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

Giuseppe Tosto\textsuperscript{a,b}, Molly E. Zimmerman\textsuperscript{c,d}, Jamie L. Hamilton\textsuperscript{a}, Owen T. Carmichael\textsuperscript{e}, Adam M. Brickman\textsuperscript{a,b,*}, for the Alzheimer’s Disease Neuroimaging Initiative\textsuperscript{1}

\textsuperscript{a}Taub Institute for Research on Alzheimer’s Disease and the Aging Brain, College of Physicians and Surgeons, Columbia University, New York, NY, USA
\textsuperscript{b}Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY, USA
\textsuperscript{c}Department of Psychology, Fordham University, Bronx, NY, USA
\textsuperscript{d}Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA
\textsuperscript{e}Pennington Biomedical Research Center, Baton Rouge, LA, USA

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.

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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.
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 CSF tau pathology 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 synergistic 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 co-investigators 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 ($n = 67$).
2.4. Neuroimaging acquisition

A standardized MRI protocol for image acquisition was implemented across ADNI sites, which was validated across platforms [29]. All data acquisition was performed on 1.5-T systems. T1-weighted volumetric magnetization prepared rapid gradient echo sequences were acquired in the sagittal orientation. A proton density/T2-weighted fast spin echo sequence was acquired in the axial orientation. Sites included in the ADNI protocol were required to pass rigorous scanner validation tests and scan acquisitions for each subject included a fluid-filled phantom. Details of the validation procedures are provided elsewhere (www.adni.loni.usc.edu).

2.5. Predictors

2.5.1. White matter hyperintensities

Detailed description of WMH volumetric quantification has been provided previously [30]. Briefly, the T1-, T2-, and PD-weighted MRI scans were coregistered and skull stripped [31,32]. After bias field correction [33], WMH were detected based on corresponding PD, T1, and T2 intensities; the prior probability of WMH; and the conditional probability of WMH based on the presence of WMH at neighboring voxels. Total WMH volumes were derived by summing and multiplying the number of labeled voxels by voxel dimensions. Regional WMH volumes, from frontal, temporal, parietal, and occipital lobes, were derived for the baseline scans. Total and regional WMH volumes were natural log transformed before analysis.

2.5.2. CSF biomarkers

Cerebrospinal fluid samples were collected at study baseline by lumbar puncture and shipped to the ADNI Biomarker Core laboratory at the University of Pennsylvania Medical Center for long-term storage at −80°C. Details regarding the assay technology, validation, and quality control can be found online in a data primer for these CSF analyses (www.adni.loni.usc.edu). The established CSF AD biomarkers Aβ42, t-tau, and phosphorylated tau (p-tau) were measured using the multiplex xMAP Luminex platform (Luminex Corp, Austin, TX, USA) with the INNOBIA AlzBio3 kit (Innogenetics, Ghent, Belgium). The biomarkers considered in the present study (Aβ42 and t-tau) were treated as dichotomous variables by dividing values according to established diagnostic thresholds validated in the ADNI cohort (i.e., for total tau = 93 pg/mL) [34]. In addition to baseline CSF biomarkers, we examined longitudinal CSF t-tau assessment over 3 years of follow-up available for a subset of patients (n = 67).

2.6. Outcomes

2.6.1. Neuroimaging outcomes

Structural MRI parcellation and segmentation data were downloaded from the ADNI website. ADNI structural MRI data were analyzed with the longitudinal processing stream in FreeSurfer, version 4.3 (https://surfer.nmr.mgh.harvard.edu), at the University of California, San Francisco after the T1-weighted MRI scans were converted to NiFTI format and preprocessed at Mayo Clinic [35]. FreeSurfer was used to derive entorhinal cortex volume and total intracranial volume.

2.6.2. Clinical outcomes

All subjects were diagnosed with MCI at baseline. The main clinical/diagnostic outcome was time to conversion to AD.

2.7. Covariates and APOE genotyping

Sex, number of years of education, and age at baseline were included as covariates in all the models presented. In addition, all models were adjusted by total cranial volume at baseline to correct for individual differences in head size. APOE genotyping was based on allelic combinations of single-nucleotide polymorphisms rs7412 and rs429358.

