Progression and biomarkers for Parkinson disease
Merging motor with nonmotor symptoms

The conceptualization of clinical aspects of Parkinson disease (PD) and its pathophysiology has changed considerably since Braak’s description of a “bottom-up” progression of Lewy body pathology from the lower medulla and the olfactory bundle. Substantia nigra involvement, once the hallmark of PD pathology, is now recognized to occur at a substantially later stage, with nonmotor symptoms (NMS) occurring before classical motor signs are evident. Recent diagnostic criteria have been devised to predict prodromal PD in which PD NMS underpin the prodromal stage. The phenotypic heterogeneity of PD reflects the convergence of deficits in multiple transmitter systems and non-dopamine pathways, including the cholinergic, noradrenergic, and serotonergic systems. This formulation has now been translated to clinical practice with the recent description of several nonmotor subtypes of PD.

The complexity of phenotypic expression and pathophysiology of PD creates problems with translation of animal model–based pharmacologic data to human neuroprotection or neuromodulation strategies. Although research foundations and pharmaceutical companies have spent millions to develop drugs for neuroprotection, not a single one has shown clinically meaningful effects in humans. In large part, this is due to lack of robust endpoints or markers, which in most cases have relied on standard motor measures such as the Unified Parkinson’s Disease Rating Scales (UPDRS), or imaging surrogates, such as the dopamine transporter scans, which are unable to discriminate among the different parkinsonian syndromes. CSF-based markers have been proposed as putative markers of disease progression, but show considerable overlap with other conditions. More recently, α-synuclein transcripts in peripheral blood have been proposed as biomarkers of PD, but there is overlap with other neurodegenerative conditions, as well as lack of evidence for change over time. Disease progression in PD can also take variable trajectories and studies indicate that motor and NMS may not have similar natural history with variable progression patterns. Longitudinal PD markers that reflect true disease progression, both motor and nonmotor, are thus a key unmet need.

In this issue of Neurology®, Mollenhauer et al. describe an elegant longitudinal single-center cohort study exploring a range of multimodal progression markers for PD in newly diagnosed patients with PD and age-matched, neurologically healthy controls. Moving away from the established fashion of relying on motor assessment and dopamine transporter imaging as markers of disease progression, the authors describe a medley of possible candidate biomarkers encompassing a comprehensive clinical assessment of NMS, using validated tools, including sleep dysfunction, dysautonomia, and cognition; and laboratory tests, such as polysomnography (PSG) for REM sleep behavior disorder (RBD). The authors also examine the longitudinal validity of several proposed CSF-based markers, as well as imaging, using voxel-based morphometry. Based on a 24-month review of data, the authors propose 10 markers that reflect worsening or improvements in assessments commensurate with motor and nonmotor progression of PD. These include worsening in part 1 of the Movement Disorder Society (MDS) UPDRS scale, autonomic assessments, daytime somnolence, as well as PSG measures of RBD, and imaging evidence of cortical and hippocampal gray matter loss; improvements occurred in overall NMS and depression scales. The latter datasets reflect the fact that many studies have now shown that several NMS, such as depression, may actually be driven by dopaminergic mechanisms; therefore, dopaminergic treatment initiated in the follow-up period would have improved Nonmotor Symptom Scale (NMSS) and depression scale scores, particularly as the NMSS is sensitive to change.

Interestingly, an extensive range of cognitive assessments and CSF markers that have been proposed as biomarkers of PD (total α-synuclein, β-amyloid 1-42, total and phosphorylated tau protein,
neurofilament light chain proteins) did not show any longitudinal change.

This is one of the first studies to build on the baseline data the authors presented in a paper in Neurology in 2013 (the de novo Parkinson [DeNoPa] cohort), highlighting the need for global assessments, including motor and a comprehensive NMS assessment; and addressing sleep problems, such as RBD and excessive daytime sleepiness, rather than relying on cognitive and motor markers alone.11 Strengths include the longitudinal assessments, controlled datasets, and an impressive range of clinical scales, biochemical and laboratory assessments that provide a comprehensive attempt at addressing progression and its markers in PD. There are some inconsistencies, however. The nonmotor part of the MDS-UPDRS scale worsens, but the overall NMSS data show improvement; and quality of life assessments did not worsen at follow-up, as some would expect. However, this could be explained by the fact that the more extensive measures provided in the NMSS (30 symptoms) may be more sensitive to change from therapeutic interventions than the abbreviated NMS assessments provided in the MDS-UPDRS. Similarly, given that the NMS burden is one of the key determinants of quality of life, the lack of deterioration of quality of life in this study may be linked to the improvements registered in the NMSS secondary to treatment provided in the longitudinal phase.12

The data provide possible insights to the early pathophysiology of PD and inform our changing concepts of symptoms expression in PD.13 The longitudinal data from this study also underpin the development of a PD biomarker battery rather than single tests, including clinical scales of motor and NMS including dysautonomia, voxel-based morphometric brain imaging focused on cortical gray and hippocampus, as well as laboratory (or clinical) assessments for RBD. This reflects the multiphase, multiregional pathology of PD and aligns with attempts to refine the diagnostic criteria for PD.10,13,14 In particular, validation of these potential markers in larger multicenter longitudinal studies will be invaluable in our quest for neuroprotection in PD.

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DISCLOSURE
The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

REFERENCES