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Longitudinal whole-brain atrophy and ventricular enlargement in nondemented Parkinson's disease

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ABSTRACT

We investigated whole-brain atrophy and ventricular enlargement over 18 months in nondemented Parkinson's disease (PD) and examined their associations with clinical measures and baseline CSF markers. PD subjects (n = 100) were classified at baseline into those with mild cognitive impairment (MCI; PD-MCI, n = 36) and no cognitive impairment (PD-NC, n = 64). Percentage of whole-brain volume change (PBVC) and ventricular expansion over 18 months were assessed with FSL-SIENA and ventricular enlargement (VIENA) respectively. PD-MCI showed increased global atrophy (−1.1% ± 0.8%) and ventricular enlargement (6.9 % ± 5.2%) compared with both PD-NC (PBVC: −0.4 ± 0.5, $p < 0.01$; VIENA: 2.1% ± 4.3%, $p < 0.01$) and healthy controls. In a subset of 35 PD subjects, CSF levels of tau, and Aβ42/Aβ40 ratio were correlated with PBVC and ventricular enlargement respectively. The sample size required to demonstrate a 20% reduction in PBVC and VIENA was approximately 1/15th of that required to detect equivalent changes in cognitive decline. These findings suggest that longitudinal MRI measurements have potential to serve as surrogate markers to complement clinical assessments for future disease-modifying trials in PD.

1. Introduction

Up to 80% of Parkinson's disease (PD) patients eventually develop dementia (PD-D) (Aarsland et al., 2003). However, the pathophysiological substrates of cognitive dysfunction leading up to the demented state remain only partially understood (Nombela et al., 2014; Williams-Gray et al., 2009; Winder-Rhodes et al., 2013, 2015; Yarnall et al., 2013). In parallel with a recent shift toward early interventions and the prospect of disease-modification

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(e.g., immunotherapy and apomorphine) in nondemented PD (Yarnall et al., 2015), there is an urgent need to identify surrogate markers to track disease progression and perform risk-stratification to improve patient enrollment in clinical trials.

At present, psychometric tests and severity rating scales (i.e., Unified Parkinson's Disease Rating Scale, UPDRS) are the *de facto* standard for evaluating disease progression in PD. There is however increasing interest in adopting longitudinal neuroimaging techniques as adjunctive markers of disease progression with the expectation that MRI measurements may provide better sensitivity and precision than standard clinical measures (Jack et al., 2003; Nestor et al., 2008; Schott et al., 2005). In this regard, advances in neuroimaging analyses have contributed to the validation of whole-brain atrophy rates (Smith et al., 2002) as sensitive markers of disease progression in mild cognitive impairment (MCI; Sluimer et al., 2010), frontotemporal dementia (Knopman et al., 2009), and Alzheimer's disease (AD; Fox and Freeborough, 1997; Mak et al., 2015b). In addition, ventricular enlargement has emerged as another viable surrogate but not nonspecific marker of neurodegeneration in MCI and AD (Ferris et al., 2009; Jack et al., 2004; Nestor et al., 2008). Instead of a mere proxy of widespread tissue loss, ventricular enlargement has been linked to a broad range of cognitive and memory deficits, reduced brain reserve against neurodegeneration (Cavedo et al., 2012), and decreased survival in dementia (Olesen et al., 2011).

Power calculations in MCI and AD have consistently shown that whole-brain atrophy and ventricular enlargement would require far smaller sample sizes (approximately 3–10 times reduction) compared with cognitive tests to show differences from controls (Jack et al., 2004; Ridha et al., 2008). This has significant implications on the design of early-intervention and secondary prevention trials that are often hampered by subtle disease-related decline in the prodromal stages (i.e., weak effect sizes) and greater uncertainty that participants are on course for developing dementia (i.e., greater variance in measurements). As a result, these trials would require very long follow-up duration as well as large samples to detect any disease-modifying effects.

Therefore, it is surprising that there are only limited studies investigating the utility of whole-brain atrophy and ventricular enlargement in PD. While increased whole-brain atrophy rates have been reported in PD-D compared with controls (Burton et al., 2005), it remains to be established if MRI-derived measurements of global atrophy are sensitive to changes in a prodromal stage such as PD-MCI, and whether these measurements are feasible in a clinical trial targeting cognitive symptoms in PD. Ventricular enlargement has also been less studied in PD (Camicioli et al., 2011) despite its associations with both motor and cognitive impairment (Apostolova et al., 2012).