2.8. Statistical analysis

Analyses were restricted to ADNI 1 phase, which includes up to 36 months of follow-up data at 6-month interval. General estimating equation (GEE) analysis was used to investigate the impact of baseline regional WMH volumes and t-tau on the rate of entorhinal cortex atrophy. This method takes into account that fact that each subject has multiple visits and that measurements over time are likely to be correlated; furthermore, GEE allows for missing values and violation of normality [36]. Separate GEE models were run for each baseline regional WMH volume, time (in months from baseline), and their interaction as predictors (model 1). Cerebrospinal fluid–derived measures of t-tau at baseline, time, and their interaction were entered as predictors in model 2. A third series of models tested the two- and three-way interactions of baseline regional WMH volumes, baseline t-tau, and time controlling for the main effects of each predictor (model 3). Significant interaction terms with time would indicate that regional WMH volume or t-tau predicts the rate of entorhinal cortex atrophy. A significant three-way interaction would suggest that t-tau levels predict rates of atrophy and that this effect is modified by regional WMH burden, or equivalently that regional WMH volumes predict the rates of atrophy and that this effect is modified by t-tau levels. We included in a separate model CSF Aβ42 as an additional covariate to test if it had any confounding and/or modifying effects on the interaction between WMH volumes and t-tau (model 3b). Similarly, this analysis was repeated after restricting the subject group to individuals defined as “amyloid positive” (n = 124) by cut points established in ADNI [34]. Finally, GEE analysis was again used to investigate whether regional WMH volumes at baseline could affect rate of
change of t-tau over time. All analyses involving t-tau levels as a baseline predictor used a dichotomized variable as explained in the section of CSF biomarkers.

Cox proportional hazards models were constructed to examine the impact of baseline regional WMH volumes on progression to AD. Additional analyses were carried out to include t-tau and its interaction with the baseline regional WMH volumes. We used the enter selection method and the importance of predictive factors was assessed with Wald-type test statistics, the hazard ratio (HR), and its 95% confidence interval (CI) for survival. α levels were set a priori at 0.05.

3. Results

Clinical and demographic data are reported in Table 1.

3.1. Rate of entorhinal cortex atrophy

Results of the primary GEE analyses are listed in Table 2. Participants with high baseline t-tau showed faster atrophy rates compared with those with low t-tau as expected (significant baseline t-tau × time interaction). However, baseline regional WMH volumes modified the effect of t-tau on entorhinal cortex atrophy rates; those with lower baseline t-tau and higher frontal and parietal WMH volumes had disproportionately greater entorhinal cortex atrophy rates compared with those with low baseline t-tau and lower regional WMH volumes (significant baseline t-tau × baseline regional WMH × time interaction). For graphical purposes (Fig. 1), we dichotomized subjects in high and low baseline parietal lobe WMH volumes and plotted rates of entorhinal cortex atrophy, stratifying by baseline t-tau level. The results did not change when $A\beta_{42}$ was introduced as an additional covariate (Table 2, model 3b); similarly, when restricting the analyses to individuals defined as amyloid positive, the t-tau × parietal WMH × time interaction, the effect was almost identical ($β = −1.29$, CI = 3.00–0.43).

Table 2

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time $^*$ frontal WMH</td>
<td>0</td>
<td>.99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time $^*$ temporal WMH</td>
<td>$−0.20$</td>
<td>.51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time $^*$ parietal WMH</td>
<td>0.07</td>
<td>.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time $^*$ occipital WMH</td>
<td>$−0.19$</td>
<td>.58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time $^*$ t-tau</td>
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<td>.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time $^<em>$ frontal WMH$^</em>$ t-tau</td>
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<td>.005</td>
<td>$−2.06$</td>
<td>.007</td>
</tr>
<tr>
<td>Time $^<em>$ temporal WMH$^</em>$ t-tau</td>
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<td>.07</td>
<td>$−1.01$</td>
<td>.07</td>
</tr>
<tr>
<td>Time $^<em>$ parietal WMH$^</em>$ t-tau</td>
<td>$−1.51$</td>
<td>.009</td>
<td>$−1.44$</td>
<td>.010</td>
</tr>
<tr>
<td>Time $^<em>$ occipital WMH$^</em>$ t-tau</td>
<td>$−0.65$</td>
<td>.25</td>
<td>$−0.56$</td>
<td>.32</td>
</tr>
</tbody>
</table>
| Abbreviation: WMH, white matter hyperintensity. NOTE: The table displays results from GEE analyses that determined whether baseline measures of regional WMH and/or t-tau (predictors) are associated with rate of entorhinal cortex atrophy (outcome). Two-way interactions with time indicate that the rate of entorhinal cortex atrophy varies as a function of each unit measurement of the predictor. For example, the significant interaction between tau and time (model 2) indicates that entorhinal cortex volume declines on average 5.14 mm$^3$ per month less in the low tau group compared with the high tau group (reference). When three-way interactions are considered, the rate of change over time in entorhinal cortex volume is a function of increasing WMH in the low t-tau group as compared with the high t-tau group (reference group). In model 1, separate GEE analyses were run for each baseline regional WMH volume. Model 2 considered baseline t-tau levels as a primary predictor of entorhinal cortex atrophy. Model 3 included separate GEE analyses that examined the interactions between baseline regional WMH and t-tau on entorhinal cortex volume. Boldface values indicate statistical significance.

