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The Significance of α-Synuclein, Amyloid-β and Tau Pathologies in Parkinson's Disease Progression and Related Dementia

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Abstract

Background—Dementia is one of the milestones of advanced Parkinson's disease (PD), with its neuropathological substrate still being a matter of debate, particularly regarding its potential mechanistic implications.

Objective—The aim of this study was to review the relative importance of Lewy-related α-synuclein and Alzheimer's tau and amyloid-β (Aβ) pathologies in disease progression and dementia in PD.

Methods—We reviewed studies conducted at the Queen Square Brain Bank, Institute of Neurology, University College London, using large PD cohorts.

Results—Cortical Lewy- and Alzheimer-type pathologies are associated with milestones of poorer prognosis and with non-tremor predominance, which have been, in turn, linked to dementia. The combination of these pathologies is the most robust neuropathological substrate of PD-related dementia, with cortical Aβ burden determining a faster progression to dementia.

Conclusion—The shared relevance of these pathologies in PD progression and dementia is in line with experimental data suggesting synergism between α-synuclein, tau and Aβ and with studies testing these proteins as disease biomarkers, hence favouring the eventual testing of therapeutic strategies targeting these proteins in PD.

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Keywords

Parkinson's disease; Dementia; Lewy-type pathology; Alzheimer-type pathology; α-Synuclein; Tau; Amyloid-β; Biomarkers

Dementia and other milestones of Parkinson's disease (PD) progression such as hallucinations and falls dominate the clinical picture of 20-year survivors [1]. Clinically, PD with dementia (PDD) and dementia with Lewy bodies are very similar, and therefore, their distinction is merely one of clinical convenience [2]. Besides the potential role of alternative pathologies such as degeneration of cholinergic nuclei or vascular damage, Lewy-type (α-synuclein aggregates) and Alzheimer-type [amyloid-β (Aβ) plaques and tau neurofibrillary tangles] lesions co-exist in PD [3,4,5]. Our group showed a significant linear relationship between cortical Aβ and α-synuclein in a subgroup of PD [5], in accordance with experimental data indicating that these proteins might mutually promote each other's aggregation [6], probably with a selective cross-seeding ability of distinct strains of these proteins [7]. A better understanding of this heterogeneous PDD neuropathology is important as cerebrospinal fluid (CSF) and molecular neuroimaging (PET) biomarkers that allow the investigation of these pathologies in vivo, are already available [8,9,10] and might prove helpful for selecting the appropriate therapeutic approaches in the future.

Here, we review the available evidence on the topic, focusing particularly on studies conducted using archival material from the Queen Square Brain Bank, University College London Institute of Neurology, UK.

Neuropathology of PD Subtypes and PD Progression

The differences across PD phenotypes were examined by a systematic review of 242 pathologically proven PD cases [11]. Thus, early-onset cases were shown to have a longer disease course and delay to the onset of falls and cognitive milestones. In contrast, non-tremor-dominant cases had a significantly greater burden of both Lewy- and Alzheimer-type pathologies and accounted for most of the early dementia cases. Subsequently, four milestones of advanced disease (falls, visual hallucinations, dementia and nursing home placement) were considered in 129 pathologically proven PD cases with regard to their age at onset [12]. Accordingly, the time of the first milestone negatively correlated with age at disease onset in such a way that the younger the patients were at disease onset, the later the first milestone appeared ($r = -0.62$; $p < 0.0001$). However, the time between the milestones and death was similar in each age-at-onset group, suggesting an exponential rather than a linear relationship where younger-onset cases with a longer disease course eventually speed up to match the accelerated disease course of older-onset ones. The number of milestones showed a modest yet significant correlation with Lewy body scores ($r = 0.36$; $p < 0.0005$).

Neuropathology of PDD

Fifty-six pathologically proven cases with clinical information detailed enough to retrospectively classify them as demented (n = 29) or not (n = 27) were assessed to determine the relative and combined associations of cortical α-synuclein, Aβ and tau

pathologies with PDD [13]. Despite a trend for non-demented cases towards a lower Braak α-synuclein stage than demented ones (stages 5 vs. 6, respectively), almost all had reached the stage of cortical α-synuclein pathology [14], whereas semiquantitative and quantitative measures of Lewy pathology were more discriminant of dementia than Braak PD stages. Regarding neurofibrillary tau pathology [15], this was mostly restricted to the entorhinal areas in non-demented cases, spreading out to the rest of the limbic system, lateral temporal areas and even beyond in the demented ones. All regional and total cortical and subcortical Aβ plaque scores were significantly greater in demented versus non-demented cases. While each type of pathology (cortical Lewy and Aβ scores, and tau stages) showed a modest dementia-discriminant ability, the combination of the three pathologies almost perfectly discriminated demented from non-demented cases. A greater cortical Aβ load was the pathological type determining a faster rate to dementia from disease onset, as previously suggested by others [16,17].

These Findings in Perspective

Despite the usual limitations of the retrospective clinical assessment and the cross-sectional assessment of end-stage neuropathology, along with the relatively modest sample sizes, these findings are similar to other neuropathological studies [4,16,17,18,19,20] and in keeping with experimental evidence of a synergistic interaction between Lewy- and Alzheimer-related proteins [6,7]. Furthermore, CSF and PET biomarkers of Alzheimer-type pathology have been associated in PD with neuropsychological deficits [21,22], quantitative MRI measures of brain atrophy [23,24], longitudinal progression of cognitive impairment [25,26] and the non-tremor and postural instability phenotypes [27,28]. However, the in vivo assessment of the combined associations of Lewy and Alzheimer pathologies with PD progression and dementia still requires proper validation of candidate CSF α-synuclein biomarkers [10].

Conclusions

Non-tremor dominant PD is associated with dementia and more widespread Lewy- and Alzheimer-type pathologies.

Lewy body scores correlate with the accumulation of milestones of poor prognosis, which show an exponential progression across age-at-onset groups.

The combination of cortical Lewy bodies, Aβ plaques and neurofibrillary pathology stages is the most robust neuropathological substrate of PDD, with high cortical Aβ determining a faster progression to dementia.

These neuropathological findings are in keeping with experimental and in vivo biomarker studies, suggesting a relevance of these mixed pathologies in PD progression and dementia.

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