Is α-synuclein rising to the surface as a diagnostic biomarker for Parkinson disease?

William P. Cheshire, MD
Ronald F. Pfeiffer, MD

Correspondence to
Dr. Cheshire:
cheshire@mayo.edu

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In his historic manuscript on the "shaking palsy," James Parkinson expressed the hope "that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped."[1] Realization of that hope will require not only the discovery of a treatment that can halt or slow the progression of Parkinson disease (PD), but also the identification of early, accurate, and accessible biomarkers, for by the time the cardinal clinical signs of bradykinesia, rigidity, tremor, and postural instability appear, substantial destruction of nigrostriatal dopaminergic neurons has already occurred.

The histopathologic hallmark of PD is the degeneration of neurons in which cytosolic filamentous inclusions (Lewy bodies) develop within the perikarya and dystrophic Lewy neurites within cellular processes. Both are composed of aggregates of the protein α-synuclein. α-Synuclein in normal neurons localizes to presynaptic vesicles and nuclei (hence the name *syn-nuclein*) and adopts a variable tertiary structure. Under certain as-yet-unknown conditions, α-synuclein undergoes a conformational shift, misfolding into a β-helical structure that can self-aggregate to form toxic oligomers, which may be the mechanism whereby missense mutations in the α-synuclein gene cause rare familial forms of PD.[2]

PD actually is a multifocal disease, and increasing evidence indicates parallel, and perhaps antecedent, involvement of the peripheral autonomic nervous system. Constipation, for example, may predate the onset of cardinal signs by many years. Postmortem findings of α-synuclein pathology in the dorsal motor nucleus of the vagal nerve and the olfactory bulb in the early stages of PD led Braak et al.[3] to propose a sequential topographical paradigm in which PD-related pathology begins in the peripheral or enteric nervous system and ascends through synaptically connected neurons via the vagus nerve, eventually to involve the midbrain and ultimately the forebrain. In support of the paradigm, hemivagotomy has been shown to protect against ipsilateral substantia nigra dopaminergic neuronal death in a mouse model of PD.[4] Ultimate proof of this intriguing paradigm awaits elucidation of the relationship of abnormal α-synuclein deposition to progressive neuronal loss, since such deposits are not invariably accompanied by neuronal deterioration and, in fact, frequently are found in asymptomatic elderly individuals.[2,5,6]

In the search for PD biomarkers beyond the brain, abnormal α-synuclein deposits, in some cases accompanied by neuronal loss, have been discovered in olfactory nerves, cardiac sympathetic nerves, vagus nerve, paravertebral sympathetic chain ganglia, autonomic nuclei of the spinal cord, and colonic submucosal plexus.[6] None of these sites is appropriate for routine premortem diagnosis or staging of PD, as biopsy of these structures is invasive and carries potential risks. If, however, neuronal pathology leading to PD was shown to involve peripheral nerves and to be present in a more safely accessible tissue, such as the skin, the ability to detect diagnostically valid α-synuclein pathology at the body's surface would be a welcome advance.

Wang et al.,[7] in this issue of *Neurology*®, utilized confocal microscopy to quantify the proportion of intraepidermal nerve fibers containing immunoreactive α-synuclein in skin biopsies of 20 patients with PD and 14 controls matched for age and sex. They found increased α-synuclein deposition in cutaneous adrenergic (pilomotor) and sympathetic cholinergic (sudomotor), but not sensory, fibers in all of their patients with PD, compared with controls. Higher amounts of α-synuclein correlated significantly with Hoehn and Yahr motor staging and with clinical measures of autonomic dysfunction.

At least 2 factors may account for this study's greater sensitivity in detecting increased cutaneous α-synuclein, compared with the results of previous investigators. Wang et al.[7] examined thicker sections containing a greater number of nerve fibers, and they used a less selective α-synuclein antibody. Both Ikemura et al.,[8] who found α-synuclein in 70% of skin biopsies in PD, and Miki et al.,[9] who found α-synuclein in only 10%, utilized antibodies to ser129-phosphorylated α-synuclein. Their rationale was that a majority of α-synuclein in PD is phosphorylated at ser129,[10] but

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From the Department of Neurology (W.P.C.), Mayo Clinic, Jacksonville, FL; and Department of Neurology (R.F.P.), University of Tennessee Health Science Center, Memphis.

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it is not known whether the same form affects other involved sites or stages. Wang et al.'s use of a nonspecific α-synuclein antibody is allowable, because increased expression even of normal α-synuclein protein in patients whose genotypes duplicate or triplicate the α-synuclein gene leads to PD. More importantly, Wang et al. were able to show that the ratio of α-synuclein—not to skin volume, but to nerve density—was increased in PD, and that this correlated with decreased autonomic nerve fiber density, impaired autonomic function, and staging of PD, which when considered together are convincingly pathologic.

These findings hold promise that further clues to a deeper understanding of the molecular and neuronal pathology of PD may be accessible just beneath the body's surface where affected autonomic nerves innervate cutaneous structures. Clinical use of skin biopsies to diagnose or stage PD would be premature at this time. Larger studies are needed first to confirm the findings of Wang et al., not only in PD, but also in comparison to other α-synucleinopathies, including dementia with Lewy bodies, pure autonomic failure, and multiple system atrophy. Further studies also should assess whether cutaneous α-synuclein appears early in the course of PD, when such changes appear in relation to the onset of motor signs, in what sort of structural conformations, whether and where the α-synuclein is phosphorylated, in what proportion it exists as oligomers, and in association with what other proteins. Prospective studies also might examine sequential skin biopsies in asymptomatic individuals at genetic risk of developing familial PD. The future is bright with possibilities of new discoveries that hopefully will attain Parkinson's vision for an effective intervention to impede the progression of disease.

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