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Featured Article

The effect of white matter hyperintensities on neurodegeneration in mild cognitive impairment

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Abstract

Introduction: It is unclear whether white matter hyperintensities (WMHs), magnetic resonance imaging markers of small-vessel cerebrovascular disease, promote neurodegeneration and associated clinical decline in Alzheimer's disease (AD), or simply co-occur with recognized pathogenic processes.

Methods: In 169 patients with mild cognitive impairment, followed for 3 years, we examined the association of (1) baseline regional WMH and cerebral spinal fluid–derived t-tau (total tau) with entorhinal cortex atrophy rates, as a marker of AD-related neurodegeneration, and conversion to AD; and (2) baseline regional WMH with change in t-tau level.

Results: In participants with low baseline t-tau, higher regional WMH volumes were associated with faster entorhinal cortex atrophy. Higher parietal WMH volume predicted conversion to AD in those with high t-tau. Higher parietal and occipital WMH volumes predicted increasing t-tau.

Discussion: WMHs affect AD clinical and pathologic processes both directly and interacting with tau.

Keywords: White matter hyperintensities; CSF tau; Alzheimer's disease; Mild cognitive impairment

1. Introduction

There has been an increased interest in the potential contributions of small-vessel cerebrovascular disease to the clinical presentation and pathogenesis of Alzheimer's disease (AD). Despite consistent observations supporting the role of vascular factors in AD [1–5], they have not been incorporated into the prevailing pathogenic models nor into newly implemented research criteria for AD and its antecedent conditions [6–8]. It is unclear whether cerebrovascular disease represents an independent pathologic factor that confers additive risk for clinical severity and course, whether it is a result of AD pathology, and/or whether it plays a primary role by promoting AD-related neurodegenerative changes. Understanding the role of cerebrovascular disease in AD is especially critical as it could clarify the prospect of vascular risk reduction as a preventive strategy for AD.

Small-vessel cerebrovascular disease typically manifests as white matter hyperintensities (WMHs), areas of increased signal on T2-weighted magnetic resonance imaging (MRI). In addition to being present in most individuals by the mid 60s [9] and correlating reliably with cognitive functioning in normal aging [10], we and others have shown that WMH may play a specialized role in AD. White matter

[1]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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hyperintensity volume is elevated among individuals at risk for AD by virtue of being diagnosed with mild cognitive impairment (MCI) [5]; predicts rate of cognitive decline in MCI [11] and in AD [12]; and increases risk for future development of AD [13]. Furthermore, WMH distributed in the parietal lobes, in particular, increase risk for later development of AD [14], progress more rapidly among individuals who develop AD [15], and are associated with genetic risk for AD [16]; although there is also evidence that WMH distributed in anterior regions is associated with cognitive impairment and markers of AD pathology [17–19]. The purpose of the present study was to examine whether WMH, as a marker of small-vessel cerebrovascular disease, confers risk for regional brain atrophy reflective of AD-related neurodegeneration independently or interactively with cerebrospinal fluid (CSF) markers of tau pathology in individuals with MCI. We also examined whether WMH predict change in diagnostic status and longitudinal increase in CSF tau. Based on our previous observations with parietal lobe WMH and a recent report that showed that parietal WMH and tau have synergistic effects on predicting progression from MCI to AD [20], we hypothesized that parietal lobe WMH in particular would modify the effect of tau pathology on brain atrophy and clinical decline among individuals at risk for AD.

2. Materials and methods

2.1. Overview

Using data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we examined whether regional WMH volumes are related to the biological or clinical markers implicated in current hypothetical pathogenic models of AD [21,22]. Our primary question was whether regional WMH confers independent or synergistc effects on neurodegeneration with regard to tau pathology. Secondary questions addressed whether WMH has a similar effect on progression from MCI to AD and whether baseline measures of WMH predict increase in CSF tau over time. For markers of neurodegeneration, we chose entorhinal cortex volume as the main outcome because of its well-established role as a structural biomarker, important for memory function and vulnerable to neurofibrillary tangle pathology early in the pathogenic process of AD [23]. We examined progression from MCI to AD status as the primary clinical outcome. Finally, we examined the possibility that WMH promotes the progression of AD pathology by testing whether regional WMH volumes predict subsequent changes in tau pathology. Additional analyses with $A\beta_{42}$ as covariates tested whether the effect of WMHs and their interaction with total tau was independent of markers of amyloid pathology.

2.2. Data set

Analyses for the present study used data from first phase of the ADNI (ADNI 1) (www.adni.loni.usc.edu). 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 MRI, PET, other biological markers, and clinical and neuropsychologic assessment can be combined to measure the progression of MCI and early AD. Determination of sensitive and specific markers of very early AD progression is intended to aid researchers and clinicians to develop new treatments and monitor their effectiveness, as well as lessen the time and cost of clinical trials.

The principal investigator of this initiative is Michael W. Weiner, MD, VA Medical Center and University of California–San Francisco. ADNI is the result of efforts of many coinvestigators from a broad range of academic institutions and private corporations, and subjects have been recruited from >50 sites across the United States and Canada. The initial goal of ADNI was to recruit 800 subjects but ADNI has been followed by ADNI-GO and ADNI 2. To date, these three protocols have recruited >1500 adults, ages 55–90 years, to participate in the research, consisting of cognitively normal older individuals, people with early or late MCI, and people with early AD. The follow-up duration of each group is specified in the protocols for ADNI 1, ADNI 2, and ADNI-GO. Subjects originally recruited for ADNI 1 and ADNI-GO had the option to be followed in ADNI 2. For up-to-date information, see www.adni-info.org.

2.3. Participants

Data from subjects diagnosed with amnestic MCI were downloaded from the ADNI website (www.adni.loni.usc.edu) and included demographic, cognitive, CSF biomarkers at baseline and longitudinal structural MRI scans data (n = 186). The ADNI study was designed to parallel procedures used in a clinical trial and thus only included participants who were in good medical health. Individuals were excluded from participation if they had significant vascular disease history, defined as a modified Hachinski score >4 [24]. Diagnosis of MCI was based on standard research criteria and included age between 55 and 90 years, a memory complaint (study subject or informant), objective evidence of abnormal memory, clinical dementia rating [25] score of 0.5, with a memory domain score of at least 0.5, Mini-Mental State Examination [26] score between 24 and 30 (inclusive), general cognition preserved such that a diagnosis of AD could not be made, stable medication, and not depressed (Geriatric Depression Scale [27] score of <6). Recruitment and diagnostic procedures have been reported in detail previously [28]. For the current analyses, participants were included if they had diagnosis of MCI at baseline, demographic variables, *APOE* genotype, CSF biomarkers ($A\beta_{42}$, total tau [t-tau]), and WMH assessment at baseline and longitudinal MRI scans. Seventeen subjects were excluded because of radiological evidence of infarcts resulting in a final sample size of 169 individuals. A subset of these subjects had longitudinal t-tau data available (n = 67).