ALZHEIMER DISEASE

Closer to a blood test for Alzheimer disease

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Plasma levels of tau phosphorylated at residue 181 (P-tau181) are a marker of Alzheimer disease (AD), according to two new studies published in *Nature Medicine*. The measure could form the basis of a diagnostic blood test for AD that would transform clinical practice and AD drug development.

Currently, a biomarker-supported diagnosis of AD can only be obtained with use of amyloid-β (Aβ)-PET, which is expensive and not widely available, or by analysis of Aβ and tau in the cerebrospinal fluid (CSF), which is invasive. A diagnostic blood test for AD would provide a widely available and more affordable alternative.

Previous work has shown that blood levels of P-tau181 are higher in patients with AD than in healthy individuals, but whether this measurement is sufficiently specific to diagnose AD has been unclear. The two new studies aimed to provide some clarity.

In the first study, Adam Boxer and colleagues aimed to determine whether plasma levels of P-tau181 can differentiate AD from frontotemporal lobar degeneration (FTLD), a tauopathy that underlies frontotemporal dementia (FTD).

"Particularly in younger patients with mild symptoms, differential diagnosis between AD and FTLD can be challenging," explains Boxer. "Current biomarkers are expensive and/or invasive, therefore limiting their usefulness in routine practice, particularly when screening large populations."

The study involved 293 individuals with mild cognitive impairment (MCI), a clinical diagnosis of AD or a variant of FTD, and 69 healthy controls. The researchers measured levels of P-tau181 in the blood of participants and compared these with Aβ-PET findings and CSF measurements of P-tau181.

Blood levels of P-tau181 were higher among patients with clinically diagnosed AD than among any of the other groups, and the difference was sufficient to distinguish clinically diagnosed or autopsy-confirmed AD from clinically diagnosed or autopsy-confirmed FTLD. Blood levels of P-tau181 were strongly associated with Aβ-PET and CSF P-tau181 measures and enabled identification of patients with positive Aβ-PET scans, regardless of their clinical diagnosis.

The findings suggest that measurement of P-tau181 could be used as a diagnostic blood test for AD, thereby facilitating not only clinical management but also development of treatments. "We are particularly interested in how the test might be used to find participants in clinical trials of disease modifying agents for AD," says Boxer.

In the other study, Oskar Hansson and colleagues also assessed how useful plasma levels of P-tau181 are for diagnosis and prognosis in AD. They conducted a prospective study of two cohorts including 526 individuals who had AD, mild cognitive impairment, non-AD neurodegenerative diseases or no neurological disease. Blood levels and CSF levels of P-tau181 were measured, and participants underwent Aβ-PET and tau-PET.

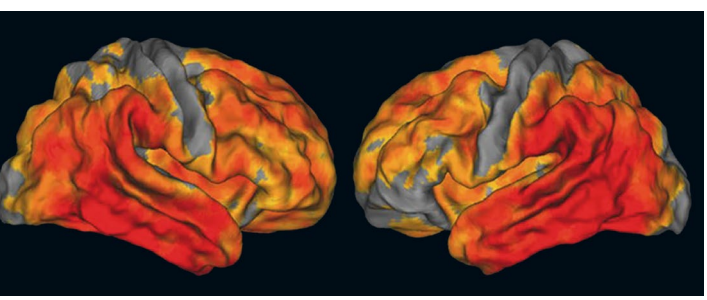
Plasma levels of P-tau181 correlated with CSF levels and with levels of pathology identified with PET. Blood levels of P-tau181 also enabled individuals on the AD spectrum to be distinguished from healthy controls and distinguished AD from non-AD neurodegenerative disease with a sensitivity of 92% and a specificity of 87%.

P-tau181 levels increased with progression from mild cognitive impairment to late AD, and among patients without cognitive impairment at baseline, higher blood levels of P-tau181 were associated with a higher risk of subsequent AD, indicating that the measure can predict development of AD.

In a third cohort of 63 patients, antemortem plasma levels of P-tau181 were associated with post-mortem neuropathology. This observation confirmed that the blood test reflects pathology in the brain.

"I think this blood test has potential to improve the diagnostic work-up of dementia disorders in specialized memory clinics and in primary care," says Hansson. "I think this is a major breakthrough and I believe this blood test can be used clinically in only few years."

Ian Fyfe



Association between serum P-tau181 and tau-PET; the more red areas indicate a stronger correlation between tau-PET signal and serum P-tau181. Adapted with permission from Janelidze, S. et al. *Nat. Med.* https://doi.org/10.1038/s41591-020-0755-1 (2020), Springer Nature Limited.

ORIGINAL ARTICLES Janelidze, S. et al. Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat. Med.* https://doi.org/10.1038/s41591-020-0755-1 (2020) | Thijssen, E. H. et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat. Med.* https://doi.org/10.1038/s41591-020-0762-2 (2020)