MRI-based biomarkers of preclinical AD

An Alzheimer signature

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Recently proposed criteria for prodromal Alzheimer disease (AD),[1] mild cognitive impairment (MCI) due to AD,[2] and probable AD dementia[3] incorporate molecular evidence of amyloid-β (Aβ) pathology and also consider measures of brain structure and function as supportive biomarkers. MRI-based biomarkers are also proposed as supportive evidence for a diagnosis of preclinical AD[4] in cognitively normal individuals, posing new challenges for definition, validation, and interpretation of these biomarkers. A number of MRI-based biomarkers, such as volumes of hippocampus and entorhinal cortex, show robust differences between groups of patients with AD and controls. However, these measures have limited sensitivity and specificity in predicting who will develop AD in individual patients. The development and validation of new structural neuroimaging biomarkers sensitive to early changes in the disease process will be critical to implementation of the new research criteria for preclinical AD.

In this issue of *Neurology*®, Dickerson and Wolk[5] investigate the utility of a potential MRI biomarker of neurodegeneration, based on a previously identified set of 9 brain regions that show cortical thinning in AD, MCI, and cognitively normal individuals with Aβ deposition on PET imaging. Using MRI data from 159 cognitively normal individuals in the Alzheimer's Disease Neuroimaging Initiative (ADNI), the authors test the hypothesis that individuals at high risk for preclinical AD based on this "AD signature" of regional cortical thinning would be at increased risk for subsequent cognitive decline over a 3-year follow-up. Based on the AD signature scores, cognitively normal individuals were classified as high, average, or low risk of preclinical AD. Significant cognitive decline was operationalized as an increase of $\geq$1.0 on the Clinical Dementia Rating Scale Sum of Boxes score and a decline of $\geq$1 SD on one of the following measures: immediate recall on a measure of verbal learning, verbal delayed free recall, or executive function measured by Trails B. The authors report that normal individuals at high risk for preclinical AD are more likely to show cognitive decline, with risks of cognitive decline equal to 21% in the high-risk, 7% in the average-risk, and 0% in the low-risk group. This represents a 3-fold increase in risk for cognitive decline for each 1 SD of cortical thinning. In addition, 60% of the high-risk group had CSF characteristics (low CSF Aβ) suggestive of AD in the subsample for which CSF data were available.

Dickerson and Wolk provide additional support for the utility of MRI-based biomarkers in identifying cognitively normal individuals at increased risk for cognitive impairment and AD. Importantly, the regions contributing to the cortical thinning "AD signature" were defined in previous work by the authors and were applied in the current investigation to a new sample, the ADNI controls who had prospective cognitive follow-ups. The use of multiple brain regions to develop a composite measure of brain abnormality is an additional strength of this work. The authors show that their composite AD signature, compared with entorhinal cortex thickness, provides better discrimination between individuals who show cognitive decline vs stable performance at follow-up. Composite measures of networks of brain regions that discriminate between normal and pathologic brains are likely to yield more informative prediction on an individual patient basis as compared to single regions alone, as shown in prior studies using support vector machine learning methods to distinguish spatial patterns of abnormality that identify the earliest stages of AD.[6]

Although the sample size in the current study was small (only 14 individuals with complete cognitive follow-up data met the criteria for high risk for preclinical AD) and longer follow-up intervals will be required to validate the AD signature against other (imaging) biomarkers, the ability to identify cognitively normal individuals at higher risk for subsequent cognitive decline is an important step toward

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implementing and evaluating the new criteria for preclinical AD. Combinations of Aβ biomarkers and structural imaging biomarkers of subtle regional neurodegeneration, along with their time course, may also help distinguish cognitively normal individuals with Aβ pathology who will develop disease from those who will remain asymptomatic during their lifetime. Data from autopsy and PET amyloid imaging studies show that about 30% of individuals with normal cognitive function have substantial amyloid pathology. Although some argue that this group represents preclinical AD,[2] the absence of antemortem cognitive decline in prospective autopsy samples of "asymptomatic AD" suggests that a subgroup of individuals may demonstrate cognitive resilience despite substantial pathology.[7] In this group in particular, the presence of the "AD signature" in the structural, downstream, imaging marker may be predictive of who will actually decline. Distinguishing individuals who will decline from those who will remain asymptomatic is essential for patient selection and monitoring in therapeutic trials and for identification of individuals most likely to benefit from potential treatments to delay the onset of cognitive impairment.

AUTHOR CONTRIBUTIONS

Dr. Resnick: drafting/revising the manuscript. Dr. Scheltens: drafting/revising the manuscript.

DISCLOSURE

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