White Matter Hyperintensities and Cerebral Amyloidosis

Necessary and Sufficient for Clinical Expression of Alzheimer Disease?

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**Importance:** Current hypothetical models emphasize the importance of β-amyloid in Alzheimer disease (AD) pathogenesis, although amyloid alone is not sufficient to account for the dementia syndrome. The impact of small-vessel cerebrovascular disease, visualized as white matter hyperintensities (WMHs) on magnetic resonance imaging scans, may be a key factor that contributes independently to AD presentation.

**Objective:** To determine the impact of WMHs and Pittsburgh Compound B (PIB) positron-emission tomography–derived amyloid positivity on the clinical expression of AD.

**Design:** Baseline PIB–positron-emission tomography values were downloaded from the Alzheimer’s Disease Neuroimaging Initiative database. Total WMH volume was derived on accompanying structural magnetic resonance imaging data. We examined whether PIB positivity and total WMHs predicted diagnostic classification of patients with AD (n=20) and control subjects (n=21). A second analysis determined whether WMHs discriminated between those with and without the clinical diagnosis of AD among those who were classified as PIB positive (n=28). A third analysis examined whether WMHs, in addition to PIB status, could be used to predict future risk for AD among subjects with mild cognitive impairment (n=59).

**Setting:** The Alzheimer’s Disease Neuroimaging Initiative public database.

**Participants:** The study involved data from 21 normal control subjects, 59 subjects with mild cognitive impairment, and 20 participants with clinically defined AD from the Alzheimer Disease’s Neuroimaging Initiative database.

**Main Outcome Measures:** Clinical AD diagnosis and WMH volume.

**Results:** Pittsburgh Compound B positivity and increased total WMH volume independently predicted AD diagnosis. Among PIB-positive subjects, those diagnosed as having AD had greater WMH volume than normal control subjects. Among subjects with mild cognitive impairment, both WMH and PIB status at baseline conferred risk for future diagnosis of AD.

**Conclusions and Relevance:** White matter hyperintensities contribute to the presentation of AD and, in the context of significant amyloid deposition, may provide a second hit necessary for the clinical manifestation of the disease. As risk factors for the development of WMHs are modifiable, these findings suggest intervention and prevention strategies for the clinical syndrome of AD.


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The ability to quantify amyloid deposition in vivo with positron-emission tomography (PET) imaging has been one of
the most exciting advancements in applied neuroimaging research. Amyloid imaging studies have produced findings consistent with observations from autopsy series, confirming significant amyloid deposition among most symptomatic individuals. However, also consistent with autopsy studies, up to about 30% of older individuals without symptoms of AD have amyloid levels that are elevated to the same degree as their symptomatic counterparts. Furthermore, the amount of measurable amyloid deposition is a relatively weak correlate of symptom severity among individuals with AD or individuals at risk for AD. Together, these findings suggest that β-amyloid is necessary but perhaps not sufficient to cause the syndrome associated with the disease.

Despite consistent observations linking vascular factors to AD, cerebrovascular disease is considered a distinct process that is not a core feature of the disease. In fact, recently reformulated diagnostic criteria for AD treat evidence of cerebrovascular disease as an explicit exclusionary criterion. Yet, a preponderance of literature suggests that the severity of small-vessel cerebrovascular disease is increased among individuals with AD and those at risk for AD, reliably predicts who will develop AD in the future, and predicts the rate of decline of cognitive symptoms among individuals diagnosed as having AD. Small-vessel cerebrovascular disease is commonly visualized on T2-weighted magnetic resonance imaging (MRI) as increased signal intensity in white matter or white matter hyperintensities (WMHs). However, it is unclear whether WMHs confer an increased risk for AD above and beyond the risk conferred by β-amyloid. It is also unclear whether or how WMHs interact with β-amyloid.

