alzheimer's research&therapy

VIEWPOINT

Pro: Can biomarkers be gold standards in Alzheimer's disease?

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Abstract

Recent advances in biomarkers for Alzheimer's disease (AD) now allow the visualization of one of the hallmark pathologies of AD *in vivo*, and combination biomarker profiles can now approximate the diagnostic accuracy of autopsy in patients with dementia. Biomarkers are already employed in clinical trials in prodromal AD for both subject selection and in monitoring therapeutic response. Ultimately the greatest utility of biomarkers may be in the preclinical stages of AD, to identify and track progression of the disease prior to significant cognitive impairment, at the point when disease-modifying therapies are likely to be most efficacious.

The past decade has seen tremendous advances in the development of biomarkers for Alzheimer's disease (AD), raising the question as to whether these markers are now ready to serve as a gold standard. The definitive diagnosis of AD currently requires pathologic confirmation, but it is likely that several of the currently available biomarkers can add sufficient precision to the clinical diagnosis of AD dementia to approach a level of accuracy similar to autopsy diagnosis.

Elegant work by Cliff Jack and colleagues has suggested there is a dynamic temporal sequence of biomarkers that evolves over the course of AD, and thus the optimal set of biomarkers for diagnosis and/or tracking progression is probably dependent on the stage of AD [1]. The predictive value of biomarkers early in this sequence is particularly relevant to the widely acknowledged need to move therapeutic interventions earlier in the pathophysiologic process of AD for maximal efficacy. Broadly, these biomarkers can be divided into three categories: evidence of amyloid-β deposition, detected by positron emission tomography (PET) amyloid imaging or cerebrospinal fluid (CSF) markers of Aβ; evidence of synaptic dysfunction, detected by [^{18}F]fluorodeoxyglucose-PET or functional magnetic resonance imaging (MRI); and evidence of neurodegeneration or neuronal loss, detected by CSF tau and atrophy detectable with volumetric MRI. We will briefly review the utility of these biomarkers in clinical diagnosis and research criteria across the continuum from AD dementia back to cognitively normal older individuals who may be in presymptomatic stages of AD.

By the stage of AD dementia, there is clear evidence of abnormality in all biomarker categories, including low CSF Aβ and elevated CSF tau, increased PET amyloid tracer retention, [^{18}F]fluorodeoxyglucose hypometabolism, default network disruption on functional MRI, cortical thinning and hippocampal atrophy on volumetric MRI. It is widely acknowledged that a small percentage of clinically diagnosed AD patients do not meet autopsy criteria for AD – even in academic specialty clinics – and, similarly, a small proportion of clinically diagnosed AD patients do not show evidence of amyloid on either CSF or PET amyloid imaging markers. Although it is thought that these biomarker-negative dementia patients are probably misdiagnosed with AD, this remains to be proven with longitudinal follow-up and/or autopsy confirmation. There are a handful of case reports of patients with autopsy-confirmed AD who had false-negative PET amyloid imaging or CSF results, suggesting that there will probably never be perfect agreement. The convergence of evidence thus far, however, suggests that, at the stage of clinical dementia, the absence of amyloid positivity should raise concern that a non-AD process is responsible for dementia.

At the stage of prodromal AD, biomarkers appear to be useful in characterizing the heterogeneous population of individuals under the general rubric of mild cognitive impairment (MCI). Autopsy studies suggest a substantial percentage of MCI subjects do not have evidence of AD pathology at autopsy [2], similar to the proportion of amyloid-negative MCI subjects in PET amyloid imaging series [3] (Figure 1). Both CSF and PET amyloid imaging markers have demonstrated positive predictive value for progression to AD dementia within 2 to 3 years [3-5].

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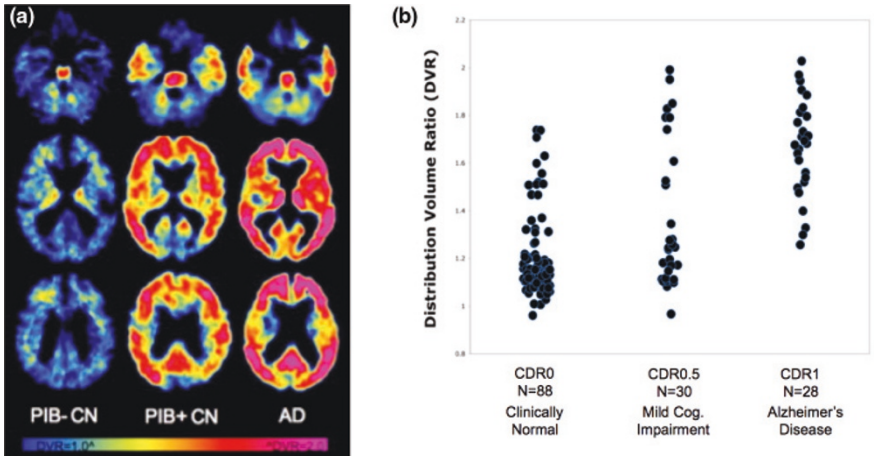

