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Pattern of brain atrophy rates in autopsy-confirmed dementia with Lewy bodies

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ABSTRACT

Dementia with Lewy bodies (DLB) is characterized by preserved whole brain and medial temporal lobe volumes compared with Alzheimer's disease dementia (AD) on magnetic resonance imaging. However, frequently coexistent AD-type pathology may influence the pattern of regional brain atrophy rates in DLB patients. We investigated the pattern and magnitude of the atrophy rates from 2 serial MRIs in autopsy-confirmed DLB patients (n = 20) and mixed DLB/AD patients (n = 22), compared with AD (n = 30) and elderly nondemented control subjects (n = 15), followed antemortem. DLB patients without significant AD-type pathology were characterized by lower global and regional rates of atrophy, similar to control subjects. The mixed DLB/AD patients displayed greater atrophy rates in the whole brain, temporoparietal cortices, hippocampus and amygdala, and ventricle expansion, similar to AD patients. In the DLB and DLB/AD patients, the atrophy rates correlated with Braak neurofibrillary tangle stage, cognitive decline, and progression of motor symptoms. Global and regional atrophy rates are associated with AD-type pathology in DLB, and these rates can be used as biomarkers of AD progression in patients with LB pathology.

1. Introduction

Pathologically, dementia with Lewy bodies (DLB) is characterized by unremarkable global brain atrophy on gross inspection, and microscopically by α-synuclein aggregates (Spillantini et al., 1997) in Lewy bodies (LBs) (Kosaka, 1978; Lewy, 1912) and Lewy neurites. However, a frequent concomitant finding is varying the degree of Alzheimer's disease (AD) type pathology, that is, β-amyloid in neuritic plaques and hyperphosphorylated tau in neurofibrillary tangles (NFT) (NIA-Reagan, 1997). This overlap between the 2 most common, yet distinct neurodegenerative dementias in terms of underlying pathology and clinical characteristics, often makes antemortem diagnosis challenging. This applies particularly to DLB patients with a high Braak NFT stage (Merdes et al., 2003) who are often misdiagnosed as having AD in the clinical settings (Schneider et al., 2007). Mixed DLB/AD dementia patients are of considerable interest because of the high frequency of the mixed pathology (Hamilton, 2000; Hansen et al., 1990; Schneider et al., 2007, 2009), their hypersensitivity to neuroleptics, and most important of all, their excellent response to acetyl-cholinesterase inhibitors (Graff-Radford

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et al., 2012; McKeith et al., 2004). Accessible, preferably noninvasive biomarkers, such as those derived from magnetic resonance imaging (MRI), would have an important role in differential diagnosis, tracking of disease progression, evaluation of treatment response, and designing clinical trials with disease-specific therapeutic agents or redesigning those with the currently available treatments in patients with DLB. Moreover, usage of longitudinal MRI measurements may reduce interindividual variability and provide a better insight into the biology of the disease than a single measurement.

Patients with AD are characterized by greater rates of whole brain and hippocampus atrophy, accompanied by greater ventricle expansion over time compared with control subjects in both clinically diagnosed and autopsy-confirmed cohorts (Fox et al., 2000; Jack et al., 2000, 2004; Whitwell et al., 2007a, 2007b). Atrophy rates on MRI have been used to assess treatment response in clinical trials on patients with AD and mild cognitive impairment (MCI) (Fox et al., 2000; Jack et al., 2003, 2008). Greater rates of atrophy on antemortem MRI have been positively associated with high Braak NFT stage and NFT density at autopsy (Josephs et al., 2008a; Silbert et al., 2003).

Relatively preserved medial temporal lobe volumes characterize patients with DLB compared with patients with AD; however, whether DLB patients have sufficient gray matter loss to be distinguished from normal control subjects, remained unclear in clinically diagnosed cohorts that likely included cases with mixed DLB/AD pathology (Barber et al., 2000; Burton et al., 2002, 2004; Harvey et al., 1999; Hashimoto et al., 1998). The involvement of frontal (Ballmaier et al., 2004; Barber et al., 2000, 2002; Whitwell et al., 2007a, 2007b), temporoparietal (Ballmaier et al., 2004; Harvey et al., 1999; Whitwell et al., 2007a, 2007b), and occipital cortices (Middelkoop et al., 2001; O'Donovan et al., 2013) has been observed in patients with DLB, although the findings have been inconsistent.

In autopsy-confirmed cohorts, medial temporal lobe atrophy on cross-sectional MRI has been associated with mixed AD-type pathology in patients with DLB (Burton et al., 2009). Specifically, greater atrophy in the hippocampus and amygdala has been associated with a high Braak NFT stage (Kantarci et al., 2012) and tau-NFT density (Murray et al., 2013) in patients with LB pathology.