This study represents an early step in addressing these issues. Using data from the Alzheimer’s Disease Neuroimaging Initiative (ADNI), we first asked the question of whether the severity of WMHs discriminates between individuals with prevalent AD and control subjects independently of the effects of β-amyloid measured with Pittsburgh Compound B (PIB). From a clinical perspective, it is essential to identify which factors contribute to dementia among older adults with evidence of significant amyloid deposition to inform treatment and preventive strategies and to determine prognosis. Thus, the second purpose of this study was to examine whether, among individuals who were PIB positive, WMH severity discriminated between those who met clinical criteria for AD and those who were classified as normal control subjects. Our final goal was to examine whether the severity of WMHs provides prognostic information regarding individuals with mild cognitive impairment (MCI). To do so, we examined whether baseline information about WMHs, in addition to PIB status, predicted future development of AD. By applying a threshold value to define high and low WMH burden derived from the second analysis to the subjects with MCI, this analysis allowed us to forward apply our cross-sectional analyses to an independent sample to determine its prognostic value.

METHODS

ADNI

Data used for this article were obtained from the ADNI database (adni.loni.ucla.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 non-profit 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 neuropsychological 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 reduce the time and cost of clinical trials.

The principal investigator of this initiative was Michael Weiner, MD, of the Veterans Affairs Medical Center and University of California, San Francisco; the ADNI is the result of efforts of many co-investigators from a range of academic institutions and private corporations. Subjects have been recruited from more than 50 sites across the United States and Canada (for up-to-date information, see www.adni-info.org). Appropriate human subjects ethics review and approval was obtained at each site, and all participants gave written informed consent.

SUBJECTS

Data from normal control subjects (n=21), subjects with MCI (n=59), and participants with clinically defined AD (n=20) were downloaded from the ADNI database. Demographic features are presented in the Table. The 3 groups were similar in age, sex distribution, and modified Hachinski Ischemic Scale score. The 3 groups differed, as expected, on Mini Mental State Examination scores. Subject selection from the overall ADNI database was limited to those with available PIB data from the so-called ADNI 1 cohort at the first follow-up visit with available PIB data; data from all subjects with available data were included in analyses. Diagnosis of participants in the ADNI database was made following standardized procedures (adni.loni.ucla.edu) that did not consider imaging data. All participants with AD met criteria for probable AD. Individuals with MCI met standard research criteria for amnestic MCI, which included age between 55 and 90 years, a memory complaint, objective evidence of abnormal memory, Clinical Dementia Rating score of 0.5, a Memory Box score of at least 0.3, a Mini Mental State Examination score between 24 and 30 (inclusive), general cognition preserved such that a diagnosis of AD could not be made, stable medication, and absence of depression. Recruitment and diagnostic procedures for the ADNI have been reported previously. Clinical data closest in time to the PET scan were used for diagnostic classification in the current study.

NEUROIMAGING WITH PIB PET

Data from carbon 11–labeled PIB-PET scans were downloaded from the ADNI database. Regional standardized uptake ratio values (normalized to cerebellum) were used, and a mean cortical value was calculated. Following previous reports, this value represented the arithmetic mean of uptake values in the anterior cingulate, frontal cortex, lateral temporal cortex, parietal lobe, and precuneus. Based on the extent literature, a threshold value of 1.50 was chosen to define PIB...
positivity or showing evidence of significant amyloid deposition. Of the 41 scans from patients with AD and control subjects, 28 (68%) were classified as PIB positive; 11 of these 28 were clinically defined as normal control subjects and the remaining were clinically defined as AD. Of the scans from the 59 subjects with MCI, 41 (69%) were PIB positive. Figure 1 shows an example of a PIB-positive vs a PIB-negative PET scan. A greater proportion of individuals diagnosed as having AD were PIB positive than those with MCI, who, in turn, were more likely to be PIB positive than control subjects (Table).

