EDITORIAL

Divining progression in Parkinson disease with a blood test

NfL

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Blood NfL: A biomarker for disease severity and progression in Parkinson disease

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In their article in this issue of *Neurology*®, Lin and colleagues[1] provide compelling evidence for the utility of a neurofilament light chain (NfL) blood test in predicting progression in Parkinson disease (PD) and in distinguishing PD from multisystem atrophy (MSA). If confirmed by independent studies, this would be a major advance for clinical and basic research. Such a test also may have complex consequences for clinical care.

Available tools for prognosis in PD are limited. Clinical factors, including advanced disease at diagnosis, male sex, and advanced age, are associated with more rapid progression.[2] The utility of classifying PD phenotypes into tremor-predominant relatively benign, compared to postural-instability gait disorder relatively more rapidly progressive, has been questioned.[3] Genetic variation and CSF biomarkers (mainly α-synuclein) have shown utility as biomarkers of PD progression.[2,4] Imaging and multimodal risk modeling may also be useful.[2,4] However, none of these biomarkers are universally accepted, and some are limited to specific patient populations.

NfL is a an abundant neuronal cytoskeletal protein. There has been much interest in NfL as a biomarker for neurologic injury, particularly in Alzheimer disease, inherited peripheral neuropathy, multiple sclerosis, amyotrophic lateral sclerosis, and acute brain injury.[5] Most of this research has been based on NfL as measured from the CSF. More recently, a good correlation of NfL levels in CSF and serum has been reported.[5]

The Chin et al. study prospectively enrolled 178 participants, including 116 with PD, 22 with MSA, and 40 healthy controls. The study cohort may be small for stroke, but for PD/MSA, this is a substantially sized cohort, and follow-up averaged 3 years. The correlation of motor and cognitive status and NfL was found both cross-sectionally and longitudinally. In addition, serum NfL levels distinguished MSA from PD. The authors were able to establish a cutoff level that separated participants with PD with stable disease at 3 years from those who progressed. There was marked divergence in Kaplan-Meier–plotted clinical trajectories for both motor and cognitive symptoms. At the end of the 3-year study, motor progression occurred among all participants with PD with baseline NfL levels ≥21.84 pg/mL, while only about half of patients with lower NfL levels showed progression. Cognitive progression occurred by the end of the study period in all participants with NfL ≥18.34 pg/mL and among approximately one-third of those with lower NfL levels. Hence, NfL levels more robustly foretell bad than good news.

A caveat here is that the definitions of motor and mental decline on the United Parkinson's Disease Rating Scale part III (decline of >2 points) and Mini-Mental State Examination (<26 points) were not necessarily of a magnitude that would reach clinical relevance; in fact, studies designed to address the changes that make clinically important differences using these measures suggest that these changes may not be clinically important.[6,7] However, over the 3-year period of the study, the difference between progressors and nonprogressors was increased. Further longitudinal follow-up and confirmation are needed to determine whether these divergent trajectories persist.

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While NfL levels distinguished PD from healthy controls and patients with MSA from those with PD, it needs to be emphasized that all participants met clinical diagnostic criteria for PD or MSA by the time of entry into the study. Hence, while it raises hopes for the future, the present study was not designed to address the usefulness of NfL for early diagnosis of either PD or MSA.

Emerging technologies to predict future risk are not themselves without risk.[8] Experience from other tests to predict neurologic diseases, while not fully analogous, suggest that, with careful consideration, not all persons want to know what the future holds and that predictive testing can have adverse effects even for those whose results yield "good news."

The model for Huntington disease involving extensive pretest and posttest counseling has been proposed for other types of predictive testing.[8] Advances in technology will make more predictive tests available. At the same time, an increasingly skeptical public is leaning away from "whatever you say, doc" and toward other information sources, including the internet. Whole-body CTs and MRIs are available for "screening" on the private market. Similarly, genetic profiles are proposed by private companies as being able to identify a large range of risks, including hereditary cancers and degenerative diseases. Risk profiles, albeit of uncertain accuracy, are available directly to consumer and are widely used.[9] These are tricky waters to navigate. Further research is needed not only to define the value of NfL as a surrogate biomarker for PD progression but also to understand the clinical import and social ramifications of the availability of predictive testing in neurology. If confirmed, the present data would suggest that the practicing neurologist would have a test to robustly predict progression but likely not to reassure nonprogressors.

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