Levels of CSF markers have been shown to be promising candidate markers in AD (Blennow and Hampel, 2003; Frisoni et al., 2010) and more recently in PD (Kang et al., 2016). Elucidating the potentially unique role of each CSF marker in the later events of neurodegeneration (i.e., structural atrophy) will have important implications for informing strategies targeting the underlying protein pathologies. In a pooled sample of PD patients, both CSF T-Tau and Aβ levels have been cross-sectionally associated with lateral ventricular size (Beyer et al., 2013), whereas there are only limited studies investigating the involvement of CSF markers and progressive atrophy in PD (Compta et al., 2013).

To address the aforementioned gaps in the literature, we undertook a new study with 3 main objectives: (1) to investigate the suitability of global longitudinal measurements of brain volume (whole-brain atrophy and ventricular enlargement) to monitor disease progression over 18 months in newly-diagnosed PD patients; (2) to evaluate the relationships between baseline CSF markers of neurodegeneration (α-synuclein, tau-protein) and structural changes on imaging using tensor-based morphometry; and (3) to assess the impact of using MRI measurements on future clinical trials in nondemented PD patients by estimating the sample sizes needed to detect a 20%–50% reduction in whole-brain atrophy, ventricular enlargement, and global cognition.

2. Method

2.1. Participants

The Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation-PD is a longitudinal observational study with 2 centers (Newcastle and Cambridge) to understand the disease mechanisms underlying the evolution of PD-D from disease onset (Yarnall et al., 2014). Patients were recruited from community and outpatient clinics in the North East of England. In this study, we included PD subjects (n = 104) and healthy controls (n = 38) who completed baseline and follow-up clinical and T1 MRI imaging at 18 months. PD was diagnosed according to the UK Brain Bank criteria by a movement disorders specialist (Hughes, 2002). Full inclusion and exclusion criteria have been previously described (Yarnall et al., 2014); patients were excluded at baseline if they had a clinical diagnosis of PD-D or scored <24 on the Mini–Mental State Examination. The study was approved by the Newcastle and North Tyneside Research Ethics Committee. All subjects provided written informed consent.

2.2. Clinical and neuropsychological assessment

Clinical assessments were performed by trained examiners and included a standardized neurological examination and rating disability with the Movement Disorders Society (MDS; UPDRS III; Goetz et al., 2008), and Hoehn and Yahr (H&Y) staging (Hoehn and Yahr, 2001). In accordance with MDS Task Force recommendations (Litvan et al., 2012), 5 cognitive domains were assessed: attention was measured using the Cognitive Drug Research computerized battery (Wesnes et al., 2002). Mean response times of simple reaction time, choice reaction time, and digit vigilance were summed to produce a Power of Attention score. Digit vigilance accuracy was also evaluated as part of this domain. Memory was assessed with pattern recognition memory, spatial recognition memory, and paired associates learning from the computerized Cambridge Neuropsychological Test Automated Battery (Fray and Robbins, 1996). Executive function was determined using the modified "One Touch Stockings" (OTS) version of the Tower of London task from the Cambridge Neuropsychological Test Automated battery, phonemic fluency (words beginning with "F" in 1 minute) and semantic fluency (animals in 90 seconds). The pentagon copying item of the MMSE was graded using a modified 0 to 2 rating scale as a measure of visuospatial function (Williams-Gray et al., 2009). Language domain was assessed using the naming (0–3) and sentence (0–2) subsets of the MoCA test. All participants were assessed while they were on their usual dopaminergic medication at baseline and 18 months. Levodopa equivalent daily dose (LEDD) value was calculated using the Tomlinson et al. formula (Tomlinson et al., 2010). Global cognitive function was assessed using the Mini–Mental State Examination (MMSE) (Folstein et al., 1975) and the Montreal Cognitive Assessment (MoCA; Dalrymple-Alford et al., 2010). As our schedule of neuropsychological tests preceded the introduction of the MDS criteria for PD-MCI, we used a modified MDS level II criteria as described previously (Lawson et al., 2016; Yarnall et al., 2014), in that only 1 test (i.e., pentagon copying) was specific to the visuospatial domain. A subject was diagnosed as PD-MCI if he or she performed 1.5 standard deviations (SDs) or