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Progression of small vessel disease correlates with cortical thinning in Parkinson's disease

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ABSTRACT

Objective: Cerebral small-vessel disease (SVD) is a risk factor for dementia in Parkinson's disease (PD), however the pathophysiological role of SVD in PD-dementia is unclear. We investigated the impact of baseline and progression of SVD on cortical thickness and the correlation to cognition.
Methods: Seventy-three mild PD patients with baseline and follow-up structural MRI scans, serial clinical and neuropsychological assessments were studied. SVD included the load of white matter hyperintensities (WMH), lacunes and perivascular spaces (PVS). WMH progression was assessed using the modified Rotterdam Progression scale, while for lacunes and PVS, development of new lesions was considered as lesion progression. Patients were classified as having SVD-progression and SVD-no-progression based on the longitudinal changes in their SVD measures. *Freesurfer* was used to measure baseline and follow-up regional cortical thickness and subcortical volumes and correlated to cognitive performance.
Results: Fourteen patients were classified as SVD-progression and 59 as SVD-no-progression. Over 18 months, PD SVD-progression demonstrated significant cortical thinning in the left frontal and bilateral parietal regions with associated decline in memory, executive function, and motor functions. PD SVD-progression also had reduced volumes in the nucleus accumbens and amygdala at baseline and greater atrophy in the caudate nucleus over 18 months.
Discussion: The extent and progression of SVD is associated with focal cerebral atrophy and domain-specific cognitive dysfunction. Measures to retard SVD may be potentially useful in preventing dementia in PD.

1. Introduction

Parkinson's disease (PD) is the second most common chronic neurodegenerative disease affecting up to 2% of individuals above 65 years [1]. Besides the classical presentation of motor symptoms, cognitive deficits and the prevalence of mild cognitive impairment in early PD are also frequent and usually occur early in the disease [1–3]. It has been reported that nearly 80% of PD patients eventually develop dementia [4].

Concomitant cerebral small vessel disease (SVD) could be a significant contributor to cognitive dysfunction in PD patients [3,5]. Previous studies have shown the association between individual markers of SVD – such as white matter hyperintensities (WMH), lacunes, perivascular spaces (PVS), and microbleeds – and cortical atrophy in affecting cognition [3,6–9]. However, a previous study did not reveal any significant association between volume and regional distribution of WMH and cognitive dysfunction [2]. This heterogeneity could be related to the use of different SVD quantifications scales or the lack of sensitivity of voxel based morphometry to detect early cortical changes.

To understand the pathophysiological relationship between SVD

Abbreviations: MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; SVD, Cerebral Small Vessels Disease; PD SVD-no-progression, Parkinson's disease with no progression of Cerebral Small Vessels Disease progression over 18 months; PD SVD-progression, Parkinson's disease with progression of Cerebral Small Vessels Disease over 18 months.

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and cognition in PD, it would be imperative to study the differential effects of SVD progression on atrophy patterns and clinical-cognitive outcomes. At present, studies investigating the relationship of vascular risk factors, grey matter deficits, and cognition in PD tend to emphasise on WMH and not the other SVD lesions. Although individual markers of SVD have been studied, the findings are inconclusive. While some found that WMH and lacunes could be representative of a clinical subtype of PD characterised by a more rapid neurodegenerative process, others did not find such effect [2,3,7]. This warrants the need to examine SVD as a composite measure instead of individual elements, which could have a compounded effect on the structural integrity of the brain and may more severely affect cognition [5]. Furthermore, serial imaging would be crucial to provide insights into the vulnerability of certain brain regions as well as their trajectory of atrophy and how the progression of SVD can exacerbate this atrophy.

We investigated the spatiotemporal progression of cortical thinning and subcortical atrophy in SVD-progression and SVD-no-progression. Correlation of cortical thickness with cognitive scores was also performed. As shown previously that brain volume is reduced in SVD patients [10], we hypothesised that PD SVD-progression would have a more severe pattern of cortical thinning and subcortical atrophy with cognitive decline compared to SVD-no-progression.

2. Methods

2.1. Participants

Patients with mild PD defined by Hoehn and Yahr staging of <3 without pre-existing dementia were recruited (n = 93) from a tertiary neurology centre between August 2011 and March 2012 and followed up for 18 months [11]. Over the study, 21 patients withdrew and one deceased. 73 patients with baseline and follow-up assessments were included in the study. Singhealth institutional ethics review board approved the study and informed consent was obtained from all patients.

