NEURODEGENERATIVE DISEASE

Biomarker test for Alzheimer disease

A diagnostic test that identifies biomarker signatures has been shown to accurately diagnose or rule out Alzheimer disease (AD). The test, which measures concentrations of amyloid-β peptide 1–42 ($A\beta_{1-42}$) and tau protein in the cerebrospinal fluid (CSF), can also predict whether an individual with mild cognitive impairment (MCI) will develop AD over time.

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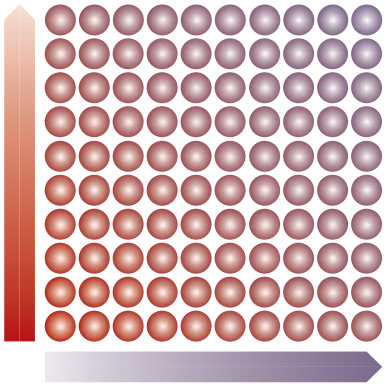
Biomarker-based tests that detect and accurately diagnose AD at an early stage could enable disease-modifying therapies to be initiated before substantial neurodegeneration has occurred, and could be used to monitor disease progression and evaluate responses to treatment.

Investigators led by Leslie Shaw of the University of Pennsylvania, USA, sought to standardize biomarker methods for detecting and monitoring progression of AD, as part of the ongoing multicenter Alzheimer's Disease Neuroimaging Initiative (ADNI) study. Previous investigations identified $A\beta_{1-42}$ and tau protein in the CSF as pathological biomarkers for AD. Decreases in $A\beta_{1-42}$ in the CSF suggest accumulation of these peptides in the brain, forming Aβ plaques; increases in the CSF concentration of tau proteins indicate neuron degeneration as tau proteins are released from damaged and dying neurons.

Shaw's team analyzed CSF samples provided by 100 patients with mild AD, 196 patients with MCI, and 114 elderly individuals with normal cognition all enrolled in the ADNI study. Levels of $A\beta_{1-42}$, total tau protein, and tau phosphorylated at a threonine residue at position 181 were measured in the ADNI group using the Luminex xMAP multiplexed microbead immunoassay system. Memory function and imaging tests were performed at enrollment and at regular intervals thereafter.

The biochemical biomarker signature for AD was established independently using CSF samples collected several years before death in 56 patients who had autopsy-confirmed AD and 52 age-matched individuals with normal cognition. $A\beta_{1-42}$ was identified as the most sensitive biomarker for AD, with a detection rate of 96.4%.

Compared with normal healthy adults, concentrations of tau increased and $A\beta_{1-42}$ decreased with disease progression in patients with MCI or AD. "We detected the biomarker profiles characteristic of AD in 87% of the ADNI subjects who were mildly



cognitively impaired at entry into the study but who by 1 year later had converted to AD," Shaw comments.

About one-third of the individuals with normal cognition had abnormally low $A\beta_{1-42}$ levels akin to those seen in patients with AD, a finding that suggests the researchers require substantial follow up to determine whether low $A\beta_{1-42}$ in the CSF predicts development of MCI, and ultimately AD. "This is an important possibility since early detection of this disease before it reaches the 'brain failure' stage is thought to be a stage when the disease is more likely to respond to potential treatment to delay its progression," Shaw explains.

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