ALZHEIMER DISEASE

Validating biomarkers for cognitive decline in AD is not an easy task

Validating specific biomarkers that correlate well with the progression of complex diseases such as Alzheimer disease (AD) is proving extremely difficult. Brain uptake of ^{11}C-labeled Pittsburgh compound B (^{11}C-PIB), an amyloid-β (Aβ) ligand, has potential as an AD biomarker, but Noora Scheinin and colleagues (Turku PET Center, Turku, Finland) have shown that the rate of ^{11}C-PIB uptake does not correlate with either brain atrophy or the observed decline in cognitive abilities. "Our 2 year follow of ^{11}C-PIB uptake, volumetric MRI and neuropsychological assessments indicated that the Aβ load in brain remains relatively unchanged in clinical AD in patients who show progression in brain atrophy and cognitive decline," confirms Scheinin.

A total of 14 patients diagnosed with AD and 13 healthy controls were assessed for cognitive ability at baseline and 2 years later. The rate of ^{11}C-PIB uptake was also measured at both time points, and all participants underwent MRI scans to detect volumetric brain changes. Although patients with AD consistently showed greater ^{11}C-PIB uptake than the controls, at group level the uptake of ^{11}C-PIB did not increase over time. By contrast, patients with AD did show a progressive decrease in brain volume in the hippocampal region, the temporal cortex and the precuneus, as well as advancing cognitive impairment.

In a separate study, William Jagust and colleagues also showed that ^{11}C-PIB uptake, as measured by PET scanning, does not relate to cognitive impairment. They also investigated several other biomarkers, and did note a positive association between ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake and cognitive ability. "From a clinical perspective we showed that ^{11}C-PIB uptake and other biomarkers for Aβ, whether taken from cerebrospinal fluid (CSF) or using a PET scan, are highly congruent. However, none of these biomarkers show good correlation with the severity of disease, glucose metabolism PET scans or measures of tau in the CSF. Of all the biomarkers, glucose metabolism [^{18}F-FDG uptake] shows the highest agreement with the observed severity of disease," he explains.

The Jagust study involved 10 patients with AD, 11 healthy controls and 34 people with mild cognitive impairment from the AD Neuroimaging Initiative (ADNI). CSF levels of the 42 amino acid Aβ peptide, total tau and phosphorylated tau were measured, and PET imaging was used to assess the level of brain uptake of ^{18}F-FDG and ^{11}C-PIB at various time points over 3 years (Figure 1). Standard tests of memory function and cognition were also performed. Analysis of the data revealed strong agreement between ^{11}C-PIB uptake and Aβ protein CSF levels, a more modest agreement between ^{11}C-PIB uptake and the levels of phosphorylated tau, and negligible agreement with the other markers. Neither ^{11}C-PIB uptake nor the levels of Aβ in the CSF correlated with the level of cognitive impairment in individual participants, but there was a strong correlation between ^{18}F-FDG uptake and cognitive ability scores.

"The findings of both studies reinforce the hypothesis that in AD, brain amyloid accumulation precedes the onset of symptomatic disease, but the temporal pattern of AD pathophysiology needs to be unveiled little by little to find causal links," comments Scheinin. Jagust agrees and points out that the nature of the ADNI, in which participants undergo multiple biomarker measurements, provides a unique opportunity to study biomarkers within the same individuals. "The dissociation between these types of biomarkers—those that track Aβ and those that track clinical stage—became apparent by looking at these relationships within the same subjects," he says.

Scheinin reports that the same individuals will now be followed up over a longer period to establish whether a change in brain Aβ load occurs that could be too slow to be detectable over 2 years. "We also intend to follow up the healthy controls to give more insight into the evolution of AD—some controls showed increased ^{11}C-PIB uptake—and future analyses should tell us whether these subjects are prone to developing a memory deficit," she explains. The ADNI study will continue to refine our understanding of biomarkers in AD and, in particular, to investigate the relevance of different biomarkers at different stages of the disease. "Different types of biomarkers may be differentially useful at every stage from normal cognitive function, through mild cognitive impairment to dementia," concludes Jagust.

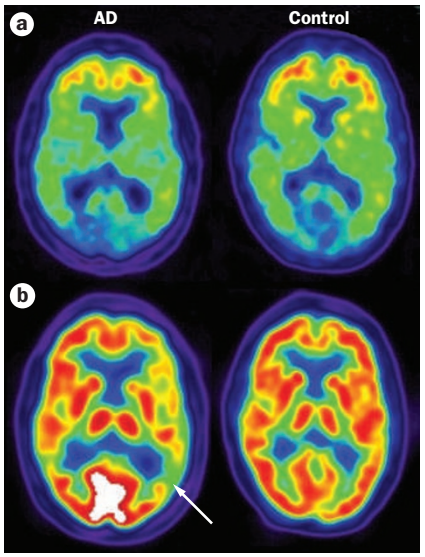

Figure 1 | ^{11}C-PIB-PET (a) and ^{18}F-FDG-PET (b) scans of a patient with Alzheimer disease (AD) and a healthy older control. The scans demonstrate equivalent fibrillar amyloid-β deposition (^{11}C-PIB scans) but a metabolic lesion in the patient with AD (arrow). Image provided by Professor William Jagust.

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Original articles Scheinin, N. M. *et al.* Follow-up of [^{11}C]PIB uptake and brain volume in patients with Alzheimer disease and controls. *Neurology* **73**, 1186–1192 (2009).
Jagust, W. J. *et al.* Relationships between biomarkers in aging and dementia. *Neurology* **73**, 1193–1199 (2009).