

The Neuropathologic Substrate of Parkinson Disease Dementia

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Dementia has been increasingly recognized to be a common feature in patients with Parkinson disease (PD), especially in old age, referred to as Parkinson disease dementia (PDD), and in dementia with Lewy bodies (DLB), which are currently believed to represent two phenotypes in a disease spectrum, characterized pathologically by deposition of α -synuclein (α -Syn) within nerve cells (Lewy bodies, LBs) and dystrophic (Lewy) neurites in the central and autonomic nervous system, and clinically by a variable mixture of cognitive, neuropsychiatric, extrapyramidal, and vegetative features.¹⁻³ Clinical and pathological diagnostic criteria for PDD and DLB and interrater assessment of α Syn pathology have been published recently.²⁻⁶

Dementia in PD with incidence rates of 95-112.5/100 patient-years (odds ratio for dementia in PD of 3.5), a point prevalence close to 30% and a cumulative prevalence between 48 and 78% after 15 and 18 years follow-up, respectively, is suggested to have a 4 to 6 times increased lifetime incidence rate compared to age-matched controls.⁵ Prevalence estimates for DLB, depending on criteria, range from 0 to 5% of the general population and, in several autopsy series, from 0 to 30% (mean 15-20%) of all dementia cases, with an incidence of 0.1 per year for the general population and 3.2% per year for new dementia cases.⁷ A recent clinico-pathologic study confirmed essential clinical differences between PD with and without dementia and DLB: PDD patients were significantly older at death and had a shorter duration of illness and lower mini-mental status examination (MMSE) scores than non-demented PD cases.^{8,9}

Morphologic Substrates of Cognitive Impairment in Parkinson Disease

Central nervous system lesions contributing to cognitive impairment in PD are heterogeneous, including dysfunction of subcortico-cortical (striato-subfrontal, cholinergic fore-brain) networks due to neuronal loss in brainstem and limbic areas, cholinergic deficits in cortical regions and thalamus, associated with decreased striatal dopaminergic function,^{10,11} widespread decrease of nicotinic acetylcholine receptors,¹² and, in particular, limbic and cortical LB and Alzheimer pathologies with loss of synapses and neurons,^{2,6,13-15} presynaptic α Syn aggregates causing synaptic dysfunction,¹⁶ or variable combinations of these changes that may have common origins with mutual triggering due to suggested synergistic reactions between α Syn, amyloid peptide and tau protein, the major protein markers of both LB diseases and AD.^{9,17-20} Although a few cortical LBs are found in virtually all cases of sporadic PD (brainstem type of LB disease), the impact of cortical LB and AD pathologies on cognitive impairment in PD is a matter of discussion. Recent studies have demonstrated that the number of LBs in the frontal gyri is the most significant predictor of cognitive status in PD,²¹ and that LB densities in the limbic cortex are a better predictor of dementia in PD than Alzheimer-type pathology.²²⁻²⁴ Some authors demonstrated increasing cognitive decline (with decreasing MMSE scores) with increasing LB stages from 3 to 6, i.e. progression of α Syn pathology,¹⁴ while others have not found such an association.^{9,25-29} In an autopsy series of 330 elderly patients with clinical parkinsonism (37.6% of which with dementia), only 1.6% of the demented patients (MMSE<20) showed LB Braak stages 3-5, which was found in the majority of non-demented PD cases, while 35.5% of demented PD cases revealed morpho-

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logic LB stages 4 or 5 with superimposed severe Alzheimer-type pathology (neuritic Braak stages 5 and 6). More than half of them showed a strong relationship between the severity of α Syn and tau pathologies, particularly in the limbic system. DLB with low or high-grade Alzheimer lesions were seen in 40% of PDD patients, but almost one-third of diffuse DLB cases, i.e. those with mild AD lesions restricted to amyloid plaques or tau pathology in the limbic system, did not show considerable dementia.⁶ Neuropathology revealed lower brain weight in PDD than in the two other groups, and significantly more severe Alzheimer-type pathology (neuritic Braak stages, cortical amyloid plaque load and generalized cerebral amyloid angiopathy, CAA) in PDD and DLB than in non-demented PD cases, while the LB scores were moderately increased in PDD and highest in DLB. Significantly increased amyloid plaque load in the cerebral cortex in PDD and DLB is in agreement with previous studies,³⁰⁻³³ whereas others did not find any correlation between cortical A β deposition and cognitive impairment in DLB.³⁴ Increase of amyloid load in meningeal and cortical vessels (CAA) in both PDD and DLB is also in agreement with previous studies.^{35,36} In general, significant association between cortical amyloid plaque load, general CAA and neuritic Braak stages, the latter increasing with age, is observed, suggesting an influence of Alzheimer-related pathology on the progression of the neurodegenerative process and, in particular, on cognitive decline in both PDD and DLB. On the other hand, both these factors in PD and DLB appear to be largely independent from coexisting vascular pathology, except in cases with severe cerebrovascular lesions or those related to neuritic Alzheimer pathology.⁹

Morphologic Comparison between Parkinson Disease Dementia and Dementia with Lewy Bodies

The neuropathology of PDD and DLB shows similarities and slight differences. The morphology and immunohistochemistry of cortical and subcortical LBs and the ascending spreading pattern of α Syn pathology with onset in the low brainstem and progression via midbrain, dorsal forebrain, amygdala limbic system to the neocortex³⁷ do not significantly differ between both phenotypes, the late stages 5 and 6 of LB pathology (involvement of sensory association and prefrontal primary sensory and motor areas) suggesting transition between PD and DLB.² However, there are some deviations between DLB and PDD in the severity and distribution pattern of lesions in substantia nigra compacta (less severe damage in DLB involving dorsolateral versus medioventral nuclei in PD) and more frequent α Syn pathology in the hippocampal subarea C 2/3 in DLB (79 vs. 36%). A major difference is the usually more frequent severe diffuse amyloid plaque load and less severe tau pathology in the striatum in DLB cases, irrespec-

tive of the severity of cortical neuritic Alzheimer lesions, while non-demented PD cases are virtually free of striatal amyloid plaque load.^{38,39} The question, whether PD, PDD and DLB are different disorders or represent a single entity with distinct clinical and pathologic phenotypes is still considered controversially, while some genetic and biochemical differences argue for a separation between DLB/PDD and AD.² Recent studies indicating synergistic interactions between α Syn, amyloid peptide and tau protein, common markers for both PD and AD, and the frequent co-occurrence of these pathologies³¹ suggest common underlying mechanisms inducing both neurodegeneration and fibrillary protein aggregation that are typical of these disease processes (double or triple amyloidosis⁴⁰), but it is unclear whether these lesions represent different pathogenic pathways or a final pathology leading to neuronal degeneration causing both movement disorders and dementia. The molecular background and clinical/pathophysiological impact of these and other pathologies on the progression and development of cognitive impairment in PD and other LB disorders remain to be further elucidated.

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