MRI

Accompanying structural MRI data, including T1-weighted, T2-weighted, and proton density (PD) sequences, were downloaded. Scans that were acquired within 6 months of the PIB-PET scans were used for analysis. Total WMH volume was derived for each subject with in-house–developed software that used multimodal fuzzy logic classification for voxel labeling. Briefly, the implementation of our approach was similar to work by Admiraal-Behloul and colleagues but was modified to quantify WMHs without fluid-attenuated inversion recovery T2-weighted images (as is the case for ADNI 1). Ours was a 2-stage automatic segmentation method comprising an adaptive stage and a reasoning stage. White matter hyperintensities appeared as increased signals on T2-weighted and PD images. On T1-weighted images, the intensity values for these voxels fell within the intensity distribution of gray matter tissue, despite their propensity for appearing within the white matter.

During the adaptive stage, first T1-weighted, T2-weighted, and PD images were brain extracted and bias field corrected with the Functional MRI of the Brain Software Library. The T1-weighted image was registered using a 6 degree of freedom transformation into the T2-weighted/PD image space. A WMH template—derived with an intensity thresholding and seed growing algorithm applied to fluid-attenuated inversion recovery images from a community-based study of more than 750 older adults—and Montreal Neurological Institute gray matter templates were registered into the T2-weighted/PD space. T1-weighted, T2-weighted, and PD images were segmented into their linguistic variables (dark, medium, or bright) using a hidden Markov Random Field Model. A fuzzy inference system was used for the reasoning stage. The system evaluated each voxel and labeled it as WMH or non-WMH, depending on the combination of linguistic variables. Finally, thresholding, erosion/dilation, and small cluster removal were applied to remove artifacts. The total WMH vol-

### Table. Characteristics of Study Participants

<table>
<thead>
<tr>
<th>No.</th>
<th>NC</th>
<th>MCI</th>
<th>AD</th>
<th>Test</th>
<th>P Value</th>
<th>Post Hoc Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>21</td>
<td>59</td>
<td>20</td>
<td>F = 1.90</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>76.20 (5.97)</td>
<td>75.72 (7.86)</td>
<td>73.00 (8.55)</td>
<td>F = 55.87</td>
<td>&lt;.001</td>
<td>NC&gt;MCI&gt;AD</td>
</tr>
<tr>
<td>Women, %</td>
<td>38</td>
<td>31</td>
<td>40</td>
<td>χ² = 5.09</td>
<td>.02, linear</td>
<td></td>
</tr>
<tr>
<td>MMSE score</td>
<td>28.71 (1.35)</td>
<td>27.22 (1.95)</td>
<td>21.20 (4.28)</td>
<td>F = 2.87</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Modified Hachinski score</td>
<td>0.67 (0.80)</td>
<td>0.67 (0.86)</td>
<td>0.70 (0.57)</td>
<td>F = 0.708</td>
<td>.67</td>
<td></td>
</tr>
<tr>
<td>PIB+ individuals, %</td>
<td>52</td>
<td>70</td>
<td>85</td>
<td>χ² = 5.09</td>
<td>.02, linear</td>
<td></td>
</tr>
<tr>
<td>Cortical PIB uptake values</td>
<td>1.59 (0.36)</td>
<td>1.81 (0.41)</td>
<td>1.82 (0.35)</td>
<td>F = 2.87</td>
<td>.06</td>
<td></td>
</tr>
<tr>
<td>Total WMH volume, cm³</td>
<td>2.26 (2.80)</td>
<td>4.07 (5.78)</td>
<td>9.34 (9.84)</td>
<td>F = 7.158</td>
<td>.001</td>
<td>NC = MCI&lt;AD</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; PIB, Pittsburgh Compound B; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; NC, normal control; WMH, white matter hyperintensity.

![Figure 1. Example brain scans. A, Example of a Pittsburgh Compound B (PIB)–negative scan. B, Example of a PIB-positive scan. Color bar represents mean uptake values. Scans were classified as PIB positive if the mean uptake value of the anterior cingulate, frontal cortex, lateral temporal cortex, parietal lobe, and precuneus was greater than 1.50. The color bar also displays the scale for uptake values.](image)
Volume was the sum of all labeled voxels multiplied by the voxel dimensions. Figure 2 displays an example of WMH segmentation from an ADNI participant. We have previously shown this labeling system to be valid and reliable.33 Patients diagnosed as having AD had significantly greater WMH volumes than subjects with MCI or control subjects (Table).

