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PD biomarkers—use of α-synuclein reaches new levels

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Abstract

Biomarker development is important to the therapeutic imperative for neurodegenerative diseases, as biomarkers hold transformative promise for the design and conduct of clinical trials and, ultimately, for medical management of these diseases. Some of this promise is now being realized in Alzheimer disease, and progress in Parkinson disease is accelerating.

The common age-related neurodegenerative diseases, Alzheimer disease (AD) and Parkinson disease (PD), are already major public health problems for older individuals and are poised to amplify tragically with our increasingly aging population. PD is one of a group of neurodegenerative diseases called 'synucleinopathies', all of which share the pathological feature of α-synuclein containing inclusions, whether in neurons or glia. Other diseases in the synucleinopathy set include dementia with Lewy bodies (DLB, a complex mix of at least two entities that commonly is comorbid with AD), and multiple system atrophy (MSA, which can be difficult to distinguish clinically from PD, especially in early stages of disease). These facts compel a therapeutic imperative that is pursued currently by many laboratories worldwide in search of etiologies, key pathogenic steps, and effective interventions that at least treat, and hopefully even cure, these diseases. A key component of the response to this therapeutic imperative is the development of biomarkers, a type of laboratory data that can be used in disease evaluations, and the role of which is to signal the presence and/or burden of disease. As with decreased cerebrospinal fluid (CSF) levels of amyloid-β ($A\beta)_{42}$ in AD, concentrations of α-synuclein have been observed to be decreased in patients with PD compared with controls by several groups of investigators; however, not all groups have been able to reproduce this finding, leading to discussions about the specific protocols used, the degree of CSF contamination by blood, and sample storage. In a study published by The Lancet Neurology, Mollenhauer and colleagues[1] contribute to this literature by confirming that α-synuclein levels are decreased in the CSF of patients with PD, and in those with other synucleinopathies, and could be a useful diagnostic biomarker for these diseases.

In their excellent cross-sectional study, Mollenhauer and colleagues[1] assessed levels of α-synuclein in control individuals without neurological disease, patients with AD, patients with PD or other synucleinopathies, and patients with a mix of other neurological diseases. Total α-synuclein levels in the CSF and serum, as well as total CSF tau levels, were

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measured in three cohorts of patients, a training cohort (n = 273), a cohort with autopsy-confirmed neurological disease (n = 41) and a validation cohort (n = 407). The researchers confirmed that α-synuclein concentration (as determined by enzyme-linked immunosorbent assay) was substantially reduced in patients with any one of the three synucleinopathies (PD, DLB and MSA).

Mollenhauer and colleagues[1] also investigated CSF tau and $A\beta_{42}$ levels in their cohorts and observed the expected changes of increased tau and decreased $A\beta_{42}$ concentrations in patients with AD, but no marked changes in either protein was observed in patients with PD. Many groups have investigated these AD biomarkers in patients with PD and the literature is conflicting. One important variable may be the level of cognitive impairment in patients with PD, which has received increasing attention and was probably underappreciated in early studies. Some work from the past year suggests that patients with PD plus dementia have reduced CSF levels of $A\beta_{42}$ compared with controls, but not increased CSF levels of tau.[2] One speculation from these data is that the dopaminergic neurodegeneration that occurs in PD may clinically unmask AD at an early stage in some patients, when $A\beta_{42}$ is being deposited in parenchyma (and decreasing in CSF), but before the occurrence of large-scale neuron death and increasing concentrations of tau in CSF.

Biomarkers are quantitative measures of dynamic processes that reflect ongoing disease. This notion stands in sharp distinction to risk assessment, (commonly carried out in the laboratory setting by genetic testing), because risk factors are, at least for now, immutable and are used to estimate the likelihood of future disease. The roles of biomarkers in neurodegenerative disease are potentially transformative and include: detecting disease in its latency and thereby providing an opportunity for early intervention; aiding in diagnosis and thereby guiding the assemblage of more-uniform clinical trial cohorts with reduced variance and smaller required size; providing robust quantitation of disease progression and thereby reducing the time to primary outcome in clinical trials; and, ultimately, assisting health-care providers in the medical management of patients with these diseases. My colleagues and I have proposed a simple and practical five-level ranking for the development of biomarkers for use in the clinic (Box 1).[3] The AD Neuroimaging Initiative has now taken the arduous step of moving to level IV biomarker development criteria for reduced CSF $A\beta_{42}$ levels and increased CSF tau concentrations in individuals with AD at dementia and prodromal stages, and probably in latency as well.[4] Furthermore, elegant imaging studies, a few buttressed by subsequent postmortem examination, indicate that decreased CSF levels of $A\beta_{42}$ in individuals with AD is associated with increased accumulation of this peptide in brain.[5] The basis for increased CSF tau concentration in AD is more speculative, but occurs in several degenerative and destructive diseases of the brain and may be a consequence of neuronal injury.

Box 1

Biomarker development levels

■	Level I: initial association found between biomarker and disease
■	Level II: confirmation of association in separate cohort using same assay

■	Level III: biomarker validation in separate cohort using a different assay
■	Level IV: standardized application of biomarker in multicenter clinical investigations
■	Level V: incorporation of biomarker into best medical practice

Given the clinical potential of biomarkers and the successes achieved so far in AD, many investigators are pursuing biomarkers for other neurodegenerative diseases. PD is now a major area of focus for biomarker research, as evidenced by the establishment of the Parkinson's Progression Markers Initiative (PPMI), sponsored by the Michael J. Fox Foundation, and the Parkinson's Disease Biomarkers Identification Network (PDBIN) by the National Institute of Neurological Disorders and Stroke, USA. The finding by Mollenhauer and co-workers[1] is an important step forward and, combined with the results from another 2011 study[6] that reached similar conclusions, achieves solid level III development criteria for decreased CSF levels of α-synuclein as a biomarker for synucleinopathies. The next step to achieve level IV development for this synucleinopathy biomarker awaits the outcome of large multicenter studies, such as PPMI and PD-BIN.

Interestingly, several studies, including the one by Mollenhauer et al.,[1] have yet to identify abnormal CSF α-synuclein concentrations in a subset of asymptomatic control patients, as has been observed with CSF $A\beta_{42}$ and tau,[3] perhaps because of reduced prevalence of latent synucleinopathies. Moreover, the results from these studies indicate that the performance characteristics of CSF α-synuclein concentrations as a clinical laboratory test are insufficient as a single measure, and that the need for improved laboratory testing for individuals with PD or related diseases is clear. Some areas for future investigation of α-synuclein as a PD biomarker include the relevance of specific isoforms, application in different at-risk groups of PD, and use of other biofluid compartments (such as plasma or saliva) for the measurement of this protein.[7,8] The search continues for risk factors, molecular neuroimaging agents, and other biomarkers to combine with measures of CSF α-synuclein concentrations, to improve performance of clinical laboratory testing for PD.

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