Comparing Cerebral White Matter Lesion Burdens between Parkinson’s Disease with and without Dementia

Cerebral white matter lesions (CWMLs) have been suggested to be associated with an increased risk of dementia, disability, and death. CWMLs are more common in individuals with Alzheimer’s disease (AD) than in normal elderly individuals of comparable age. Only a few studies have been done to determine whether CWMLs may influence cognitive decline in Parkinson’s disease (PD). Fully developed PD with concurrent AD was reported to likely cause impaired cognition in spite of accumulating evidence suggesting that PD with dementia (PDD) is more closely associated with Lewy body (LB) pathology. Currently, contradictory data on the neuropathology of dementia in PD require further prospective clinicopathological studies in larger cohorts to elucidate the impact of AD and α-synuclein (SCNA) pathologies on the cognitive status in these disorders. Previous reports did not suggest CWMLs to be associated with an increased risk of PDD. After adjusting for age at death, age at onset of PD, and duration of PD, our recent study investigating CWMLs in PDD via autopsy has shown a positive correlation between the burden of CWMLs and PDD. The frequent co-existence of both LB and AD lesions suggests that both pathologies independently or synergistically contribute to both movement disorders and cognitive impairment. The individual and cumulative burden of CWMLs, LB lesions, and AD lesions may synergistically contribute to cognitive decline in LB disorders such as PDD.

Key Words: Parkinson’s disease, White matter lesions, Dementia.
aim to stimulate discussion and further research on CWMLs in relation to PDD pathology.

**Cerebral White Matter Lesions in Dementia**

CWMLs have been described in various conditions, including normal aging, vascular dementia (VD), and AD. These lesions are commonly observed on magnetic resonance imaging (MRI) scans of elderly people and are associated with an increased risk of stroke, dementia, and depression. Despite a number of neuropathological studies, the pathologic correlates of white matter hyperintensities remain unclear; it is believed, however, that CWMLs are of vascular origin, most notably ischemia. Even though demyelination is the most consistent finding, a range of pathologies has also been reported, including arteriosclerosis, axon loss, gliosis, dilated perivascular spaces, spongiosis, and lacunar infarcts. The accumulation of CWMLs and incident lacunar infarcts not only predicts cognitive decline, but also parallels it over time, strongly suggesting that these lesions play a causative role. Progression of CWMLs also correlates with cognitive decline, but this association is complex and modulated by other morphological factors such as brain atrophy. Periventricular white matter hyperintensities (PVWMH), a form of CWMLs, are considered benign, but probably underlie impairment in cognitive processing speed. According to a recent study, subcortical ischemic vascular disease (SIVD)-as a manifestation of cerebral small vessel disease and defined according to imaging criteria-is related to progressive cognitive impairment and development of dementia. SIVD seems to specifically contribute to the deterioration of psychomotor speed, executive control, and global cognitive function.

**Cerebral White Matter Lesions and Lewy Body Disorders**

Several studies have investigated CWMLs in patients with PD. Piccini et al. suggested PVWMH as a marker for a clinical subtype of PD characterized by a more rapid neurodegenerative process. Sohn and Kim showed the possible influence of CWMLs (observed via MRI) on parkinsonian motor symptoms, particularly gait, bradykinesia, and response to levodopa. Widespread microstructural damage to frontal and parietal white matter has recently been noted to preferentially occur in PD compared with normal controls.

Only a few studies have examined whether CWMLs influence cognitive decline in PD. The MRIs of patients with Lewy body dementia (LBD) revealed significantly more extensive CWMLs than those of control patients. The concomitant presence of white matter lesions in patients with PDD had no significant effect on cortical acetylcholinesterase (AChE) activity. Burton et al. observed the significant progression of CWMLs on brain MRIs in PDD and suggested that CWMLs might contribute to dementia in PD. Some authors have observed more severe white matter pathology in the temporal and visual association fibers in patients with LBD than in patients with PDD. Vascular risk factors, along with white matter vascular abnormalities, most likely did not contribute to the cognitive impairment in patients with PD. Another study investigated the difference of total volume or spatial distribution of white matter hyperintensities on brain MRIs between mild cognitive impairment (MD-CI) and cognitively normal (PD-cogNL) subjects with PD, as well as normal control subjects, and found no significant differences among the three groups. MRI volumetric measurements for brain atrophy and white matter hyperintensities were not significant predictors of cognitive functions in PD patients. We recently studied CWMLs in PDD through autopsy, excluding cases with concurrent pathology meeting criteria for AD, hippocampal sclerosis (HS), VD, and progressive supranuclear palsy (PSP). The crude mean white matter score and the prevalence of positive white matter scores were not higher in the 26 PDD patients compared with the 25 PD-cogNL patients. However, after adjusting for confounding factors like age at death, age at onset of PD, and duration of PD, the odds ratio for dementia versus positive white matter scores was 2.6 (95% CI = 0.43-16), suggesting a significant correlation between the burden of white matter changes and dementia in PD patients.