2.2. Assessments

All patients underwent clinical, neuropsychological, and MRI assessments at baseline and month 18. Clinical assessments included medical history, Unified PD Rating Scale (UPDRS) to ascertain patients' motor and functional ability, and Hoehn and Yahr to determine their disease stage. Neuropsychological assessments evaluated global cognition using MMSE and MoCA and the five cognitive domains using the following tests: word-list delayed and recognition recall from the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-Cog) for episodic memory [12]; digit span backwards and the 10-point clock drawing for executive functions [12]; digit span forward and colour trails 1 for attention [12]; time taken and number of errors made on Maze test on ADAS-Cog for visuospatial [13]; and 20-point object naming and comprehension of test instructions on ADAS-Cog for language [13]. Scores were converted into Z-scores. Composite summary index for each domain was derived from the corresponding averages of the individual tests.

2.3. Quantification of cerebral small vessel disease (SVD)

SVD, which included WMHs, lacunes, and PVS, was determined using T1 and FLAIR images. Two raters (HF and YTT), blinded to the clinical information, performed the SVD rating. Inter-rater reliability for WMH, lacunes, and PVS (expressed as Cohen's kappa) were 0.742, 0.796, and 0.630 at baseline; and 0.653, 0.706, and 0.693 for follow-up scans respectively. Intra-rater reliability was determined using the follow-up scans (expressed as Cohen's kappa), which were scored twice by each rater for WMH progression, number of new lacunes and PVS respectively, were 0.825, 0.980, and 0.831 for HF; and 0.874, 0.924, and 0.885 for YTT. Technical details have been previously described [5]. Baseline WMH was assessed using the modified Fazekas 12-point scale. Lacunes have a hyperintense rim around the cavity on FLAIR images and are mostly ovoid/spheroid cavities between 3 mm and 10 mm whereas PVS are smaller and follow the vessel [5]. The burden of baseline and follow-up lacunes as well as PVS was scored in five brain regions: frontal, parieto-occipital, temporal, basal ganglia, and infratentorial [5]. At follow-up, visual rating of WMH progression and new lacunes was performed in a side-by-side fashion blinded to clinical information [5]. Progression of WMH was assessed using the modified Rotterdam Progression scale (absence/presence of progression in 9 brain regions) [5]. New lacunes and PVS were counted in the same region. As a previous postmortem study has demonstrated that 12–18 months follow-up is adequate to see the progression of microscopic vascular lesions [14], this study used 18 months as the benchmark to determine patient's longitudinal SVD status. Either the presence of progression of WMH measured on the modified Rotterdam Progression scale or development of new lacunes and/or PVS was classified as SVD-progression. Subjects who did not meet the criteria for SVD-progression were classified as SVD-no-progression.

2.4. Image acquisition and analyses

All patients underwent MRI on a 3.0 T GE scanner. High-resolution T1-weighted MPRAGE (axial acquisition, 176 slices, matrix size = 256 × 256, voxel size = 1.0 × 1.0 × 1.0 mm^3, TE = 3.2 ms, TR = 7 ms, TI = 850 ms, flip angle 8°, field of view 256 × 256 mm^2) was acquired for all patients at each time-point. Whole brain 3D FLAIR (turbo spin echo, TR = 8000 ms, TE = 340 ms, T1 = 2400 ms, matrix = 256 × 256, slice thickness = 1 mm, 170 slices, voxel size = 1.0 × 1.0 × 1.0 mm^3) was also acquired for all patients.

Cortical reconstruction and volumetric segmentation were performed using *FreeSurfer 5.3* image analysis suit (http://surfer.nmr.mgh.harvard.edu/). In summary, image processing procedures include: motion correction and average of multiple volumetric T1-weighted images, removal of non-brain tissue, automated Talairach transformation, intensity normalization, segmentation of the subcortical white and deep grey matter volumetric structures, tessellation of the grey/white matter boundary, automated topology correction, and surface deformation to optimally place the grey/white and grey/cerebrospinal fluid boundaries [15]. All surface models were inspected for accuracy and manual corrections were performed in the event of tissue misclassification and/or white matter errors while blinded to the diagnostic information. Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a full width at half maximum (FWHM) of 15 mm to reduce local variations in the measurements [16,17].

Comparisons between groups were assessed using a vertex-by-vertex general linear model, including age, gender, education, and baseline intracranial volume as confounders in all analyses. For baseline comparison, the model included cortical thickness as dependent factor and diagnostic group (SVD-no-progression and SVD-progression) as independent factor. For longitudinal analyses, vertex-wise comparison of percentage change of cortical thickness among the progression groups was analyzed using a longitudinal two-stage model, where percentage of cortical thickness was the dependent factor and the diagnostic group was the independent factor. We also examined correlations in regional cortical thickness with clinical-cognitive outcomes. Multiple comparisons were

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