**STATISTICAL ANALYSIS**

Total WMH, PIB positivity (0 = PIB negative, 1 = PIB positive), age, and sex were entered into a logistic regression analysis with AD diagnosis (0 = normal, 1 = AD) as the dependent variable. The model was rerun with a WMH by PIB positivity interaction term. Next, the analyses were restricted only to individuals who were PIB positive, and a logistic regression analysis was used to determine whether total WMH discriminated between those who met clinical criteria for AD and those who did not; this analysis also allowed us to determine the WMH volumetric cutoff that best separated the 2 groups with the highest specificity and sensitivity.

This WMH volume cutoff score was forward applied to the subjects with MCI to derive 4 PIB/WMH groups: PIB negative/low WMH, PIB negative/high WMH, PIB positive/low WMH, and PIB positive/high WMH. Participants in the ADNI were re-evaluated every 6 months. We examined differences in the proportion of subjects with MCI who converted to AD during the follow-up period with \( \chi^2 \) analysis. Additionally, to see whether WMHs increased the risk for future development of AD among patients with MCI, we performed a logistic regression analysis, with final diagnosis (0 = remained nondemented, 1 = converted to AD) as the dependent variable and PIB/WMH group as the independent variable, along with time interval between baseline evaluation and diagnostic visit (or last assessment in the case of those who remained nondemented) and age as additional predictors/covariates.

**RESULTS**

**BASELINE ASSESSMENT OF PARTICIPANTS CLASSIFIED AS NORMAL OR AD**

There were 28 participants (68%) classified as PIB positive, of whom 17 met clinical criteria for AD; 13 participants classified as PIB negative, of whom 3 met criteria for AD (\( \chi^2 = 5.03, P = .03 \)). The mean [SD] total WMH volume was 5.71 [7.92] cm\(^3\) (median, 2.27 cm\(^3\)). Total WMH volume did not differ between PIB-positive and PIB-negative individuals (\( t_{39} = 0.911, P = .17 \)); however, when we examined the relationship between cortical PIB uptake values and total WMH volume among all participants (including those with MCI), there was a significant negative association between the 2 (Spearman rho \( \rho \) = 0.203, \( P = .04 \)).

Results from the logistic regression model (overall model: \( \chi^2 = 16.69, P = .001 \)), showed that higher WMH volume (\( \beta = 0.247, P = .02 \)) and PIB positivity (\( \beta = 1.881, P = .049 \)) were each independently associated with AD diagnosis. Age was not associated with diagnosis (\( \beta = -0.022, P = .56 \)). When the model was rerun with a WMH by PIB positivity interaction term, that variable was not associated significantly with diagnosis (\( \beta = 0.163, P = .45 \)).

Restricting the analysis to individuals who were PIB positive only, increased WMH volume was also associated with AD diagnosis (\( \beta = 0.335, P = .05 \); overall model: \( \chi^2 = 9.516, P = .002 \)). Because it was not associated with AD diagnosis or PIB positivity, age was not included in this analysis. Figure 3 displays the distribution of WMH volume as a function of diagnosis among those who were PIB positive. Setting a cutoff at 1.25 cm\(^3\) total WMH volume yielded a sensitivity and specificity of AD classification of 83% and 64%, respectively.

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Figure 2. Example of white matter hyperintensity (WMH) segmentation on a single Alzheimer’s Disease Neuroimaging Initiative participant. T1 indicates T1-weighted, T2, T2-weighted; PD, proton density.

