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What does it mean to be ‘amyloid-positive’?

This scientific commentary refers to ‘Independent information from cerebrospinal fluid amyloid- β and florbetapir imaging in Alzheimer's disease’ by Mattsson *et al.* (10.1093/brain/awu367).

Studies of fluid and imaging biomarkers of Alzheimer's disease have contributed greatly to our understanding of disease pathobiology, and in so doing have fuelled a paradigm shift in the conceptualization of Alzheimer's disease as a chronic condition characterized by a long (~10–20 year) pre-clinical phase during which hallmark pathologies develop, before the appearance of cognitive symptoms (dementia) clinically defined as Alzheimer's disease. Revisions in diagnostic criteria to incorporate biomarker results have recently been proposed (Dubois *et al.*, 2010; Albert *et al.*, 2011; McKhann *et al.*, 2011; Sperling *et al.*, 2011) in order to increase confidence in identifying Alzheimer's disease as the underlying aetiology of a clinical impairment and to permit a diagnosis across the disease continuum, eventually perhaps in the asymptomatic period. Biomarkers are currently being used in clinical

trials for participant enrolment, evaluation of target engagement and as outcome measures (Hampel *et al.*, 2011). Thus, validation of Alzheimer's disease biomarkers is of critical importance. In this issue of *Brain*, Mattsson and colleagues (2015) evaluate and compare two amyloid-related biomarkers—CSF levels of amyloid- β_{42} (the primary component of amyloid plaques) versus amyloid imaging via PET with florbetapir (AMYVIDTM), a radiolabelled tracer approved by the US Federal Drug Administration in 2012 for the detection of brain amyloid—in their ability to predict clinical diagnosis and other measures and features of Alzheimer's disease (Mattsson *et al.*, 2015). Importantly, while the study confirms the previously reported diagnostic and prognostic utility of these two markers, the data expand upon previous results by exploring the discordance of these two measures in a large research cohort that spans the range of Alzheimer's disease stages, from asymptomatic to mildly symptomatic to dementia. In addition to providing insight into processes associated with amyloid metabolism and aggregation into plaques, the results of Mattsson

and colleagues will likely have an impact on the use of these two markers in ongoing and future clinical trials.

Low levels of CSF amyloid- β_{42} have long been associated with symptomatic Alzheimer's disease (Motter *et al.*, 1995), and are hypothesized to reflect the sequestration of soluble brain amyloid- β into insoluble plaques with a resultant reduction in the amount of amyloid- β_{42} that is cleared into the CSF. However, it was not until the advent of amyloid PET imaging with Pittsburgh Compound B (PIB) (Klunk *et al.*, 2004) that this relationship between brain amyloid deposition and CSF amyloid- β_{42} could be demonstrated in living individuals (Fagan *et al.*, 2006). This finding has subsequently been confirmed by many groups in many cohorts, leading to the use of CSF amyloid- β_{42} and amyloid-PET as often interchangeable metrics in defining ‘amyloid-positivity’. However, as is invariably the case with human biology, the story is not that simple. Whereas amyloid-positivity by PET is almost always associated with low CSF amyloid- β_{42} in individuals with symptomatic Alzheimer's disease,

