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Orthostatic hypotension, cerebral hypoperfusion, and visuospatial deficits in Lewy body disorders

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ABSTRACT

Background: Orthostatic hypotension and cognitive impairment are two non-motor attributes of Lewy body spectrum disorders that impact independence. This proof-of-concept study examined cerebral blood flow (perfusion) as a mediator of orthostatic hypotension and cognition.
Methods: In fifteen patients with Lewy body disorders, we estimated regional perfusion using pseudo-continuous arterial spin labeling MRI, and quantified orthostatic hypotension from the change in systolic blood pressure between supine and standing positions. Executive, visuospatial, attention, memory, and language domains were characterized by neuropsychological tests. A matching sample of non-demented adults with cerebral small vessel disease was obtained to contrast perfusion patterns associated with comorbid vascular pathology.
Results: Compared to the vascular group, patients with Lewy body disorders exhibited lower perfusion to temporal and occipital lobes than to frontal and parietal lobes ($q < 0.05$). A greater orthostatic drop in systolic pressure was associated with lower occipito-parietal perfusion in these patients (uncorrected $p < 0.005$; cluster size ≥ 20 voxels). Although orthostatic hypotension and supine hypertension were strongly correlated ($r = -0.79$, $p < 0.001$), the patterns of association for each with perfusion were distinct. Specifically, supine hypertension was associated with high perfusion to anterior and middle cerebral arterial territories, as well as with low perfusion to posterior regions. Perfusion within orthostatic hypotension-defined regions was directly related to performance on visuospatial and attention tasks, independent of dementia severity ($p < 0.05$).
Conclusions: These findings provide new insight that regional cerebral hypoperfusion is related to orthostatic hypotension, and may be involved in domain-specific cognitive deficits in Lewy body disorders.

1. Introduction

Lewy body disorders (LBD), including dementia with Lewy bodies (DLB) and Parkinson's disease (PD), are neurodegenerative syndromes characterized by intraneuronal alpha-synuclein deposits. Autonomic dysfunction and cognitive impairment are two non-motor attributes of LBD that reduce quality of life and increase

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healthcare utilization [1]. Dysautonomia results from pathophysiological changes to brainstem nuclei, medullary axons, and postganglionic fibres, although clinical expression is variable [2]. Cardiovascular symptoms, expressed primarily as orthostatic hypotension (OH), are the third most prevalent manifestation of dysautonomia in LBD [1], but are also one of the earliest symptoms and can precede diagnosis by up to 5 years [3].

OH is defined as a decrease in systolic blood pressure (SBP) of 20 mm Hg or diastolic blood pressure (DBP) of 10 mm Hg, within 3 min of moving from supine lying to active standing. The prevalence of OH in LBD can be up to twice that observed in the general population, reaching ~40% in advanced disease [4]. Concurrence of OH and cognitive impairment occurs with increasing disease severity [5], supporting a possible link between these two attributes. In particular, visuospatial [6,7], sustained attention [6,7], and verbal memory [7] impairments are exacerbated by OH in PD and PD with dementia (PDD). Furthermore, a recent prospective cohort study identified that OH in PD is independently associated with an increased risk of developing dementia [8]. Determining possible mechanisms through which dysautonomia (and in particular OH) can affect cognition may provide insight into factors potentially contributing to cognitive dysfunction in LBD.

A vascular hypothesis posits that the association between OH and impaired cognition is a consequence of cerebral hypoperfusion [9]. White matter hyperintensity (WMH) volume, regarded as a hallmark of underlying cerebral small vessel disease, has been correlated with the prevalence of OH in PD [9] and dementia with Lewy bodies [10]. In addition, distinct parieto-temporo-occipital hypoperfusion in LBD are evident on single photon emission computed tomography (SPECT) [11] and arterial spin labeling (ASL) MRI [12,13]. Only one study, however, has compared CBF between PD patients with ($n = 15$) and without OH ($n = 13$) – reporting reduced regional CBF in the bilateral anterior cingulate gyri of the former group [14]. Further evaluation of the inter-related associations between OH, CBF, and cognitive impairment is needed.

In this proof-of-concept study, we hypothesized that the degree of OH would be associated with regional cerebral hypoperfusion, and that these deficits would contribute to impairment on domain-specific cognitive testing. To control for the potential impact of comorbid cerebrovascular pathology unrelated to LBD, we compared CBF in LBD to a convenience cohort with small vessel disease (SVD) matched for age, sex, and education.