Figure 1. Amyloid deposition in cognitively normal elders, mild cognitive impairment and Alzheimer's disease. (a) Representative ^{11}C-PiB positron emission tomography images from a cognitively normal older individual (CN) without evidence of amyloid pathology (PiB–), from a normal older individual with elevated PiB retention indicating amyloid deposition (PiB+), and from a patient with mild Alzheimer's disease (AD) with extensive amyloid deposition. **(b)** Scatterplot of PiB distribution volume ratio (DVR) for CN, mild cognitive impairment (MCI) and AD groups, demonstrating a subset of CN and MCI individuals with evidence of amyloid deposition in the range of AD patients.

Markers of amyloidosis and volumetric MRI appear to provide complementary information in diagnostic accuracy and in prediction of cognitive decline [6], and it has been suggested that amnestic MCI plus Aβ deposition and/or significant atrophy may already represent early AD [7]. By the point of late MCI, amyloid deposition is thought to be well underway, perhaps already beginning to plateau, and markers of downstream neuronal dysfunction and neurodegeneration may be more useful in tracking progression from late MCI into dementia [1].

Biomarkers may have particular utility in selecting appropriate patients for inclusion in clinical trials and for monitoring therapeutic response. As the majority of current therapeutic trials in MCI and mild AD are anti-amyloid agents, it seems critical to test these drugs in individuals with amyloid pathology. This is of particular importance in the heterogeneous MCI population, since inclusion of a significant proportion of individuals without amyloid pathology introduces noise into the clinical trial, and may expose individuals without the target pathology to needless risk. The selection of a particular biomarker to monitor therapeutic response will probably depend on the specific drug mechanism of action and on the ability to correlate biomarker change with clinical response, but recent reports suggest that biomarkers can at least detect evidence of biological activity [8].

Biomarkers may ultimately prove most useful in identifying cognitively normal older individuals in the presymptomatic or preclinical stages of AD. Specifically, converging data suggest that amyloid accumulation begins years, perhaps at least a decade, prior to the onset of clinical impairment. Skeptics of the amyloid hypothesis have used the mismatch between pathological and clinical states as evidence against amyloid being the primary pathologic entity. Early evidence suggests, however, that the presence of either CSF or PET markers of amyloid pathology in clinically normal older individuals is associated with AD-like alterations on functional and structural imaging [9-11], increases in CSF tau [12], worse cognitive performance [13], and increased likelihood of cognitive decline and progression to early dementia [14]. There is, however, likely to be considerable variability in the emergence of clinical symptomatology due to other factors, such as cognitive reserve [13], or due to the presence of additional cerebral insults, such as cerebrovascular disease [15].

At this point, it remains unknown whether the presence of amyloid pathology is both necessary and sufficient to predict the progression to clinical AD. Several longitudinal studies in older individuals characterized by their amyloid status are ongoing, as well as studies in asymptomatic apolipoprotein E ε4 carriers and presymptomatic carriers of autosomal dominant mutations, which should provide critical information regarding the sequence of biomarkers in the preclinical stages of AD, and should serve to move the field towards earlier diagnosis and therapeutic intervention. It is entirely possible that amyloid-modifying therapies will be maximally efficacious prior to any cognitive impairment. The analogy to cholesterol and cardiovascular and cerebrovascular disease may be particularly relevant here. Although there is clear evidence that lowering certain forms of cholesterol significantly reduces the likelihood of myocardial infarction, there is little benefit to reducing

cholesterol at the stage of advanced ischemic cardiomyopathy. If this is the case for early amyloid pathology and AD, we may need to rely solely on biomarkers to identify individuals in the presymptomatic stages of AD and to track their response to therapeutic intervention prior to the emergence of clinical symptomatology.

Abbreviations

AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

Competing interests

KJ has served in the past as a consultant to GE HealthCare, who retains the commercial rights to PiB-PET amyloid imaging.

