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Neuroimaging

White matter hyperintensities are more highly associated with preclinical Alzheimer's disease than imaging and cognitive markers of neurodegeneration

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Abstract

Introduction: Cognitive tests and nonamyloid imaging biomarkers do not consistently identify preclinical AD. The objective of this study was to evaluate whether white matter hyperintensity (WMH) volume, a cerebrovascular disease marker, is more associated with preclinical AD than conventional AD biomarkers and cognitive tests.

Methods: Elderly controls enrolled in the Alzheimer's Disease Neuroimaging Initiative (ADNI, n = 158) underwent florbetapir-PET scans, psychometric testing, neuroimaging with MRI and PET, and *APOE* genetic testing. Elderly controls the Parkinson's progression markers initiative (PPMI, n = 58) had WMH volume, cerebrospinal fluid (CSF) $A\beta_{1-42}$, and *APOE* status measured.

Results: In the ADNI cohort, only WMH volume and *APOE* ε4 status were associated with cerebral Aβ (standardized β = 0.44 and 1.25, $P = .03$ and .002). The association between WMH volume and *APOE* ε4 status with cerebral Aβ (standardized β = 1.12 and 0.26, $P = .048$ and .045) was confirmed in the PPMI cohort.

Discussion: WMH volume is more highly associated with preclinical AD than other AD biomarkers.

Keywords: Alzheimer's disease; Aging; MRI; PET; White matter; Leukoaraiosis; Preclinical Alzheimer's disease; Amyloid

1. Introduction

Owing to the recent failures of several clinical trials in treating symptomatic Alzheimer's disease (AD) [1], focus in therapeutic trials is shifting from reversing the effects of AD to preventing cognitive decline due to AD at the preclinical stage, before any noticeable cognitive change has occurred [2]. Preclinical AD is defined based on the presence of cerebral amyloidosis, detected by either amyloid PET or measurement of cerebrospinal $A\beta_{1-42}$ [3]. We focus here on preclinical AD, which is simply defined as presence of cerebral Aβ [3]. Presence of preclinical AD does not

Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf.

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necessarily imply that clinical AD will result but does appear to come with a higher risk of developing clinical AD [4]. Because of the importance of preclinical AD, an accurate and thorough understanding of the cognitive and brain changes at this stage is critical. Furthermore, predictors of preclinical AD are potentially valuable in the context of clinical trials to enrich populations before the use of more expensive or invasive amyloid measurement.

Within cognitively normal older adults, two predictors of amyloid status have already been relatively well established: age and apolipoprotein E (*APOE*) status [5,6]. Beyond these risks, it is possible that other neurodegenerative biomarkers and cognitive changes that presumptively represent the downstream effect of the presence of cerebral Aβ, such as hippocampal atrophy, hypometabolism, and subjective cognitive impairment, may also be sensitive to preclinical AD [7–9]. Although these markers clearly predict conversion from mild cognitive impairment (MCI) to probable AD [10–14] and the presence of cerebral amyloid in MCI to varying degrees [15], their value in preclinical disease is less well established.

One neuroimaging measure that has received less, but growing, attention in relationship to AD is the presence of white matter hyperintensity (WMH) volume. WMH volume has been associated with clinical AD [16,17], cognitive ability [18], cortical atrophy [19], and AD pathology in cognitively normal populations [20], but no study has examined the association of WMH volume with preclinical AD in the context of more established imaging and cognitive AD biomarkers. Here, we compare the association of a variety of biomarkers, including neurodegenerative, genetic, functional, and cognitive biomarkers, as well as WMH volume, with preclinical AD. This comparison sheds light on the pathogenesis of AD and can inform subsequent studies on longitudinal trajectories of AD biomarkers.

2. Methods

2.1. Clinical data

2.1.1. Subjects

Data used in the preparation of this article were obtained from two publicly available data repositories: the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu) and the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data). The ADNI was launched in 2003 by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, the Food and Drug Administration, private pharmaceutical companies and nonprofit organizations, as a $60 million, 5-year public-private partnership. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of MCI and early Alzheimer's disease (AD). For up-to-date information on the PPMI study, visit www.ppmi-info.org.

Data used in this article were downloaded from the ADNI website in November 2014. We included all cognitively normal subjects from ADNI2 and ADNI-GO who had undergone florbetapir-PET scans to obtain a measure of cerebral amyloidosis, *APOE* genotyping, FDG-PET, structural magnetic resonance (MR) imaging, and all cognitive tests examined. Only subjects with Freesurfer cortical and hippocampal segmentations judged acceptable by the structural MR processing core were included. Inclusion criteria for the study and diagnostic criteria for establishing disease state were as previously reported [21]. For up-to-date information on specific inclusion and exclusion criteria, please see www.adni-info.org. Data were also downloaded from the PPMI website, October 2014. Inclusion criteria for these study data included a baseline diagnosis of cognitively normal, a T1-weighted and Flair MRI, CSF analysis of AD biomarkers, and *APOE* genotyping. For up-to-date information on the PPMI study, visit www.ppmi-info.org.

2.2. Psychometric testing

The following measures were included in the analysis: the mini-mental state examination [22], Rey Auditory Verbal Learning Test [23], immediate and delayed recall of the Logical Memory Test [24], the Trail Making Test [trails A and trails B] [25], category fluency [animals [26]], and Boston Naming Test [27]. Given the importance of memory in prodromal AD, we examined several of the AVLT measures, which depend on differential aspects of episodic and working memory [28]. For the present study, we analyzed performance on the fifth immediate memory trial (AVLT Trial 5 Recall), 5-minute and 30-minute delayed recall (AVLT 5-min Recall, AVLT 30-min Recall), and recognition memory discrimination (AVLT recognition discrimination). To account for false alarms to nonstudied items, we calculated a measure of discriminability, d-prime (d'), in a standard fashion [29].

In addition to psychometric measures, we also examined a measure of cognitive complaints via the Everyday Cognition (ECog) questionnaire [30,31], using both informant-report and self-report data. Informants and participants are separately queried as to the degree to which particular everyday functioning has changed compared to 10 years earlier. Responses for ADNI were obtained on a five-point scale, with increasing values indicating more complaints and 5 indicating "do not know". The global scores were averaged separately over informant-rated and self-rated scales, excluding values of 5.

2.3. Determination of amyloid status

Florbetapir-PET was administered in accordance with the ADNI PET protocols available online (http://adni.loni.usc.edu/data-samples/pet), and image processing