2. Methods

2.1. Participants

A prospective cohort of LBD patients was recruited consecutively from the Cognitive & Movement Disorders clinic at Sunnybrook Health Sciences Centre. A neurologist with subspecialty expertise in cognitive and movement disorders (MM) characterized the LBD group in terms of diagnosis, Hoehn & Yahr staging, and the Unified Parkinson's Disease Rating Scale (Part III – motor examination). Classification into DLB, PDD, and PD with mild cognitive impairment (PD-MCI) followed current consensus criteria. Vascular risk factors, duration of cognitive complaints, and duration of Parkinsonism were identified through clinical history and corroborated by medical records and current medications. A non-demented comparison group with evidence of SVD was obtained retrospectively from individuals recruited for a separate study [15], based on subjective memory complaints, prior imaging, or history of vascular risk factors. We selected participants from this larger pool to best match the LBD group for age, sex, and education. The matching set excluded individuals with diagnosed Alzheimer's or vascular dementia, a genetic predisposition to SVD, severe carotid stenosis, or cortical infarcts larger than 20 mm in axial diameter. The Research Ethics Board at Sunnybrook Health Sciences Centre approved the studies, and each participant and/or their substitute decision maker provided written informed consent in accordance with the Declaration of Helsinki.

2.2. Assessment protocol

Over the span of one or two days, LBD participants completed a clinical OH test, a neuropsychological battery, and an MRI session involving structural and perfusion brain scans. Participants completed the sessions between 9am and 3pm. Medication schedules were unaltered and physiological measurements were postprandial by at least 1 h. Clinical and neuropsychological assessments were performed in the "on" state as judged from participant self-report and neurological evaluation.

A clinical test for OH assessed the change in arterial blood pressure over the first 5 min of standing after 15 min of lying supine. SBP and DBP were measured using an automated cuff wrapped around the upper arm (10 Series, Omron Healthcare, Kyoto JP). The average of three measurements over the final 5 min of supine lying was used to quantify supine blood pressure and to evaluate the presence of supine hypertension (SH; SBP $\geq$ 150 mm Hg). Blood pressure measurements were repeated at 1, 3 and 5 min after moving briskly to an active standing posture. The change in SBP (ΔSBP) between the 3rd minute of standing and the average supine value was used as a continuous variable describing OH. The degree of autonomic impairment was characterized by the Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT).

General cognition and dementia severity were assessed using the Montreal Cognitive Assessment (MoCA) and the Dementia Rating Scale (DRS), respectively. A neuropsychological battery was used to distinguish five cognitive domains for the LBD group only. Executive abilities were characterized using the Trail Making Test differential completion time and the perseverative error count during the Wisconsin Card Sort Test. Attention was assessed by the Wechsler Memory Scale-Revised Digit Symbol Substitution total score and the Stroop task colour-dot differential completion time. Visuospatial function was evaluated by the Rey–Osterrieth Complex Figure (RCF) copy task and the Benton Judgement of Line Orientation (JLO). Memory was characterized by the California Verbal Learning Test I long delay free recall and the RCF delayed recall task. Finally, language was assessed by the Boston Naming Test short form and the total count for an animal naming semantic fluency task. Standardized z-scores were calculated from raw scores and inverted, if necessary (e.g., Stroop), to operationalize so that a higher score was better performance.

2.2.1. MRI acquisition

On the same day as the OH assessment, neuroimaging was performed on a 3-Tesla MRI (Achieva, Philips Healthcare, Best NL) using a body coil transmitter and an 8-channel head coil receiver. Structural imaging included a high-resolution T1-weighted acquisition [field of view (FOV) = 240 × 191 × 168 mm^3, voxel dimensions = 0.9 × 0.7 × 1.2 mm^3, flip angle = 8°, and TR/TE = 9.5/2.3 ms], a fluid attenuated inversion recovery (FLAIR) acquisition [FOV = 240 × 240 × 156 mm^3, voxel dimensions = 0.4 × 0.4 × 3 mm^3, flip angle = 90°, and TR/TE/TI = 9000/125/2800 ms], and a T2/proton density-weighted two-volume acquisition [FOV = 230 × 230 × 156 mm^3, voxel dimensions = 0.45 × 0.45 × 3 mm^3, flip angle = 90°, and $TR/TE_{PD}/TE_{T2}$ = 2500/11/102 ms]. Pseudo-continuous ASL MRI was used to estimate CBF. The ASL labeling plane was prescribed perpendicular to the internal carotid and vertebral arteries as visualized by time-of-flight angiography. ASL acquired 35 control and 35 tag volumes with single-shot echo