Dementia with Lewy bodies and PD dementia: Part of one continuum or two distinct entities? Two distinct entities

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Age-related neuropsychiatric disorders such as Parkinson disease with and without dementia (PDD and PD, respectively), dementia with Lewy bodies (DLB), and Alzheimer disease dementia (AD) represent a growing socioeconomic challenge. These disorders show substantial clinical and neuropathological overlap, limiting diagnostic accuracy and questioning the concept of distinct clinical entities. Indeed, the notion that PD and AD may be extremes of a spectrum of neurodegenerative diseases, with DLB and PDD presenting overlapping neuropathologic and clinical features within this spectrum, has received growing attention in recent years. Although pathophysiologically and clinically different, PD and AD share some aspects in common; both are age-related neurodegenerative disorders characterized by aggregation of pathologic proteins leading to dysfunction of cerebral networks and distinct patterns of metabolic changes. Cases characterized by pure PD (α-synuclein aggregation) or pure AD (amyloid-β and tau aggregation) pathology do not represent most affected patients. Biologically and histopathologically, there is an overlap of these age-associated proteinopathies. They form a continuum with concomitant amyloid-β-, tau-, and α-synuclein aggregation as well as microvascular changes. DLB and PDD are age-related neurodegenerative disorders sharing clinical and histopathologic aspects with both PD and AD. Hence, they can be seen as intermediate neurodegenerative disorders in a spectrum between pure PD and pure AD. Because the pattern of histopathology, neuronal network dysfunction, and associated clinical deficits is indeed continuous, the traditional view of distinct disease entities is increasingly being questioned.

Temporal differences in the emergence of symptoms and clinical features warrant the continued clinical distinction between DLB and PDD. While DLB and PDD groups' neuropsychological profiles often differ from those in AD, the diagnostic sensitivity, specificity, and predictive values of these profiles remain largely unknown. PDD and DLB neuropsychological profiles share sufficient similarity to resist accurate and reliable differentiation. Although heterogeneous cognitive changes (predominantly in memory and executive function) may manifest earlier and more frequently than previously appreciated in PD, and executive deficits may be harbingers of dementia, the enthusiasm to uncritically extend the concept of mild cognitive impairment (MCI) to PD should be tempered. Instead, future research might strive to identify the precise neuropsychological characteristics of the prodromal stages of PD, PDD, and DLB which, in conjunction with other potential

biomarkers, facilitate early and accurate diagnosis, and the definition of neuroprotective, neurorestorative, and symptomatic treatment endpoints

Biomarker-based approaches targeted to disentangle histopathology-clinical relationships within this spectrum may further help to guide classification of neurodegenerative disorders and treatment stratification. Imaging and fluid biomarker studies are available that support the notion of distinct disease entities, but research also supports the idea of a continuum of cerebral changes between the two extremes of pure AD and pure PD. The present paper will present the relevant evidence and argue in favour of the two distinct entities approach.