3.2. Progression to clinical AD

Among regional WMH volumes, only baseline parietal WMH volume predicted conversion to AD at a trend level (HR = 1.07, CI = 0.99–1.16; $P = 0.077$). When baseline t-tau level and its interaction with baseline parietal lobe WMH volumes were introduced, the model predicted time to conversion to AD (HR = 1.25, CI = 1.02–1.54; $P = 0.035$); those with high t-tau levels had a 25% increase in the risk of incident AD for every cubic centimeter increase in parietal lobe WMH compared with participants with low t-tau. None of the other baseline regional WMH volumes interacted with t-tau to predict progression to AD, and none of the covariates were associated with incident AD. The results were unchanged after introducing $A\beta_{42}$ as an additional
Fig. 1. Rate of atrophy of entorhinal cortex volume stratified by total CSF t-tau level (low t-tau top panel, high t-tau bottom panel) as a function of parietal WMH volume dichotomized by mean log WMH value (for visualization purposes). Entorhinal cortex atrophy rate was particularly precipitous among individuals with low baseline CSF t-tau and high parietal lobe WMH volume. Error bars are 95% CIs. Abbreviations: CSF, cerebrospinal fluid; WMH, white matter hyperintensity; t-tau, total tau; CI, confidence interval.
covariate. Also, the results were specific for the parietal lobe; for example, when considering the total WMH volume, the interaction between WMH volume and tau levels on progression to clinical AD was not significant (HR = 1.26, CI = 0.96–1.64, P = .09). Fig. 2 displays the results of the Cox regression analysis.

3.3. Rate of change of CSF t-tau

Parietal and occipital WMH volumes at baseline were associated with rate of change of t-tau (β = 0.21, P = .04 and β = 0.14, P = .04, respectively). Fig. 3 displays t-tau change over 36 months as a function of baseline parietal lobe WMH volume. On the other hand, t-tau at baseline did not predict WMH change over time (β = 0.009, P = .27).

4. Discussion

We examined whether regional WMH volume predicts neurodegeneration and change in clinical status independently or synergistically with respect to markers of tau pathology among individuals with MCI. Several important findings were observed. As expected, greater tau predicted greater rate of entorhinal cortex atrophy, but this association was modified by WMH burden; participants with lower levels of tau pathology had a higher rate of atrophy if they also had increased WMH burden.

Consistent with current pathogenic models of AD [21,22], increased tau burden is clearly a primary source of neurodegeneration, but when tau levels are low, regionally distributed WMH burden has an important impact on neurodegeneration. However, elevated WMH, particularly in the parietal lobes, also predicted progression from MCI to AD, and this association was particularly strong among individuals with high levels of tau; those with both high tau and high parietal lobe WMH were at particularly high risk of conversion to AD. Taken together, the findings suggest that regionally distributed WMH influence AD in two ways: first, by promoting neurodegenerative changes directly and second, by potentiating the effect of tau on clinical conversion (Fig. 4). Two notable observations in this study help explain the nature of the interaction between tau pathology and WMH. First, we showed that WMH volume predicts the increase in CSF tau over time, but tau levels do not predict the accumulation of WMH over time. Second, careful examination of the interaction between tau levels and parietal lobe WMH volumes on progression of entorhinal cortex atrophy, displayed in Fig. 1, suggests a biological ordering where the effect of WMH on entorhinal cortex atrophy precedes the effect of tau on entorhinal cortex atrophy. That is, among individuals with lower levels of tau, only those with higher amounts of parietal lobe WMH have reliable decline in entorhinal cortex volume. On the other hand, among those with high levels of tau, both those with high and low parietal WMH volumes show a similarly precipitous decline in entorhinal cortex volume; in addition, baseline entorhinal cortex volumes among individuals with high parietal WMH (i.e., the intercept in the lower panel of Fig. 1) are similar to the entorhinal cortex volumes observed at the last follow-up visit for individuals with low levels of tau (i.e., values at
36-month interval in the top panel of Fig. 1). We therefore speculate that accumulating parietal lobe WMH is a relatively early phenomenon that promotes neurodegeneration among individuals with MCI and that t-tau and WMH do not necessarily represent two independent sources of impairment that have additive impact, but rather are biologically linked. It should be noted that research on the ordering of the biological and clinical changes in AD are inherently biased by the measurement precision of relevant variables; it is possible that the measurement of WMH in ADNI, which was not designed to examine cerebrovascular disease, may be less precise than other biological markers.