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References

1. Jack CR, Jr., Knopman DS, Jagust WJ, Shaw LM, Aisen PS, Weiner MW, Petersen RC, Trojanowski JQ: **Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade.** *Lancet Neurol* 2010, **9:**119-128.
2. Jicha GA, Parisi JE, Dickson DW, Johnson K, Cha R, Ivnik RJ, Tangalos EG, Boeve BF, Knopman DS, Braak H, Petersen RC: **Neuropathologic outcome of mild cognitive impairment following progression to clinical dementia.** *Arch Neurol* 2006, **63:**674-681.
3. Wolk DA, Price JC, Saxton JA, Snitz BE, James JA, Lopez OL, Aizenstein HJ, Cohen AD, Weissfeld LA, Mathis CA, Klunk WE, De-Kosky ST: **Amyloid imaging in mild cognitive impairment subtypes.** *Ann Neurol* 2009, **65:**557-568.
4. Okello A, Koivunen J, Edison P, Archer HA, Turkheimer FE, Nagren K, Bullock R, Walker Z, Kennedy A, Fox NC, Rossor MN, Rinne JO, Brooks DJ: **Conversion of amyloid positive and negative MCI to AD over 3 years: an ^{11}C-PIB PET study.** *Neurology* 2009, **73:**754-760.
5. Shaw LM, Vanderstichele H, Knapik-Czajka M, Clark CM, Aisen PS, Petersen RC, Blennow K, Soares H, Simon A, Lewczuk P, Dean R, Siemers E, Potter W, Lee VM, Trojanowski JQ: **Cerebrospinal fluid biomarker signature in Alzheimer's disease neuroimaging initiative subjects.** *Ann Neurol* 2009, **65:**403-413.
6. Vemuri P, Wiste HJ, Weigand SD, Shaw LM, Trojanowski JQ, Weiner MW, Knopman DS, Petersen RC, Jack CR, Jr: **MRI and CSF biomarkers in normal, MCI, and AD subjects: predicting future clinical change.** *Neurology* 2009, **73:**294-301.
7. Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, Cummings J, Delacourte A, Galasko D, Gauthier S, Jicha G, Meguro K, O'Brien J, Pasquier F, Robert P, Rossor M, Salloway S, Stern Y, Visser PJ, Scheltens P: **Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria.** *Lancet Neurol* 2007, **6:**734-746.
8. Rinne JO, Brooks DJ, Rossor MN, Fox NC, Bullock R, Klunk WE, Mathis CA, Blennow K, Barakos J, Okello AA, Rodriguez Martinez de Liano S, Liu E, Koller M, Gregg KM, Schenk D, Black R, Grundman M: **^{11}C-PiB PET assessment of change in fibrillar amyloid-beta load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study.** *Lancet Neurol* 2010, **9:**363-372.
9. Sperling RA, Laviolette PS, O'Keefe K, O'Brien J, Rentz DM, Pihlajamaki M, Marshall G, Hyman BT, Selkoe DJ, Hedden T, Buckner RL, Becker JA, Johnson KA: **Amyloid deposition is associated with impaired default network function in older persons without dementia.** *Neuron* 2009, **63:**178-188.
10. Mormino EC, Kluth JT, Madison CM, Rabinovici GD, Baker SL, Miller BL, Koeppe RA, Mathis CA, Weiner MW, Jagust WJ: **Episodic memory loss is related to hippocampal-mediated beta-amyloid deposition in elderly subjects.** *Brain* 2009, **132(Pt 5):**1310-1323.
11. Bourgeat P, Chetelat G, Villemagne VL, Fripp J, Raniga P, Pike K, Acosta O, Szoeke C, Ourselin S, Ames D, Ellis KA, Martins RN, Masters CL, Rowe CC, Salvado O: **Beta-amyloid burden in the temporal neocortex is related to hippocampal atrophy in elderly subjects without dementia.** *Neurology* 2010, **74:**121-127.
12. Fagan AM, Mintun MA, Shah AR, Aldea P, Roe CM, Mach RH, Marcus D, Morris JC, Holtzman DM: **Cerebrospinal fluid tau and ptau(181) increase with cortical amyloid deposition in cognitively normal individuals: implications for future clinical trials of Alzheimer's disease.** *EMBO Mol Med* 2009, **1:**371-380.
13. Rentz DM, Locascio JJ, Becker JA, Moran EK, Eng E, Buckner RL, Sperling RA, Johnson KA: **Cognition, reserve, and amyloid deposition in normal aging.** *Ann Neurol* 2010, **67:**353-364.
14. Morris JC, Roe CM, Grant EA, Head D, Storandt M, Goate AM, Fagan AM, Holtzman DM, Mintun MA: **Pittsburgh Compound B imaging and prediction of progression from cognitive normality to symptomatic Alzheimer disease.** *Arch Neurol* 2009, **66:**1469-1475.
15. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA: **Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology.** *Neurology* 2004, **62:**1148-1155.

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