
Yasushi Shimo	Department of Neurology, Juntendo University Graduate	Acquisition, analysis and interpretation of data; critical

	School of Medicine, Tokyo, Japan	revision for important intellectual content
Laura Bonanni	Department of Neuroscience Imaging and Clinical Sciences, University G. d'Annunzio of Chieti-Pescara, Chieti, Italy	Acquisition, analysis and interpretation of data; critical revision for important intellectual content
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Lily Wang	Department of Radiology, University of Cincinnati Cincinnati, Ohio, USA	Acquisition, analysis and interpretation of data; critical revision for important intellectual content
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Alessandro Lupini	Neurology Unit, Department	Acquisition of data; critical

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DATA ACCESS AND RESPONSIBILITY STATEMENT

A. Pilotto had full access to data and takes responsibility for the integrity of data and the accuracy of data analysis.

Table 1. Demographic and clinical characteristics of the studied groups.
Quantitative values are summarized with mean ± standard deviation**.**

	Entire sample	**PD**	**DLB**	**p**
Count	384	310	74	
Clinical characteristics				
Age, years	68.43 ± 11.08	65.89 ± 10.29	79.12 ± 7.23	0.001
Sex, female, count (%)	142 (36.9)	116 (37.4)	26 (35.1)	0.78
Disease duration, years	8.74 ± 5.28	9.17 ± 5.32	6.61 ± 4.36	0.001
Education, years	10.61 ± 4.24	11.28 ± 3.96	7.80 ± 4.28	0.001
MDS-UPDRS-III	23.38 ± 12.49	24.09 ± 12.87	20.70 ± 10.32	0.06
MoCA	21.26 ± 4.34	24.30 ± 2.97	16.11 ± 5.07	0.001
Vascular risk factors				
Hypertension, count (%)	90 (23.4)	58 (21.6)	32 (43.2)	0.02
Previous TIA, count (%)	8 (2.1)	4 (1.3)	4 (5.4)	0.05
Diabetes, count (%)	33 (8.6)	25 (8.1)	8 (10.8)	0.48
Heart disease, count (%)	49 (12.8)	36 (11.6)	13 (17.6)	0.18
Number of VRF	0.47 ± 0.74	0.40 ± 0.71	0.77 ± 0.79	0.07
OH, count (%)	170 (44.3)	136 (43.8 %)	34 (45.9%)	0.26

DLB, dementia with Lewy bodies; MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; OH, orthostatic hypotension; PD, Parkinson's disease; TIA; Transient Ischemic attack; VRF, vascular risk factors.

Table 2. Clinical and Demographic Features

	OH-	OH+	Severe OH+	p	OH+SH-	OH+SH+	p
Count	214	128	42		99	71	
Age, years	68.1 ± 11.1	68.0 ± 11.5	71.2 ± 8.4	0.24	6.9 ± 10.1	71.9 ± 9.6	0.05
Sex female, count (%)	78 (25.0)	16 (12.5)	19 (45.2)	0.78	25 (25)	10 (14.1)	0.87
Disease duration, years	7.9 ± 5.4	9.6 ± 4.5	10.3 ± 5.8	0.02 Δ	9.7 ± 4.9	7.9 ± 5.1	0.82
Education, years	10.48 ± 4.20	10.78 ± 4.38	10.80 ± 4.09	0.78	11.60 ± 4.08	9.62 ± 4.37	0.003
MDS-UPDRS-III	21.9 ± 11.5	24.5 ± 13.6	27.5 ± 12.9	0.02 #Δ	22.7 ± 11.2	25.7 ± 11.6	0.10
MoCA	21.8 ± 15.2	20.8 ± 4.1	20.7 ± 4.1	0.36	22.2 ± 3.27	21.3 ± 3.5	0.21
Number of VRF	0.52 ± 0.76	0.40 ± 0.69	0.43 ± 0.71	0.32	0.22 ± 0.45	1.10 ± 0.88	0.001
BP Sys-Supine	130 ± 18	126 ± 19	137 ± 18	0.001#Δ	118 ± 11	151 ± 13	0.001
BP Sys-Stand	124 ± 19	115 ± 20	107 ± 24	0.001#Δ	107 ± 19	125 ± 18	0.001
BP-Dias-Supine	78 ± 12	76 ± 11	81 ± 13	0.001Δ	76 ± 11	81 ± 13	0.001
BP-Dias-Stand	78 ± 14	72 ± 12	68 ± 14	0.001#Δ	76 ± 11	81 ± 13	0.001

Clinical characteristics of patients according to presence of OH and SH.

Quantitative data are presented as mean value ± standard deviation; statistical differences were evaluated using ANOVA and t-test for continuous variables (OH and SH subgroups, respectively) and chi square for dichotomous variables.

Post-hoc analyses (significance set with Bonferroni's correction at α=0.01): # OH- vs. OH+; Δ OH- vs. Severe OH+.