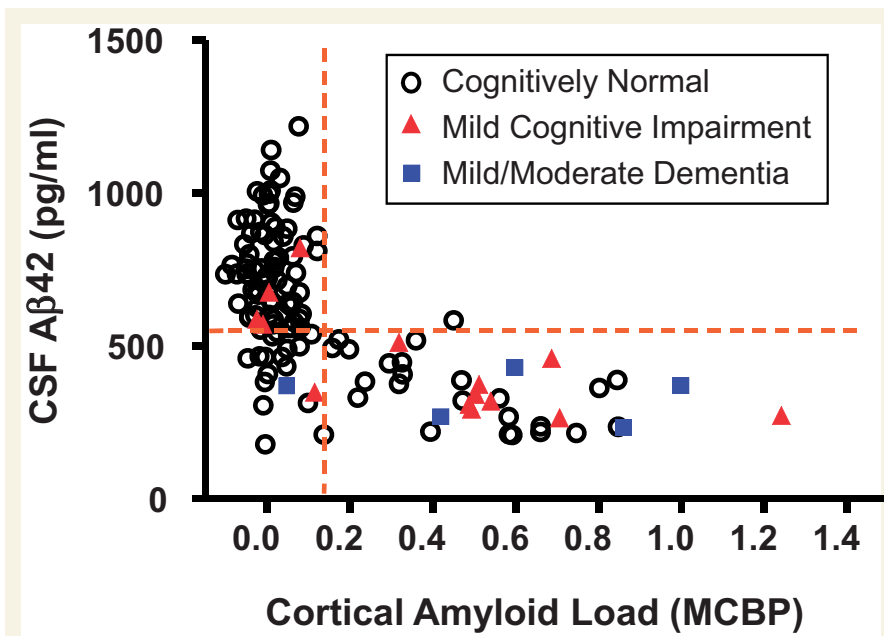


Figure 1 Illustration of the association between concentrations of CSF amyloid- β_{42} and cortical amyloid load as revealed by PET. Research participants in the Knight Alzheimer's Disease Research Centre underwent clinical assessment, CSF collection by lumbar puncture and amyloid imaging by PIB PET within a 12-month period. Cortical amyloid load is presented as the mean cortical binding potential (MCBP) calculated from the prefrontal cortex, precuneus, lateral temporal cortex and gyrus rectus, with cerebellum (very low PIB binding) as the reference region. CSF amyloid- β_{42} ($A\beta_{42}$) values were obtained with the INNOTEST[®] ELISA kit (Fujirebio, formerly Innogenetics). Dashed lines illustrate potential cut-offs for PIB (right of the vertical line) and CSF amyloid- β_{42} (below the horizontal line) positivity. The cohort (age ≥ 65 years) included 113 cognitively normal participants, 14 with mild cognitive impairment/very mild dementia, and five with mild/moderate dementia. The majority of PIB+ individuals had low CSF $A\beta_{42}$ whereas the majority of PIB- individuals had high levels of CSF $A\beta_{42}$. All but one of the 'discordant' values are to be found in the lower left quadrant (low CSF $A\beta_{42}$ /low PIB). Concordance is observed in symptomatic and asymptomatic (presumed pre-symptomatic) individuals. Symptomatic amyloid-negative individuals may have non-Alzheimer aetiologies. Reprinted from *Advances in Medical Sciences, Biomarkers of Alzheimer's disease and mild cognitive impairment: A current perspective*, available online 9 December 2014, with permission from Elsevier.

there exist persons (typically cognitively normal) with similarly low levels of CSF amyloid- β_{42} but who are amyloid-negative by PET (Fig. 1, lower left quadrant). Although many researchers tend to view these subjects as outliers, with the discrepancy considered to reflect analytical limitations of the biomarker assays and/or scans (thereby dampening enthusiasm for the clinical utility of these measures), Mattsson and colleagues have chosen to investigate this discordance, evaluating whether these two measures might in fact provide partly independent disease-related information. Specifically, using robust statistical approaches, they characterized and compared the frequency of such discordance in the

various clinical disease stages and the extent to which low CSF amyloid- β_{42} and amyloid-PET positivity were able to predict disease-related metrics including *APOE* $\epsilon 4$ carriage (the strongest genetic risk factor for Alzheimer's disease), a clinical diagnosis of Alzheimer's disease, cognitive deficits, brain hypometabolism and hypoperfusion, hippocampal atrophy, and increased CSF markers of tau-associated neuronal injury (tau and ptau181). Although previous studies, including those from their own group, have evaluated such relationships, the current study is the first to directly and comprehensively compare the performance of the two amyloid-related measures in the same (large) cohort.

