Clinical Parkinson disease subtyping does not predict pathology

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Parkinson disease is a clinicopathological construct at a crossroads. A new study reinforces the prognostic value of subtypes, but its findings challenge the relevance of pathology to the clinical expression of disease as data-driven Parkinson disease subtypes did not match up with severity or distribution of Lewy or Alzheimer pathologies.

Refers to De Pablo-Fernández, E. et al. Prognosis and neuropathologic correlation of clinical subtypes of Parkinson disease. JAMA Neurol. https://doi.org/10.1001/jamaneurol.2018.4377 (2019).

Parkinson disease (PD) is diagnosed according to clinical criteria and confirmed with certainty by documenting Lewy pathology at autopsy, a clinicopathological model of disease to which we have adhered for a century. The clinical diagnosis alone, however, does not predict a scripted course. Several slopes of decline are possible for patients with PD. Could we accurately anticipate, at disease onset, patients for whom the disease course might evolve in a benign manner, and those for whom the disease course will be malignant?

Enter PD subtyping — the concept that discrete clusters of motor and nonmotor phenotypic features might discriminate populations with distinct aetiologies, disease courses and treatment responses. Recognizing distinct trajectories of disease progression for clinical PD subtypes, we have reasoned, can help uncover their underlying pathology and biology. The earliest PD subtypes were generated using clinical motor data, largely dichotomized on the presence or absence of tremor. The tremor subtype was associated with slower accrual of milestones and longer survival than was the tremorless postural instability and gait disorder (PIGD) subtype. However, these two motor phenotypes are now known to be unstable over time. Using the longitudinal Parkinson disease Progression Markers Initiative data set, researchers showed that 20% of individuals classified as having tremor-dominant PD became PIGD dominant within 1 year, whereas 40% of those categorized as having PIGD migrated in the opposite direction.

Refinements in analytical methods for larger data sets have supported a growing list of proposed multidimensional data-driven clusters of PD subtypes. Nosology based on semiology, however, has yielded inconsistent results. The subtypes generated thus far lack reproducibility and, with one nuanced exception, lack pathological validation. The only clinicopathological study previously published, from a large set of 242 Queen Square Brain Bank cases, showed no clear correlation between neuropathological stage and clinical subtype, except for the occurrence of more-severe neocortical Lewy pathology in the tremorless subtype. Thus, the biological underpinnings of the observed clusters are unknown.

Recent entrants into the pantheon of data-driven PD subtypes are three severity-based clusters: mild-motor predominant, intermediate and diffuse malignant subtypes, defined within an average of 6 months of symptom onset. These three subtypes were recently put to the test by De Pablo-Fernández and colleagues in the second clinicopathological study of PD subtypes. The authors used retrospectively collected motor, autonomic, sleep (REM sleep behaviour disorder) and cognitive function scores at diagnosis to allocate the cohort (n = 111; mean age 62.5 years) to one of the three subtype groups using pre-defined cut-offs at the 75th percentile of distribution. The mild-motor predominant group included patients with motor and nonmotor scores below the 75th percentile, the diffuse malignant group included patients with either motor score above the 75th percentile and at least one nonmotor score or all three nonmotor scores above the 75th percentile, and the intermediate group included all individuals not meeting the criteria for the other subtypes. Four disease milestones (regular falls, wheelchair dependence, dementia and placement in residential or nursing home care) were used to evaluate progression from diagnosis to death, and time from diagnosis to death determined survival in each clinical subtype group.

De Pablo-Fernández and colleagues pursued two main aims in their analysis of the clinicopathological data. The first aim was to determine whether the cohorts progressed as predicted according to the severity implied by the clinical PD subtypes. The second aim was to assess the extent to which these clinical subtypes represented distinct pathological subtypes.

In terms of the first aim, the researchers demonstrated important prognostic differences between the subtypes. The mean rates of progression and survival mirrored the early subtypes, namely longest survival and slowest progression in the mild motor-predominant group, shortest survival and fastest progression in the diffuse malignant group, and intermediate progression and survival in the intermediate group. In conclusion, the slope of PD progression is predictable, a finding that can be shared with our patients: the best way to predict what’s ahead is to look at what’s behind.

The second objective was answered with a sobering negative but with important implications for our prevailing model of PD. The protein aggregates found on autopsy did not distinguish between subtypes. Neither Lewy nor Alzheimer pathologies differed in severity (assessed using four validated pathology-staging scales) or distribution (brainstem, limbic or diffuse neocortical) between PD subtypes. This finding runs counter to the dictum that clinical features reflect pathology. We posit that clinical subtypes could have failed to mirror pathology subtypes because the clinical subtypes are inadequate to predict post-mortem pathology and/or the measured post-mortem pathologies are not themselves responsible for the clinical features.
The authors conclude that “different neuropathologies are important determinants of clinical subtypes and contribute to the clinical heterogeneity.” This statement is unsupported. In our view, the major conclusion is that PD subtypes and pathology subtypes do not align, as no pathology predicted a subtype. More importantly, protein aggregates identified at post-mortem might not reflect causal disease mechanisms but, rather, represent common denominators to potentially many biological processes.

Could the separate prognostic trajectories of clinical subtypes depend on biological variables independent of Lewy and amyloidopathies? An underemphasized finding by De Pablo-Fernández and colleagues might hold the key to resolving this question. Paradoxical to our prevailing clinicopathological model of disease, amyloid and tau pathology showed a significant association with older age at death. That is, individuals with more Alzheimer-type pathology lived longer. This finding suggests that the pathology used for disease nosology might indeed not be pathogenic but, instead, reflect compensatory or even protective abnormalities in a brain under biological stress. A new systematic analysis, which applied the Bradford Hill criteria for assessing causality of protein aggregates in human studies, supports this hypothesis.

The important report from De Pablo-Fernández and colleagues reinforces the prognostic value of clinically defined subtypes. The findings do, however, challenge the relevance of Lewy and Alzheimer disease-related pathology to the clinical expression of disease. The study also invites us to reconsider our approach to biomarker-discovery efforts, from the current paradigm of using phenotypic traits as the gold standard for the validation of biomarkers to biological abnormalities themselves acting as the anchors for defining disease subtypes (Fig. 1), especially those subtypes that are mechanistically or molecularly suitable for putative disease-modifying interventions.

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