MDS-UPDRS-III, Movement Disorders Society Unified Parkinson's disease Rating Scale; MoCA, Montreal Cognitive Assessment; OH-, patients without orthostatic hypotension; OH+, orthostatic hypotension; Severe OH+, severe orthostatic hypotension; OH+SH-, orthostatic

hypotension without supine hypertension; OH+SH+, orthostatic hypotension with supine hypertension; VRF, vascular risk factors.

Table 3. Brain Atrophy and Subcortical Vascular Rating

	OH-	OH+	Severe OH+	p
Count	214	128	42	
Brain Atrophy				
Anterior cingulate	1.60 ± 1.60	2.00 ± 1.70	2.19 ± 1.50	0.029
Orbito-frontal	1.15 ± 1.38	1.59 ± 1.60	1.39 ± 1.34	0.029
Anterior-temporal	1.68 ± 1.24	1.84 ± 1.13	2.46 ± 0.92	0.001 Δ*
Fronto-insular	2.13 ± 1.53	2.33 ± 1.69	2.92 ± 1.49	0.017
Medio-temporal	1.72 ± 1.67	1.88 ± 1.90	2.87 ± 1.72	0.001 Δ
Parieto-occipital	2.43 ± 1.59	2.39 ± 1.63	2.68 ± 1.44	0.60
Total atrophy	10.74 ± 6.56	11.9 ± 7.30	14.71 ± 5.15	0.004 Δ
White Matter Hyperintensities				
Frontal lobe	1.91 ± 1.68	2.11 ± 1.68	2.54 ± 1.96	0.058
Parieto occipital	1.80 ± 1.76	1.86 ± 1.89	1.94 ± 1.99	0.82
Temporal lobe	0.59 ± 1.16	0.50 ± 1.06	0.57 ± 1.07	0.80
Basal ganglia	0.78 ± 1.26	0.69 ± 1.39	0.77 ± 1.46	0.86
Infratentorial	0.35 ± 0.88	0.40 ± 1.18	0.57 ± 1.20	0.51
Total WMH	5.45± 5.33	5.49 ± 5.49	6.40 ± 6.18	0.49

Brain atrophy and subcortical vascular rating of white matter hyperintensities (WMH) in patients without orthostatic hypotension (OH-), with OH and with severe OH. Data are presented with mean ± standard deviation; statistical differences were evaluated using ANCOVA adjusted for the effect of age, sex, education, diagnosis and disease duration. For single atrophy regions and regional WMH burden, we set the statistical threshold at 0.008 and 0.01, respectively, after applying a multiple comparison adjustment ($\alpha = 0.05/6 = 0.008$, and $\alpha = 0.05/5 = 0.01$).

Post-hoc analyses (significance set with Bonferroni's correction at $\alpha=0.05/3=0.016$): Δ OH- vs. Severe OH+; ∗ OH+ vs. Severe OH+.

F, F effect size; WMH, white matter hyperintensities visual rating scoring

Table 4. Effect size for comparing brain atrophy among groups

	Groups	Mean difference	95%CI		p-value	Cohen's d
Anterior-temporal	OH- vs. OH+	0.13	-0.12	0.39	0.308	0.11
	OH- vs. severe OH+	0.77	0.36	1.18	<0.001	0.64
	OH+ vs. severe OH+	0.73	0.35	1.12	<0.001	0.68
Medio-temporal	OH- vs. OH+	0.17	-0.21	0.55	0.373	0.10
	OH- vs. severe OH+	0.91	0.34	1.47	0.002	0.53
	OH+ vs. severe OH+	0.78	0.12	1.45	0.021	0.41
Total atrophy	OH- vs. OH+	1.36	-0.01	2.73	0.052	0.20
	OH- vs. severe OH+	2.71	0.77	4.64	0.006	0.42
	OH+ vs. severe OH+	2.05	-0.32	4.43	0.09	0.30

Statistical differences were evaluated using multiple linear regression adjusted for the effect of age, sex, education diagnosis and disease duration. CI, confidence interval.

Table 5 Brain Atrophy and Subcortical Vascular Rating in OH patients with and without SH

	OH+SH-	OH+SH+	p
Count	99	71	
Brain Atrophy			
Anterior cingulate	2.19 ± 1.74	1.82 ± 1.47	0.07
Orbito-frontal	1.53 ± 1.70	1.57 ± 1.27	0.34
Anterior-temporal	1.85 ± 1.19	2.16 ± 0.97	0.41
Fronto-insula	2.38 ± 1.71	2.62 ± 1.57	0.75
Medio-temporal	1.99 ± 1.95	2.30 ± 1.86	0.64
Parieto-occipital	2.38 ± 1.61	2.59 ± 1.52	0.94
Total atrophy	12.32 ± 7.51	13.03 ± 6.09	0.59
White Matter Hyperintensities			
Frontal lobe	2.08 ± 1.84	2.42 ± 1.63	0.92
Parieto-occipital	1.72 ± 194	2.11 ± 1.85	0.57
Temporal lobe	0.49 ± 1.08	0.58 ± 1.05	0.99
Basal ganglia	0.61 ± 1.43	0.86 ± 1.37	0.65
Infratentorial	0.35 ± 1.03	0.57 ± 1.27	0.74
Total WMH	5.24 ± 5.89	6.49 ± 5.27	0.72