Although we found that WMH volume distributed in several regions is important for clinical outcomes, elevated burden in the parietal lobes was most consistent. Our study is in line with a recent report [20] that showed that neurologically healthy older adults or patients diagnosed with MCI who progressed to AD over a 6-year interval were more likely to have high levels of parietal lobe WMH at baseline if their CSF-derived measures of tau were normal. Together with our previous reports that implicate parietal lobe-distributed WMH in individuals at high genetic [16] and clinical [14,15] risk for AD, findings from the present study provide further evidence of the importance of the regional distribution of WMH. The parietal lobes have been implicated in AD pathogenesis and clinical expression for quite some time [37,38]. It is interesting to note that metabolic imaging studies classically point to parietal lobe hypometabolism in AD [39], which is typically interpreted as evidence of dysfunction to neurodegenerative changes in that region. Future studies will need to determine the extent to which metabolic dysfunction in this region is mediated by underlying vascular damage. Furthermore, the propensity for WMH distributed in the parietal lobes to be associated with risk for AD may suggest that the pathology underlying WMH may vary by region. Indeed, in theory, any fluid-restricting pathologic change that causes local damage to the white matter can cause hyperintense signal on T2-weighted MRI scans. We [40] have hypothesized that WMH in posterior regions reflects both small-vessel ischemic damage and microhemorrhagic damage due to cerebral amyloid angiopathy. Alternatively, the pathology underlying the regional distribution of WMH may be uniform, but its clinical impact may vary by region; posterior damage may impact cognitive and functional networks more so than damage to other areas.

Although most pathogenic models of AD suggest that tau-related pathology results from Aβ toxicity in AD, tau is a nonspecific marker that increases with damage to cells in the brain. When tau levels are elevated in the CSF, it is most likely because of accumulation within neurons and then release into the fluid with the degeneration of those brain cells [41], although theoretically CSF tau levels may reflect degeneration, accumulation of the protein, or both. Neuropathologic studies are consistent in demonstrating that tissue damage that results in radiological WMH is likely driven by small-vessel ischemic change [42]. Common histologic features of WMH include arteriolosclerosis, increased myelin pallor, and complete or incomplete infarction [41–43]. It is therefore conceivable that some tau increases results from the ischemic damage reflected in WMH. This conclusion is indeed a major “take home” message of this study—small vessel cerebrovascular disease is one source of the neurodegenerative changes in AD. A previous study that used data from ADNI [44] showed that WMH volume predicted clinical and cognitive decline, but was not associated with CSF-derived Aβ42 or hippocampal volume. However, that study did not consider...
regional WMH volume nor examines its impact on tau levels or entorhinal cortex volume, which may be more specific markers for neurodegenerative changes in AD. In the context of the previous report, our study suggests that regional WMH volume may affect AD-related neurodegeneration if not amyloid pathology.

There are obvious clinical and theoretical implications for this work. From a clinical perspective, our findings indicate that interventions targeted at reducing the accumulation of WMH or treating their antecedent risk factors could reduce the risk of AD and the rate of neurodegenerative changes. Participants with severe vascular risk and cerebrovascular disease are excluded from participation in ADNI, which, on the one hand, suggests that the impact of WMH may be even greater in the overall population, which includes individuals with more severe cerebrovascular disease, but on the other hand, limits our ability to generalize our findings to individuals with more severe cerebrovascular disease. Results from a recent randomized controlled trial showed that interventions directed at the amelioration of cardiovascular risk factors were successful at slowing down white matter pathology progression in early AD, but had little effect on cognition [45]. Thus, we speculate that modification of vascular risk profile would have only little effect when clinical evidence of dementia has already emerged. Future intervention studies should focus on presymptomatic individuals at risk for AD.

From a theoretical perspective, these findings challenge current hypothetical models of AD pathogenesis [22] and recently implemented diagnostic criteria [7,8]. Cerebrovascular vascular disease is considered an important “confound” that may help explain variability in symptoms onset rather than playing a primary role in pathogenesis of disease. Our findings add to an accumulating body of work that implicates small-vessel disease as an important driver of disease with similar impact as tau pathology. Thus, although amyloid pathology may be necessary for AD but not sufficient to explain the phenomenology of the disease, small-vessel cerebrovascular disease, like tau, may represent a “second hit” that is required to produce the neurodegenerative changes and cognitive changes associated with AD.

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RESEARCH IN CONTEXT

1. Systematic review: We reviewed the literature for studies involving white matter hyperintensities (WMH) and cerebral spinal fluid biomarkers as main predictors and brain imaging markers, neuropsychologic test performance, and clinical diagnosis as main outcomes. Cross-sectional and longitudinal studies were included.

2. Interpretation: We investigated the role of WMH in promoting pathogenic and clinical changes in Alzheimer’s disease (AD) and its antecedent condition, mild cognitive impairment. WMH affect brain atrophy when tau is not yet elevated. By providing evidence that WMH promotes tau accumulation, we also speculate that WMH is actively involved in the pathogenic processes that result in AD neurodegeneration.

3. Future directions: Vascular components should be considered in future pathogenic models of AD and incorporated in diagnostic criteria. Future work should consider vascular factors as a treatment or prevention target.
References