In longitudinal MRI studies, clinically diagnosed patients with DLB were reported to have greater whole brain atrophy rates than age-matched controls, similar to patients with AD and vascular dementia (O'Brien et al., 2001). However, greater whole brain atrophy and ventricle expansion rates were limited to patients with mixed DLB/AD pathology compared with control subjects in an autopsy-confirmed cohort (Whitwell et al., 2007a, 2007b). The differences across the studies can be attributed to different sampling schemes (clinical vs. autopsy-confirmed sample), and different methods used to measure the atrophy. Nevertheless, the regional pattern and magnitude of atrophy rates that characterize patients with autopsy confirmed DLB and mixed DLB/AD are unknown.

Our primary objective was to identify the regional pattern of gray matter atrophy rates on antemortem serial MRI in autopsy-confirmed DLB and DLB/AD compared with those with AD and elderly control subjects. We hypothesized that autopsy-confirmed patients with DLB would have similar rates of brain atrophy, compared with elderly control subjects, whereas those with mixed LB and AD-type pathology would be affected more in terms of topographic extent and magnitude of gray matter loss over the time. Our secondary objective was to correlate rates of atrophy with measures of cognitive decline and clinical progression in patients with DLB and DLB/AD; and finally, to report sample size estimates for a hypothetical clinical trial including patients with DLB only and for DLB/AD, using rates of atrophy as surrogate measures of outcome.

2. Methods

2.1. Participants

To be included in this study, participants had to have at least 2 serial 1.5 T brain MRIs approximately 2 years apart of sufficient technical quality and had to come to autopsy. We have chosen the participants exclusively based on the autopsy diagnosis and not the clinical syndrome. We included cases with LB pathology diagnosed as either high likelihood DLB (DLB group) or intermediate and low likelihood DLB (DLB/AD group) according to the Third Report of the DLB Consortium Criteria for DLB (McKeith et al., 2005). We also included cases with high likelihood AD with no LB pathology (AD group) and low likelihood AD with no LB pathology (control group) for comparison. Patients with amygdala-only Lewy bodies ($n = 2$) were included in the DLB/AD group as they had both LB and AD pathology. Patients were excluded if they had concomitant neurologic illness at the time of either one of the MRIs or conditions known to interfere with cognition such as cortical infarcts, normal pressure hydrocephalus, subdural hematoma, or tumor. Those with lacunar infarcts or white matter hyperintensities were included.

Participants were recruited consecutively and followed prospectively until their death between 1999 and 2009 at the Mayo Clinic Alzheimer's Disease Research Center (dementia clinic-based cohort) and Alzheimer's Disease Patient Registry (community-based cohort) (Petersen et al., 1990) in Rochester, MN, USA. During life, participants underwent approximately annual clinical evaluations including standard measures of cognitive and functional performance such as Mini Mental State Examination (MMSE) (Folstein et al., 1975) that has been widely used in the field, the Dementia Rating Scale (DRS) (Mattis, 1988), which has greater dynamic range than MMSE. The severity of parkinsonism was quantified with the motor subtest of Unified Parkinson Disease Rating Scale (UPDRS) (Fahn et al., 1987). Progression of the disease was measured by subtraction of baseline from follow-up score and then annualized for consistency with imaging measures. Clinical diagnosis was established by the consensus of neurologists, neuropsychologists, and nurses. The diagnosis of probable AD was made according to NINCDS-ADRDA criteria for AD (McKhann et al., 1984). The diagnosis of probable DLB was made using the third report of the DLB Consortium criteria for DLB (McKeith et al., 2005), and diagnosis of MCI was based on Petersen criteria (Petersen, 2004). Informed signed consent was obtained from all individuals or their proxies antemortem, and study was approved by the Mayo Clinic Institutional Review Board.

2.2. Neuropathologic examination and diagnosis

Brains were processed, sectioned, and sampled using standardized methods (McKeith et al., 2005; Mirra et al., 1991). In all 87 cases, the examination and diagnosis were conducted by one of 2 experts (Dennis W. Dickson or Joseph E. Parisi) using standard staining and standard criteria (Braak and Braak, 1996), and also immunohistochemistry to determine the distribution and to semi quantitatively measure NFT density with corresponding Braak NFT stage. For Lewy body disease, cases were classified as brainstem-, limbic-, or neocortical-predominant according to the distribution and counts of LBs immunostained with monoclonal antibodies to α-synuclein. Based on the findings, we defined the study groups as follows: (1) cases with AD ($n = 30$) had high-probability AD according to the National Institute of Aging-Reagan criteria (NIA-Reagan, 1997). That is, the presence of frequent neuritic plaques corresponding to probable or definite AD according to Consortium to Establish Registry for Alzheimer's Disease criteria for AD (Mirra et al., 1991), Braak NFT stage of V or VI and no LBs; (2) cases with DLB ($n = 20$) were