Data are presented with mean ± standard deviation; overall statistical differences were evaluated using ANCOVA adjusted for the effect of age, sex, education diagnosis and disease duration. For single atrophy regions and regional WMH burden, we set the statistical threshold at 0.008 and 0.01, respectively, after applying a multiple comparison adjustment (α= 0.05/6 = 0.008, and α= 0.05/5 = 0.01). OH+SH-, orthostatic hypotension without supine hypertension; OH+SH+,

orthostatic hypotension with supine hypertension; WMH, white matter hyperintensities visual rating scoring.

FIGURES CAPTURE AND LEGEND

Figure 1. Study Flowchart

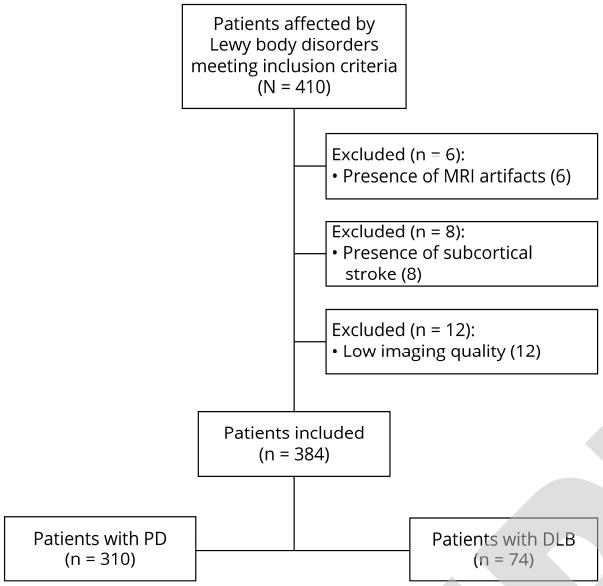
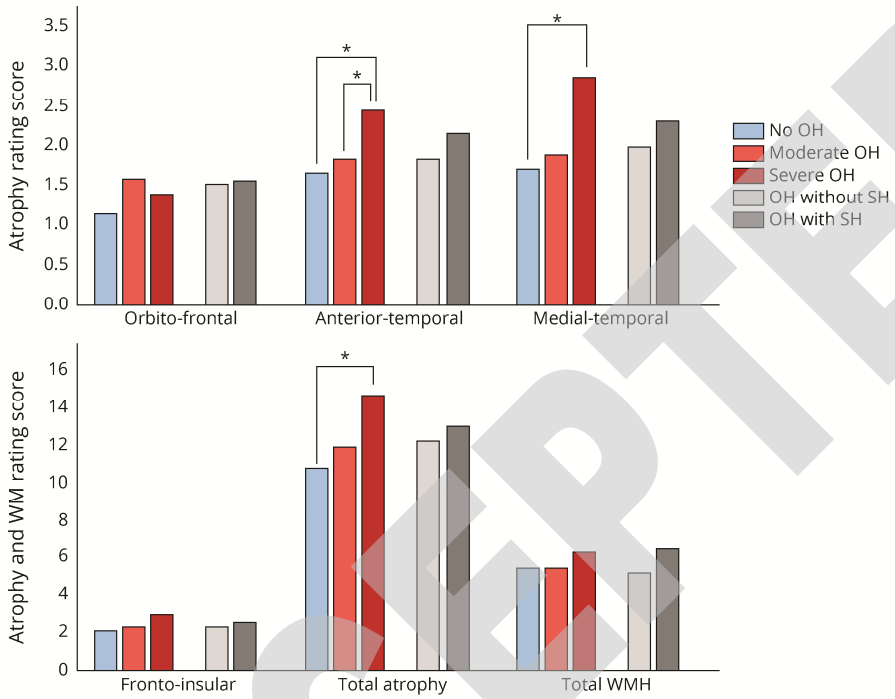


Figure 2. Atrophy and WMH rating according to OH and SH subgroups

OH, orthostatic hypotension; SH, supine hypertension; WMH, white matter hyperintensities

Post-hoc analyses (∗ significance set with Bonferroni's correction at α=0.016).



Association of Orthostatic Hypotension With Cerebral Atrophy in Patients With Lewy Body Disorders

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Neurology published online June 7, 2021
DOI 10.1212/WNL.0000000000012342