ALZHEIMER DISEASE

Biomarkers predict conversion from MCI to AD

New research published in *Brain* indicates that biomarkers of both amyloid-β (Aβ) load and neurodegeneration predict time to progression from mild cognitive impairment (MCI) to Alzheimer disease (AD).

Levels of the 42 amino acid form of Aβ ($Aβ_{42}$) in cerebrospinal fluid (CSF), Pittsburgh compound B (PIB) PET imaging of Aβ load and MRI measures of neurodegeneration are all biomarkers of AD. Aβ accumulation might occur years or decades before the cognitive symptoms associated with AD are apparent. By contrast, neurodegeneration seems to occur during later stages of the disease process. Thus, "it stands to reason that biomarkers of brain amyloidosis and biomarkers of neurodegeneration might behave differently as predictors of future cognitive decline," says lead author Clifford Jack from the Mayo Clinic and Foundation, Rochester, USA.

Jack and colleagues set out to determine whether these biomarkers were able to predict a short time to progression from MCI to AD. Using MRI, the researchers measured hippocampal volume in 218 patients with MCI, the investigators also used a new method that transforms CSF $Aβ_{42}$ measures into calculated PIB units of brain Aβ, so that Aβ data could be pooled from the study's participants.

> "...hippocampal atrophy and brain Aβ load predicted time to progression with comparable power..."

Jack and colleagues showed that among patients with MCI, those who had marked Aβ deposition were more likely to progress to AD within a 2 year period than those without such depositions. In patients with MCI who had Aβ deposits, hippocampal atrophy, but not amyloid load, predicted a short time to progression. "By contrast, when all patients with MCI were combined (amyloid positive and amyloid negative), hippocampal atrophy and brain Aβ load predicted time to progression with comparable power," says Jack.

Some differences in the capacity to predict time to progression existed between the two biomarkers. "The risk profile was linear throughout the range of hippocampal atrophy values, whereas the risk profile reached a ceiling at higher values of brain Aβ load," explains Jack. According to the researchers, these findings indicate that after a certain level of Aβ load has been reached, additional Aβ deposition does not shorten the time to development of AD further. By contrast, the degree of neurodegeneration seems to indicate how close an individual is to developing dementia.

"What we intend to do in the future, and what many in the field are also working on, is to try to arrive at data-driven comprehensive models of how biomarkers change over time as the disease progresses," says Jack. "This work will determine the role that biomarkers can and should have at various stages of the disease in new diagnostic criteria for AD that are currently being formulated. This work will also determine how biomarkers can be used to select patients for inclusion in new therapeutic treatment trials."

Nick Jones

Original article Jack, C. R. *et al.* Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain* **133**, 3336–3348 (2010)