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Searching for Neurodegeneration in the Blood of Patients With Alzheimer Disease

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A blood test for Alzheimer disease (AD) or other neurodegenerative disorders is highly sought after but has proven elusive. After all, AD pathologic features are confined to the brain, and although a cerebrospinal fluid (CSF) protein signature of AD is plausible, dilution of brain-derived proteins passing into the bloodstream, cleavage by proteases, binding to abundant proteins in plasma, and clearance by the liver and kidneys mean that blood biomarkers are several steps removed from their origin and much more challenging to detect and interpret. The advent of ultrasensitive assay methods may change this picture. Approaches to quantify peptide or protein biomarkers by refined enzyme-linked immunosorbent assay–like detection methods or by using polymerase chain reaction amplification of a tagged reporter antibody have greatly extended the lower limits of reliable detection.

Studies of neurofilament light (NFL), an indisputably neuronal protein, provide an interesting case in point. The CSF and plasma levels of NFL are increased acutely after traumatic brain injury.¹ Several studies have examined NFL as a biomarker in relation to chronic neurodegeneration. Increased levels were reported in serum NFL in AD, amyotrophic lateral sclerosis, Guillain-Barré syndrome² and in plasma NFL in progressive supranuclear palsy (PSP).³ A recent study⁴ identified increased CSF and plasma NFL levels in transgenic mouse models of A β , tau, and α -synuclein aggregation that began with the onset of proteopathic lesions in neurons, increased with progression of pathologic features, and decreased after targeted treatment. That study reported increased CSF and plasma NFL in neurodegenerative disorders, including PSP, multisystem atrophy, corticobasal syndrome, and AD, but not in Parkinson disease. Although nonspecific, NFL could represent a biomarker related to damage to axons, likely most sensitive to large-caliber projecting axons, because the highest levels of CSF and plasma NFL were noted in amyotrophic lateral sclerosis and Guillain-Barré syndrome.²

In this issue of *JAMA Neurology*, with an ultrasensitive assay for NFL that allowed sensitive quantitation in all plasma samples, Mattsson et al⁵ have analyzed CSF and plasma from the well-phenotyped Alzheimer's Disease Neuroimaging Initiative cohort. They found

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significantly increased plasma NFL in AD and mild cognitive impairment (MCI) vs controls, as well as a moderate correlation between CSF and plasma levels of NFL, suggesting substantial trafficking from CSF to plasma. However, the correlation between CSF and plasma was weaker than in the animal model investigations mentioned above.⁴

In the study by Mattsson et al,⁵ the CSF NFL levels were more markedly increased in AD and MCI vs controls than were plasma NFL levels, indicating attenuation of the signal of neurodegeneration in plasma. Plasma NFL levels correlated with the scores of timed or executive function tests rather than with memory tests, again consistent with the idea that this biomarker relates to damage to large-caliber projection fiber tracts. Levels did not correlate with measures of white matter intensities on magnetic resonance imaging, a biomarker related to vascular cognitive impairment, which could be accounted for because the Alzheimer's Disease Neuroimaging Initiative cohort underrepresents individuals with vascular risk factors. The authors were able to analyze whether patients with amyloid biomarkers consistent with AD (CSF A β 42 levels or amyloid positron emission tomography imaging) had higher NFL levels than those without, which was not the case among controls, suggesting that neurodegeneration is not extensive enough during preclinical stages of AD to be reflected in plasma NFL. Also, there were only suggestions of a difference in plasma NFL levels in patients with MCI.

Unfortunately, the degree of overlap between AD or MCI and controls for plasma NFL was too large to allow this biomarker to become a stand-alone diagnostic test.⁵ Could plasma NFL serve other uses in the diagnosis of AD? The authors raise the possibility of a screening test, in conjunction with the *APOE* ϵ 4 genotype. They note that other biomarkers related to AD pathologic features are measurable in plasma and observe that plasma tau levels are slightly increased in AD, with more overlap than is the case for NFL. Compared with controls, plasma A β 42 levels are decreased in MCI and further so in AD, but once again with substantial overlap.⁶ Perhaps a multianalyte panel of brain-derived biomarkers could form the basis for a plasma screening test, which might overcome the lack of specificity of a single biomarker alone (eg, NFL levels may increase as a result of traumatic brain injury or in PSP, as mentioned above).

Furthermore, the idea that a single biomarker may reflect the complex pathogenesis of AD may be overly simplistic: in recent years, the use of biomarkers across the spectrum of brain imaging and CSF has identified significant changes in biomarkers of brain structure, connectivity, glucose use, and synaptic damage, as well as inflammation in AD, in addition to biomarkers related to the core neuropathologic features of amyloid and tau aggregates. Several multianalyte plasma protein panels have been proposed for AD diagnosis, but many of the analytes measured in these investigations lack a clear correlation with neuropathologic events and can originate from peripheral and brain sources.⁷ To interpret what a biomarker tells us about the brain requires a deep understanding of the biological processes that the biomarker captures and summarizes.

A different application for plasma NFL may be as an index of progressive neurodegeneration in longitudinal studies, including clinical trials. To evaluate this possibility, data from longitudinally collected plasma samples from patients with different

initial stages of AD will need to be analyzed. We can generically classify CSF tau, NFL, and neurogranin and atrophy on brain magnetic resonance imaging into the category of biomarkers of neurodegeneration to study how they correlate with one another and change over time. However, understanding how they are generated and what biological processes and events they map onto will allow us to build a more comprehensive map of AD. The study by Mattsson et al⁵ makes important contributions to this map and will fuel many further investigations.

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