Regional Multiple Pathology Scores Are Associated with Cognitive Decline in Lewy Body Dementias

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Keywords
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INTRODUCTION

The pathological substrate of dementia and cognitive decline in Lewy body dementias is an important issue for the development of biomarkers to measure outcome and for intervention studies. In both dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD), the severity of dementia is often considered to be a function of cortical Lewy body formation (12) although senile plaques and neurofibrillary tangles, the pathognomonic features of Alzheimer’s disease (AD), are also found in DLB and PDD (14, 21). There has been considerable recent interest in this area with a number of studies focusing on the overlap of Alzheimer and Lewy body pathologies, although few reports have included cognitive or other clinical assessments of severity. Two recent studies (11, 24), despite only including patients with PDD and PD (and not DLB), are perhaps the most informative, highlighting the possible importance of cortical Aβ and phosphorylated tau (phosphotau) in the rate of decline into dementia. Analyses in other studies, however, support the role of α-synuclein in determining the decline in cognitive state in both PDD and DLB (23, 43).

To address this issue, in our study, neuropathology (senile plaques, phosphotau pathology and α-synuclein-positive Lewy bodies and neurites) has been analyzed in groups of DLB and PDD 34 DLB and 55 DLB patients was assessed semi-quantitatively in four regions of the neocortex. The decline in cognition, assessed by Mini Mental State Examination, correlated positively with the cortical α-synuclein load. Patients also had varying degrees of senile Aβ plaque and phosphotau pathology. Regression analyses pointed to a combined pathology (Aβ plaque plus phosphotau plus α-synuclein-positive features), particularly in the prefrontal cortex (BA9) and temporal lobe neocortex with the superior and middle temporal gyrus (BA21, 22), being a major determining factor in the development of dementia. Thus, cognitive decline in Lewy body dementias is not a consequence of α-synuclein-induced neurodegeneration alone but senile plaque and phosphorylated tau pathology also contribute to the overall deficits.

Abstract

Dementia with Lewy bodies (DLB) and Parkinson’s disease dementia (PDD) are characterized by the presence of α-synuclein-containing Lewy bodies and Lewy neurites. However, both dementias also show variable degrees of Alzheimer’s disease (AD) pathology (senile plaques and neurofibrillary tangles), particularly in areas of the cortex associated with higher cognitive functions. This study investigates the contribution of the individual and combined pathologies in determining the rate of cognitive decline. Cortical α-synuclein, phosphorylated tau (phosphotau) and Aβ plaque pathology in 34 PDD and 55 DLB patients was assessed semi-quantitatively in four regions of the neocortex. The decline in cognition, assessed by Mini Mental State Examination, correlated positively with the cortical α-synuclein load. Patients also had varying degrees of senile Aβ plaque and phosphotau pathology. Regression analyses pointed to a combined pathology (Aβ plaque plus phosphotau plus α-synuclein-positive features), particularly in the prefrontal cortex (BA9) and temporal lobe neocortex with the superior and middle temporal gyrus (BA21, 22), being a major determining factor in the development of dementia. Thus, cognitive decline in Lewy body dementias is not a consequence of α-synuclein-induced neurodegeneration alone but senile plaque and phosphorylated tau pathology also contribute to the overall deficits.