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Preclinical Biomarkers in Alzheimer Disease:

A Sum Greater Than the Parts

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As clinical trials move to earlier stages of disease and focus on cognitively normal (CN) individuals with positive biomarkers of Alzheimer disease (AD) (eg, β -amyloid [$A\beta$]), it is critical to determine the relationship between these biomarkers and cognitive change. It is especially important to determine whether this cognitive change varies by biomarker status and whether sufficient cognitive change occurs to provide clinically meaningful outcomes during short follow-up intervals. For example, the recently initiated Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease trial¹ is enrolling individuals who are CN but amyloid positive to assess the efficacy of an anti-amyloid therapy on cognitive trajectories during a 3-year follow-up period.

In this issue of *JAMA Neurology*, Mormino et al² examine trajectories of cognitive change in a global outcome measure in relation to stages of preclinical AD, considering both $A\beta$ status and neurodegeneration (ND). They evaluated 166 CN participants in the Harvard Aging Brain Study during a mean 2.09-year follow-up period and defined $A\beta$ status using positron emission tomography (PET) and Pittsburgh Compound B (PiB) and defined ND using cut points based on either regional cerebral glucose metabolism in AD-vulnerable regions or hippocampal volumes adjusted for intracranial volume. Most important, they used a threshold for PiB (standard uptake value ratio, 1.196) based on gaussian mixture models to establish a binary classification of amyloid status rather than values in the range typically observed in cognitively impaired individuals (PET PiB standard uptake value ratios >1.4 or 1.5). This definition allowed the investigators to capture $A\beta^+$ individuals at the earliest stages of amyloid deposition. Using these cut points for $A\beta^+$ and ND in combination with the criteria outlined in the recommendations of the National Institute on Aging–Alzheimer's Association work group for staging of preclinical AD,³ Mormino et al² define the following stages: stage 0 is characterized as $A\beta^-/ND^-$ ($n = 81$), stage 1 as $A\beta^+/ND^-$ ($n = 19$), and stage 2 as $A\beta^+/ND^+$ ($n = 28$). In addition, they include a fourth group composed of $A\beta^-/ND^+$ ($n = 38$), who have been categorized as having “suspected non-AD pathophysiology” (SNAP) by Jack and colleagues.⁴

The authors first investigated the probability of being classified as ND^+ in relation to $A\beta$ status and not surprisingly found that CN individuals positive for $A\beta$ were 3 times more

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likely to be ND⁺ compared with those classified as Aβ⁻. They next investigated the association between Aβ and ND on global cognitive change during the follow-up interval, adjusting for age, sex, educational level, and apolipoprotein E genotype. The Aβ status and ND status were independently associated with cognitive change, and a significant interaction between Aβ and ND suggested synergistic effects of the 2 pathologic conditions combined on cognitive trajectories. Notably, patterns of cognitive changes indicated increased performance over time consistent with practice effects in stage 0 (Aβ⁻/ND⁻) CN, a diminished practice effect in stage 1 (Aβ⁺/ND⁻) and SNAP (Aβ⁻/ND⁺) CN, and declining performance over time evident only in stage 2 (Aβ⁺/ND⁺) CN. Moreover, a follow-up analysis of subthreshold levels of Aβ in the Aβ⁻ individuals suggested smaller practice effects (less-positive slopes) in those with higher levels of Aβ. These findings validate the usefulness of the preclinical staging criteria, and of Aβ and ND status, for predicting the likelihood of cognitive change, as well as the potential sensitivity of cognitive outcomes to therapeutic response during the short follow-up intervals typical of clinical trials. They also highlight the importance of examining continuous cognitive outcomes in CN individuals because the absence of a predicted practice effect, rather than cognitive decline per se, may predict impending cognitive impairment.

The findings reported in the present study also remind us that multiple paths exist to cognitive decline and impairment, even in individuals who are still within the normal range of cognitive performance. These paths may operate independently or synergistically, as shown with Aβ and ND in the present study. While the hypothetical model by Jack and colleagues^{5,6} originally posited that ND follows amyloidosis in preclinical AD, recent findings have indicated potentially different pathways early in the disease.⁷ The joint occurrence of Aβ and ND may reflect a later stage of disease in some individuals, but as Mormino et al² suggest, a double hit of both amyloidosis and ND may accelerate the path to symptomatic disease. The negative effects of Aβ on cognitive trajectories may be more pronounced in a brain already made vulnerable by ND in much the same way that Aβ and infarcts combine to increase risk for cognitive impairment,^{8,9} although the latter association is additive rather than synergistic.

The synergistic effect of Aβ and ND in promoting cognitive decline also emphasizes the need for multiple biomarkers as we strive to elucidate the multiple factors leading to cognitive impairment in older adults. In the present study, the sample size did not permit investigation of the separate effects of structural (hippocampal volume) vs functional (glucose metabolism) measures of ND. In addition, the present study used a global measure of cognitive function, and it will be important in future studies to determine whether some aspects of cognition are more sensitive to Aβ vs ND at different stages of preclinical disease. Longitudinal findings indicate that changes in episodic memory are among the earliest detectable changes in preclinical AD and that different cognitive outcomes may be more sensitive at different disease stages.¹⁰

The present study is another reminder that we still have much to learn about the pathophysiological events leading to clinical expression of AD and neurodegenerative pathology. The model specified by Jack and colleagues⁵ has been a useful framework for

testing hypotheses about the progression of AD, but our understanding of the temporal trajectories of pathologic biomarkers in relation to cognitive change is still developing.

References

1. Sperling RA, Rentz DM, Johnson KA, et al. The A4 study: stopping AD before symptoms begin? *Sci Transl Med*. 2014; 6(228):228fs213.doi: 10.1126/scitranslmed.3007941
2. Mormino EC, Betensky RA, Hedden T, et al. Synergistic effect of β -amyloid and neurodegeneration on cognitive decline in clinically normal individuals [published online September 15, 2014]. *JAMA Neurol*.
3. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011; 7(3):280–292. [PubMed: 21514248]
4. Jack CR Jr, Knopman DS, Weigand SD, et al. An operational approach to National Institute on Aging–Alzheimer's Association criteria for preclinical Alzheimer disease. *Ann Neurol*. 2012; 71(6):765–775. [PubMed: 22488240]
5. Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010; 9(1):119–128. [PubMed: 20083042]
6. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013; 12(2):207–216. [PubMed: 23332364]
7. Jack CR Jr, Wiste HJ, Weigand SD, et al. Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity. *Neurology*. 2013; 81(20):1732–1740. [PubMed: 24132377]
8. Troncoso JC, Zonderman AB, Resnick SM, Crain B, Pletnikova O, O'Brien RJ. Effect of infarcts on dementia in the Baltimore Longitudinal Study of Aging. *Ann Neurol*. 2008; 64(2):168–176. [PubMed: 18496870]
9. Schneider JA, Wilson RS, Bienias JL, Evans DA, Bennett DA. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. *Neurology*. 2004; 62(7):1148–1155. [PubMed: 15079015]
10. Bilgel M, An Y, Lang A, et al. Trajectories of Alzheimer disease–related cognitive measures in a longitudinal sample. *Alzheimers Dement*. 2014