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Reply to the Letter to the Editor

Jellinger K, "Parkinson's Disease and Dementia with Lewy Bodies: One and the Same"

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We have read with interest the letter submitted by prof. K. Jellinger [1], and welcome the opportunity to clarify our position on the matter.

The letter summarizes several neuropathological studies, which reported group differences between patients with Parkinson's disease (PD), PD dementia (PDD), and dementia with Lewy bodies (DLB). Subjects presenting with the clinical DLB phenotype commonly show higher burdens of hyperphosphorylated tau tangles, amyloid β plaques, and cerebral amyloid angiopathy compared with PDD patients. Other differences include longer time duration since clinical diagnosis and older age at death in the PDD groups.

However, these differences are only seen at the group level, and for all these parameters, the overlap between PDD and DLB is often greater than the separation– with the possible exception of the striatal burden of amyloid β plaques. In the neuropathological consensus criteria for the diagnosis of PD, it was also concluded that PDD and DLB cannot be reliably differentiated at the individual patient level from a purely pathological perspective [2].

In our recent opinion piece, we argue that clinical PD and DLB diagnoses are suboptimal for categorizing LBD patients, since the defining criterion (i.e. 1-year rule) is arbitrary, and the patient groups overlap substantially on clinical, cognitive, imaging, and neuropathological parameters. Rather than starting from such overlapping clinical categories and working backwards, we should study how fundamental pathogenic mechanisms impact on the clinical trajectory in a prospective manner [3].

As an example, the clinical DLB phenotype seems to consist mainly of patients with body-first Lewy body disease, evidenced by RBD, constipation, and cardiac denervation before cognitive decline, in combination with a high AD co-pathology load. Increasingly refined biomarkers are being validated, which allow us to identify and diagnose such patients already in the prodromal stage. Relevant biomarkers include α-synuclein seed amplification assays of CSF, blood, and skin; polysomnography; cardiac imaging; olfactory testing; genetic testing; and CSF and plasma assays of tau and amyloid β. These prodromal patients may be ideal candidates for clinical

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trials of disease-modification to delay the onset of cognitive decline.

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