Dementia with Lewy bodies
Diagnosis is only skin deep?

Dementia with Lewy bodies (DLB) is currently diagnosed clinically by identifying dementia in combination with a number of hallmark features: REM sleep behavior disorder (RBD), prominent visual hallucinations, parkinsonism, and marked fluctuations of cognition and alertness. DLB is often underdiagnosed, suggesting a role for biomarkers. The main differential diagnosis of DLB is Alzheimer disease (AD); whereas both AD and DLB have amyloid deposition, DLB also has additional α-synuclein deposition (Lewy bodies and Lewy neurites). So, one way to establish DLB diagnosis might be to detect the α-synucleinopathy itself.

A diagnostic biomarker of α-synuclein would be useful now, but in the future, may become essential. Currently, all treatments for DLB are symptomatic; we start treatment when bothersome symptoms emerge, and adjust based upon clinical response. For both DLB and AD, we try cholinesterase inhibitors and memantine and if possible avoid neuroleptics, so incorrect diagnoses may not dramatically affect treatment. (This applies also to Parkinson disease [PD]; whether parkinsonism is due to DLB/PD or other causes, we might still try levodopa.) But imagine a future in which α-synuclein-based neuroprotective therapy exists (for example, immunotherapy against α-synuclein). Now, all patients with α-synucleinopathy would be eligible for a treatment that will likely be expensive, inconvenient (e.g., monthly IV infusions), and possibly hazardous. Moreover, unlike symptomatic therapy, there would be no measurable short-term benefit to guide treatment. So before committing to a lifetime of treatment, patients (and payers) would expect a firm diagnosis of α-synucleinopathy.

The α-synucleinopathies (DLB, PD) have peripheral autonomic nervous system manifestations, including constipation, urinary dysfunction, and orthostatic hypotension. This may be related to α-synuclein deposition in the gastrointestinal tract, cardiac sympathetic fibers, and, most notably, the skin. This peripheral localization offers an important advantage: unlike brain, peripheral tissues like skin are easily accessible. Skin biopsies require minimal training, and are relatively safe and noninvasive (smaller biopsies do not even require a stitch). Promising studies have documented abnormal α-synuclein deposition in PD. However, techniques are still being optimized; some studies find clear differences between patients and controls, whereas others note a high prevalence of nonspecific staining. Of note, a recent study documented α-synuclein deposition in skin biopsies in idiopathic RBD, the strongest marker of prodromal PD and DLB, suggesting that patients with DLB may have similar abnormalities.

In this issue of Neurology, Donadio et al. report evidence that skin biopsy can diagnose DLB. The investigators took punch biopsies from 3 skin sites: the paravertebral cervical area, proximal thigh, and distal leg. The proximal biopsies were chosen for α-synuclein deposition sensitivity, because α-synuclein is deposited in a rostral-caudal gradient. The distal leg site was chosen to detect subtle neuropathy. Eighteen patients with DLB were selected (11 with less certain DLB were excluded). Many had typical levodopa-responsive parkinsonism, and would presumably have also met PD criteria (under the new definition that allows inclusion of patients with DLB). Tissues were costained with fluorescent antibodies to identify neuronal tissue and phosphorylated α-synuclein (p-syn). Patients with DLB were compared to 23 other patients with dementia and 25 controls.

The findings were startling: 100% of patients with DLB had p-syn deposition in peripheral nervous tissue. By contrast, not a single biopsy in any control was positive. Even if only one skin sample from DLB had been taken, sensitivity would still be 95% for cervical samples (and 86% for proximal thigh, 79% for distal leg). Adrenergic (sympathetic) fibers were most affected, with deposition also in parasympathetic cholinergic fibers. Those with abnormal autonomic function tended to have more positive biopsy samples, but other differences could not be seen (probably related to ceiling effects).
On analysis of neuropathy, general autonomic denervation was seen, observed only in the distal sites. This denervation occurred without evident neuropathy on nerve conduction studies, consistent with studies suggesting that patients with PD have mild small fiber neuropathy.

So, do we have a new diagnostic test for DLB? There are several caveats and limitations to consider. A major concern is the unusual nature of the DLB cohort. This cohort was considerably younger than average, with a high number of classic DLB features; every patient had fluctuations, a large majority had parkinsonism treated with levodopa or dopamine agonists, and 67% had neuroleptic sensitivity. This last point is surprising (and concerning), considering that typical neuroleptics are rarely given to patients with dementia in most specialty practices. The dementia control group was also atypical, with a mean onset age of 59 years. Generalizability to more typical patients with DLB is therefore uncertain. A second caveat is that nothing in life, including DLB diagnosis, is perfect. Seeing 100% sensitivity prompts the question of how this could have occurred. It appears that the likeliest explanation is the rigorous selection procedures to find high clinical diagnostic certainty (including dopamine transporter scan and iodine-123-meta-iodobenzylguanidine imaging). However, this again impairs generalizability; an easily diagnosed patient will have more positive diagnostic biomarkers, including skin biopsy. Third, the 100% specificity is surprising, given that low levels of Lewy body pathology are common in clinically diagnosed AD and that 15% of controls at autopsy have incidental CNS Lewy bodies (some of these should have positive skin biopsies too, if peripheral deposition is indeed an early event).9

Given these considerations, the clear priority is to confirm these results in other more representative cohorts; these should include possible DLB cases and more typical late onset AD cases, with follow-up to see whether p-syn-positive cases evolve to probable DLB. If the findings are replicated, the implications are considerable. It is not inconceivable that dementia physicians will soon be performing skin biopsies as part of routine diagnostic practice.

AUTHOR CONTRIBUTIONS
R.B. Postuma drafted the initial version of the manuscript. Z.W. was responsible for revision of the manuscript.

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