Crossover between Lewy Body Pathology and Alzheimer’s Dementia

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Several recent studies have shown that dementia is common in Parkinson’s Disease (PD), and that in some patients, cognitive impairment occurs even at the time of diagnosis. The point prevalence of dementia in PD (PDD) is close to 30% and the cumulative prevalence is very high, up to 80% of PD patients who survive for more than 10 years will develop dementia [1]. Nearly 20% of subjects with early, untreated PD are classified as Mild Cognitive Impairment (MCI) [2]. In this study among PD-MCI patients, nearly two-thirds had a non-amnestic MCI subtype, and one third had an amnestic MCI subtype. Clinical predictors of PDD are old age, severity of motor symptoms, in particular postural and gait disturbances, mild cognitive impairment, visual hallucinations and male gender [3]. The severity of Cortical Lewy Body (CLB)/Lewyneurite (LN) pathology has been positively associated with dementia, with an odds ratio (OR) of 4.1 as has beenapolipoproteinE4 (APOE4) genotype [OR, 4.2] [4].

PD dementia is characterized by impairment in attention, memory, executive and visuospatial functions in conjunction with behavioral changes, hallucinations, and apathy. There are no specific ancillary investigations for the diagnosis; the main pathological correlate is Lewy body-type degeneration in cerebral cortex and limbic structures. Features that distinguished PDD from Alzheimer’s Dementia (AD) include cognitive fluctuations, visual and auditory hallucinations, depression, and sleep disturbance. These PDD features were identical to those observed for Dementia with Lewy Body (DLB). Galvin et al. reported that the pathologic substrates for PDD included DLB (38%), AD (32%), and nigral LB alone (24%) [5]. Another study found that nearly 30% of all PD cases had sufficient pathology for comorbid AD, of whom 90% were demented [4]. The neuropathological diagnosis of PDD+AD correlated with an older age of PD onset, higher CLB/LN burden, and cerebral amyloid angiopathy severity.

Montine et al. reported reduced CSF Aβ (42) in PD-Cognitive Impairment (PD-CI) and PDD, whereas average CSF T-tau and P181-tau were unchanged or decreased [6]. One-third of PD-CI and one-half of PDD patients had the biomarker signature of AD. These findings could indicate that abnormal metabolism of Aβ (42) may be a common feature of PD-CI and PDD. Furthermore, while dementia in Parkinson’s disease is well described, PD features in Alzheimer’s disease are being increasingly recognized.

In 20 neuropathologically confirmed AD brains, 11 cases (55%) showed PD changes (Lewy body formation, neuronal loss, and gliosis of pigmented nuclei) [7]. A history of rigidity was noted in 80% of those with PD pathology but only 14% of those without PD pathology. Tremor was not observed in either group. This may suggest that extrapyramidal signs, especially rigidity, noted in many AD patients are related to coexistent PD-related pathology.

The α-synucleinopathy, Dementia with Lewy Bodies (DLB), is the second most common cause of neurodegenerative dementia after Alzheimer’s disease. Although the mechanisms of pathogenesis in AD and DLB are different, many patients with DLB have a varying degree of AD pathology in addition to Lewy Related Pathology (LRP) [8]. Most patients with DLB are pathologically characterized by the presence of β-amyloid deposition. In addition, in vivo PET amyloid 11C-Pittsburgh Compound B (PiB) binding is noted in up to 80% of patients with DLB, although at lower levels than in AD [9]. Although amyloid deposition is central to the pathology of AD, it does not correlate with cognitive function as well as the neurofibrillary pathology of AD [10].

Furthermore, diffuse amyloid plaques, which are a common in patients with DLB [11], but not a diagnostic feature of AD contribute to PiB retention in LB diseases [12]. Unlike DLB, the pathological hallmark of AD is the presence of neuritic amyloid plaques. Brain amyloid load on amyloid ligand PET imaging by itself is insufficient for determining presence of neuritic plaques in patients with DLB [13]. On the other hand, hippocampal atrophy, as seen by MRI, has been reported as a distinguishing feature of AD compared to DLB in clinically diagnosed cohorts and autopsy confirmed cases [14]. The presence of occipital lobe hypometabolism also differentiates patients with DLB from AD in both clinically diagnosed [15]. Besides, occipital hypometabolism is associated with visual hallucinations in DLB. Alike AD, this metabolic impairment in the occipital lobe responds to cholinesterase treatment, suggesting a link between cholinergic dysfunction, clinical symptoms and occipital lobe hypometabolism in DLB [16].

The association between apolipoprotein E ε4 allele and AD is well established. More recent studies have indicated APOE ε4 allele as a strong risk factor across the Lewy Body
disease spectrum. The APOE ε4 allele frequency has been found significantly higher in the AD (38%), DLB (32%), and PDD (19%) groups compared with the control group (7%) [17]. The elevated ε4 frequency in the DLB and PDD groups, in which the overall brain neuritic plaque burden is low, indicates that apoE might contribute to neurodegeneration through mechanisms unrelated to amyloid processing. Consequently APOE ε4 could increase the likelihood of presenting with dementia in the context of a pure synucleinopathy. Along these lines, Lewy Related Pathology (LRP) has been identified in familial AD [18]. In fact, this study found that 96% of the Presenilin (PSEN) 1 mutation cases had LRP in the amygdala. The PSEN 1 mutation cases also had more frequent LRP in the amygdala and neocortex than those with the PSEN 2 mutation. These findings possibly suggest that there are genetic influences on the presence of LRP in familial AD.

In summary, CLB/LN pathology is the most significant correlate of DLB and PDD. However, AD pathology is abundant in a subset of Lewy body disease spectrum with an increased frequency in DLB relative to PDD, and could modify the clinical phenotype. In addition, APOE ε4 may increase the likelihood of presenting with dementia in the context of aα-synucleinopathy. Consequently, therapies that target α-synuclein, tau, or amyloid β could potentially improve cognitive function in PDD and DLB.

REFERENCES