**Modern Hypothesis of Pathophysiological Impact on the Development of Cognitive Decline in Parkinson’s Disease**

**LB pathology**

Autopsy studies in early clinicopathological research on PD were based largely on findings of hematoxylin-eosin and silver impregnation techniques that underestimated cortical LB. The advent of ubiquitin and α-synuclein (SCNA) immunohistochemical techniques has led to improved diagnosis by allowing more specific, sensitive detection of LB pathology. Senile plaques are frequently present in PD cases with advanced dementia, but the burden of plaque pathology is typically no greater than that found in non-demented controls. Furthermore, plaques were absent in PD cases with mild cognitive impairment (MCI). A post-mortem examination of 12 PD patients with dementia suggested that the average SCNA-stained LB counts were increased nearly 10-fold in the neocortex and limbic areas compared with nine PD patients without dementia. Dementia is nearly always concurrent with the presence of plaques and neurofibrillary tangles (NFTs), but many cases of dementia do not show plaques and NFTs. LB pathology is both sensitive and specific for the diagnosis of PDD, whereas plaques and tangles are specific but lack sensitivity.
and Matilla et al.\textsuperscript{37} showed a significant correlation between LB counts or stage and dementia. In a meta-analytic study, the sensitivity of the correlation with dementia was 100% for cortical LB compared with only 63.9% for NFTs or senile plaques.\textsuperscript{3}

**AD type pathology**

Fully developed PD with concurrent incipient AD likely caused impaired cognition.\textsuperscript{38,39} Although accumulating evidence suggests that PDD is more closely associated with LB pathology, Neuritic AD pathology, either alone or in combination with cortical and limbic LB, has recently been found to be a major cause of mental and cognitive dysfunction in PD.\textsuperscript{4} Clear evidence shows that AD and PD pathologies overlap in some patients. According to Jellinger, mental and cognitive impairment in PD may be related to a variety of lesions, including pathology of subcortical nuclei with degeneration of subcortico-cortical loops, LB pathology in cortical and limbic structures, neuritic AD pathology, or a combination of these lesions, causing neuronal and synaptic dysfunctions.\textsuperscript{40,41} In that cohort study, only single cases of stage 5 PD without accompanying pathologies were demented, whereas around one-third of PDD cases showed severe coexistent neuritic AD pathology.\textsuperscript{40} Aβ deposition may be associated with enhanced cortical SCNA lesions in LB disorders.\textsuperscript{42} Demented individuals exhibited more severe cortical AD-associated neurofibrillary pathology than non-demented patients with PD.\textsuperscript{41}

**Pathogenic relationship between LB pathology and AD type pathology and clinical impact**

Cognitive decline can develop in the presence of mild PD-related cortical pathology. Conversely, widespread cortical lesions do not necessarily lead to cognitive decline.\textsuperscript{44} Senile plaques are frequently present in PD cases with advanced dementia, but the burden of plaque pathology is typically no greater than that found in non-demented controls; furthermore, plaques are absent in PD cases with PD-MCI.\textsuperscript{36,44} The contradictory data on the neuropathology of PDD require further clinicopathological studies in larger cohorts to elucidate the impact of AD and SCNA pathologies on the cognitive status in these disorders. One study investigating the impact of vascular and Alzheimer pathologies in disorders with LB reported that superimposed AD-pathology in PD increases with age and is significantly more severe in PDD patients than in those without dementia.\textsuperscript{8,13} On the other hand, a positive association has been shown between LB score and neuritic Braak stage, suggesting an interaction between these pathologies.\textsuperscript{5} Tau and SCNA accumulation in dementia with Lewy bodies (DLB),\textsuperscript{45} as well as clinical, biochemical, and morphological overlapping features among sporadic PD, DLB, and AD, suggest that the process of LB formation might be triggered, in part, by AD pathology. The frequent co-existence of both LB and AD lesions in PD suggests that both pathologies independently or synergistically contribute to both movement disorders and cognitive impairment. Their exact pathogenic relationship and clinical impact still need further clarification, however.\textsuperscript{8,11,13,44-48} Several studies imply an association between cerebral amyloid angiopathy and cognitive decline in both PDD and DLB, particularly in cases with concomitant AD-type pathology.\textsuperscript{5,22,50,52-54} These studies suggest synergistic reactions between SCNA and Aβ peptide as well as SCNA and tau, with frequent co-occurrence of these pathologies. Further clarification is needed on the molecular and clinical pathophysiological impact of the aforementioned as well as of CVLs on the development of cognitive impairment in LB disorders.

**CWMLs’ role in cognitive decline in PD**

It remains unclear if the burden of CWMLs correlates with cognitive decline,\textsuperscript{52} even in AD.\textsuperscript{24,53,54} PVWMH, a form of CWMLs that has been considered to be benign, probably leads to impairment in cognitive processing speed.\textsuperscript{29} Some studies suggest that vascular risk factors and white matter vascular abnormalities do not contribute significantly to cognitive impairment in patients with PD.\textsuperscript{20} Some data do not suggest that CWMLs are associated with an increased risk of dementia in PD, but more recent data suggest the contrary.\textsuperscript{18,19,21} CWMLs are more common in AD than in normal elderly individuals of comparable age.\textsuperscript{17} The frequent co-existence of both LB and AD lesions in PD suggests that both pathologies may independently or synergistically affect cognitive decline in PD. Thus, it can be hypothesized that CWMLs may contribute to cognitive decline with LB and AD lesions in LB disorders such as PDD. However, further investigation is required.

**Conclusions**

Although accumulating evidence suggests that PDD is more closely associated with LB pathology, PD with concurrent AD pathology can lead to impaired cognition.\textsuperscript{39} Recent studies show a synergistic relationship between the intensity of both LB and AD lesions and the resulting movement disorder and cognitive impairment. CWMLs are more common in individuals with AD than in normal elderly individuals of comparable age\textsuperscript{7} and have been associated with increased risk of dementia. Some reports did not find an association between CWMLs and dementia in PD. More recent data, including our study, suggest that CWMLs are associated with cognitive impairment in PD. Further prospective clinicopathological studies with larger cohorts are necessary to elucidate the impact of AD, SCNA pathologies, and CWMLs on the cognitive status in LB disorders such as PDD.

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