As expected, CSF amyloid- β_{42} and amyloid PET were both associated with the various Alzheimer's disease-related processes and metrics; however, several differences in the strength of the associations were observed for the two amyloid-related measures. For example, amyloid PET positivity was a better predictor of a clinical diagnosis than was CSF amyloid- β_{42} , whereas the CSF measure was more closely associated with *APOE* $\epsilon 4$ carriage. In addition, amyloid-PET was more closely related to CSF tau-related measures of neuronal injury and cognitive deficits compared to CSF amyloid- β_{42} . While elucidation of such differences could be interpreted as promoting an 'us versus them' (CSF versus imaging) mentality in assessing biomarker utility, the greatest impact of the results is in terms of what they can tell us about underlying disease pathogenesis. Such information, in turn, may be useful in informing clinical applications.

So, what do these findings tell us about the disease process? While some may view the closer correspondence of amyloid-PET (compared to CSF amyloid- β_{42}) with Alzheimer's disease diagnosis as an endorsement for the use of PET, the frequency of discordance (almost exclusively CSF amyloid- β_{42} +/PET-) was highest in cognitively normal individuals, and decreased with increasing symptom severity. This observation is consistent with a scenario in which amyloid- β_{42} builds up and begins to aggregate in the brain early in the pre-symptomatic phase as evidenced by decreased amyloid- β_{42} in the CSF. The closer correspondence of CSF amyloid- β_{42} levels with *APOE* genotype is consistent with the known influence of *APOE* genotype on the aggregation and clearance of soluble amyloid- β (Castellano *et al.*, 2011). Once a certain threshold is reached, the amyloid then becomes detectable by PET, again during the presymptomatic phase. In the presence of fibrillar amyloid (detectable by PET), disease pathology progresses to involve tau-associated neuronal injury in vulnerable brain regions (as evidenced by increased levels of CSF tau

and ptau), regional atrophy and cognitive decline that eventually culminates in end-stage dementia. Mattsson and colleagues astutely discuss other possible contributors to the early CSF amyloid- β_{42} /PET discordance, including potential methodological variability, differences in overall amyloid- β production in certain individuals, and the impact of diffuse (non-fibrillar) amyloid- β deposits on the two biomarker patterns. It is also important to note that this model is based on cross-sectional data. The ultimate test of this hypothesis will require comparison of within-person longitudinal CSF, imaging (PET and volumetric) and cognitive/clinical data, as is currently being performed in several ongoing studies.

For researchers in the biomarker trenches, the data reported by Mattsson and colleagues add an important piece(s) to the ever-growing puzzle of Alzheimer's disease pathogenesis and biomarker development (Jack *et al.*, 2010). But how might they help clinicians who are eager to provide better care to their patients? Although CSF analysis and amyloid imaging are currently used in clinical settings, they are not universal practices. If amyloid-related biomarkers are to be used to confirm the underlying aetiology of a clinically expressed syndrome, then PET and CSF amyloid- β_{42} will likely both be informative. If biomarkers are to be used to provide pathological disease staging for use in clinical prognosis in asymptomatic or early symptomatic individuals (i.e. will I develop dementia, when and how fast will I progress?), the results of Mattsson *et al.* suggest that CSF amyloid- β_{42} may be more appropriate in the very earliest (presymptomatic) stages, whereas PET may be a more sensitive marker of subsequent disease progres-

sion (along with increases in tau-related markers such as CSF tau/ptau and/or tau imaging, which is currently in its infancy). Both CSF amyloid- β_{42} and amyloid PET will likely be useful in determining eligibility for enrolment into clinical trials, be they early clinical stage or secondary prevention trials; however, the choice of biomarker will depend on the disease stage to be enrolled, the length of the trial, and the defined outcome measure(s). Once disease-modifying therapies become available, these biomarkers could conceivably be used to monitor drug efficacy, including target engagement and effect on downstream pathological processes. It is only through elegant and comprehensive studies such as the one by Mattsson and colleagues that we will be able to refine our understanding of the disease process so as to enable the proper and most efficient use of biomarkers in clinical settings.

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