Striatal β-Amyloid Deposition in Parkinson Disease With Dementia

In a recent article, Kalaitzakis et al (1) reported a significantly greater amyloid-β peptide (Aβ) burden in the striatum of cases of Parkinson disease (PD) with dementia (PDD) than in nondemented PD patients, whereas α-synuclein (αSN) and tau deposition were similarly rare in both groups. Because neuritic Braak stages were rather low in both groups, it was concluded that Aβ deposition in the striatum, which was type independent of Alzheimer disease (AD) changes, strongly correlates with dementia in PD. These data can, at least in part, be confirmed from the results of a personal autopsy series of 64 cases of Lewy body disease (21 PD, 23 PDD, and 20 dementia with Lewy bodies [DLB]). Neuropathologic assessment was performed according to standardized methods. Multiple paraffin-embedded blocks were examined using routine stains and immunohistochemistry for tau, Aβ (clone 4G8), and αSN. Each case was staged for the degree of LB pathology (2); cortical Aβ plaque density from frontal, temporal cortex, caudate nucleus, putamen, globus pallidus, and thalamus; and generalized and capillary cerebral angiopathy using 4 different scores (for methods, see References 3 and 4) for all items. Parkinson disease with dementia patients (final Mini-Mental State Examination, 0–15; mean, 7.5) were significantly older at death than nondemented ones (final Mini-Mental State Examination, 20–29; mean, 25; mean, 86.8 ± 4.6 vs 78.7 ± 5.4 years [standard deviation]), whereas DLB cases (final Mini-Mental State Examination, 0–18; mean, 9) were slightly younger than PDD patients (mean, 84.4 ± 4.8 years [standard deviation]). Duration of illness was shortest in DLB < PDD < PD nondemented (mean, 6.6 vs 6.6 vs 12.2 years). Lewy body Braak scores were highest in DLB but similar in PDD and nondemented PD (mean, 5.9 vs 4.2 and 3.8, respectively), which did not confirm findings indicating that cognitive decline correlates with neuropathologic LB stage in PD (5), whereas neuritic Braak scores in both DLB and PDD were higher than in nondemented PD (mean, 4.2 vs 3.8 and 2.5). Likewise, cortical Aβ plaque, capillary cerebral angiopathy, and general cerebral angiopathy scores were higher in DLB than in both PD and PDD cases (4). Dementia with Lewy body cases showed a significantly higher Aβ plaque burden in putamen, caudate nucleus, and thalamus than in PDD and nondemented PD cases (mean, 2.5 vs 0.8 and 0.1, respectively). Dementia with Lewy body brains showed severe and dense Aβ plaques in striatum in 65%, moderate in 25%, and none or only very mild Aβ plaques in 10%; in PDD cases, only 26% showed moderately severe, less than 20% mild, and almost 48% no definite Aβ plaques, whereas in nondemented PD cases, only 1 of 20 brains (5%) showed occasional Aβ plaques in striatum. The globus pallidus was virtually negative in all 3 groups, whereas few αSN deposits were seen in 76% of DLB and in approximately 30% of PDD brains, but only in 10% of nondemented PD cases. Striatal Aβ plaque burden in DLB brains showed association with neuritic Braak stages, whereas in both of the other groups, such correlations were not found except in 2 cases scoring neuritic Braak Stage 5 and Aβ Phase 4 with only few or moderate numbers of striatal Aβ plaques. In addition, tau pathology in striatum of our cohort was also more frequent in DLB than in both PDD and PD, the incidence of negative cases being 70% vs 82% and 100%, respectively. These findings support a morphologic distinction between DLB and PDD, but also between PDD and nondemented PD, which, however, does not seem to be restricted to different Aβ deposition in the striatum because, at least in our material, neuritic AD pathology was more severe in both DLB and PDD than in nondemented PD. Hence, significantly greater deposition of Aβ in the striatum of PDD patients that seems to be quite independent of the extent of cortical AD pathologic findings is not a definitely novel finding, as suggested by some authors (1). Both the molecular background and clinical/pathophysiological impact of striatal pathologies in LB disease remain to be further elucidated, although some synergistic reactions between Aβ, αSN, and tau proteins have been suggested.

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Response from Authors:
We wish to thank Professor Jellinger for his comments on our recent article regarding the robust association of β-amyloid deposition in the striatum with the presence of dementia in Parkinson disease (PD) patients (1).

The pathologic and anatomic basis of dementia in PD has been a matter of controversy, with some authors reporting that cortical and limbic Lewy bodies relate to dementia in PD independently of Alzheimer disease (AD) pathology, whereas others support a primary role of neocortical AD-type changes. Although previous studies have examined the influence of Lewy body and AD pathology in cortical and limbic areas in relation to dementia in PD, a clinicopathologic study to examine the pathologic changes in the striatum between
PD and PDD has not appeared prior to our publication. This lack of examination of the striatum clearly had underestimated its importance and clinical relevance in PD pathophysiology.

Although Professor Jellinger reports a higher incidence of striatal Aβ pathology in PDD cases compared with nondemented PD cases (42% vs 10%, respectively) Aβ pathology in our PDD cohort was far more prevalent (81%). This difference may arise from the different antibodies used (4G8 [Jellinger] vs 1E8 [in our study]). The 1E8 antibody has been shown to be a very sensitive marker of Aβ pathology and picks up all Aβ species (i.e. Aβ x-40, Aβ x-42, N- and C-terminally truncated Aβ species). Therefore, the lower incidence of Aβ in the striatum of PDD cases reported by Jellinger may relate to this methodologic difference. Nevertheless, his findings support our own results of an increased Aβ burden in the striatum of PDD cases. Imaging studies using Aβ ligands also report an increased Aβ burden in the striatum of cases with dementia (2).

In our material, tau pathology was minimal or absent in the striatum and cortex. Grading of coincident AD pathology (tau and Aβ; www.ICDNS.org) revealed that 70% of PDD cases with abundant striatal Aβ did not display comparably severe cortical AD pathology, and similar results were obtained when striatal Aβ pathology was compared with semiquantitative severity ratings of both tau and Aβ pathology in cortical and limbic regions. In Jellinger’s material, however, PDD cases demonstrated a higher neuritic Braak score than PD cases (mean, 4 vs 2.2, respectively), whereas tau pathology in the striatum was minimal in the PDD cohort in accordance with our own results. The higher Braak scores reported by Jellinger might relate to a higher age at death in both the PDD and PD cases (83.2 ± 4.6 and 81.8 ± 5.4 years, respectively) compared with our cohort (PDD mean age at death, 78 years; PD mean age at death, 76 years).

The results of our study clearly demonstrate a significantly greater Aβ burden in the striatum of PDD cases compared with nondemented PD cases that is dissociated from cortical and limbic AD comorbidity. These results suggest some overlap of molecular mechanisms between PD and AD as manifested by Aβ pathology and offer a firm pathologic substrate for clinical features of subcortical dementia. Although our study and the results presented by Professor Jellinger provide a better understanding of dementia in PD, further clinicopathologic studies are now required to examine striatal pathology in PD.

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