Figure 3. Distribution of white matter hyperintensity (WMH) volume among Pittsburgh Compound B–positive participants as a function of clinical diagnosis. For illustration, data are presented in log-transformed units. At a cutoff score of 0.22 log-transformed units (approximately 1.25 cm\(^3\) raw units) of WMH volume (solid line), there is 83% sensitivity and 64% specificity for diagnostic classification. AD indicates Alzheimer disease; NC, normal control.
LONGITUDINAL ANALYSES WITH SUBJECTS WITH MCI

Subjects with MCI were followed for a mean (SD) of 29.73 (12.75) months and a median of 35 months from the time of their baseline evaluation to their incident AD diagnosis visit or to their last available follow-up assessment. Twenty-two of the 59 participants with MCI (37%) converted to AD during the follow-up interval. Those who converted and those who remained nondemented were similar in age at baseline ($F_{1,58} = 0.10$, $P = .92$) and sex distribution ($\chi^2 = 0.028$, $P = .87$). The 59 participants with MCI were divided into the 4 PIB/WMH groups previously described: 7 (11.9%) were in the PIB negative/low WMH group; 11 (18.6%) in the PIB negative/high WMH group; 17 (28.8%) in the PIB positive/low WMH group, and 24 (40.7%) in the PIB positive/high WMH group. These groups did not differ in age ($F_{3,58} = 1.334$, $P = .27$) or sex distribution ($\chi^2 = 3.87$, $P = .28$). When we compared the proportion of patients with MCI who converted to AD across these groups, there was a significant linear-by-linear association ($\chi^2 = 4.679$, $P = .03$), such that the proportion of patients who converted increased monotonically across the groups (Figure 4). Results from the logistic regression analysis (overall model: $\chi^2 = 14.083$, $P = .003$) showed that PIB/WMH group ($\beta = 0.636$, $P = .048$) and time interval between baseline and diagnostic visit or last assessment ($\beta = -0.078$, $P = .006$), but not age ($\beta = -0.025$, $P = .56$), were associated with future diagnosis of AD.

COMMENT

When comparing patients with AD and control subjects, we found that the severity of WMHs and amyloidosis, in the form of PIB positivity, were independently associated with AD diagnosis. Among individuals with amyloidosis, WMH volume discriminated between those with clinical AD and normal control subjects with excellent sensitivity and good specificity. We found that both PIB and WMH status were significant predictors of individuals with MCI who will convert to AD in the future. The findings suggest a role of small-vessel cerebrovascular disease in the clinical presentation of AD and point to the importance of incorporating WMH into the formulation of pathogenic models of the disease.

Current models of AD pathogenesis highlight β-amyloid deposition as a precipitating pathologic feature of the disease.\(^1\) Consideration of findings from both in vivo β-amyloid and autopsy studies has produced the consistent observation that not all older adults with evidence of amyloidosis manifest the clinical syndrome associated with the disease.\(^9\) These observations suggest that amyloidosis is necessary but not sufficient to cause dementia due to AD. Our findings suggest that WMHs contribute to AD presentation in addition to β-amyloid and that WMHs may be a factor that provides a second hit necessary for dementia in the context of amyloidosis. Many of the risk factors for the development of WMH in late life have been identified and tend to be vascular in nature (eg, see related studies\(^6\)). Thus, these findings add to a growing literature that suggests that treatment or prevention of peripheral vascular risk factors could help delay or prevent AD and/or mitigate the impact of AD pathology on its clinical expression.

White matter hyperintensities have been implicated in cognitive aging for some time.\(^4\) In the context of AD, the severity of WMHs has been shown to be related to the risk for incidence and course of disease progression.\(^24,26\) However, despite consistent observations of their involvement with AD, WMHs are typically thought to reflect rarefaction of white matter secondary to small-vessel occlusive disease,\(^7\) which is thought to be a pathogenic pathway distinct from AD. The association between WMHs and AD has most consistently been reported among community-based studies,\(^8\) which often do not exclude individuals with a notable vascular history. Criteria for inclusion in the ADNI study are conservative, and participants with any significant medical morbidity are excluded. Despite the rarefied sample, WMHs still emerged as a significant factor in the presentation of the disease, adding even more clinical significance to our observations. The association between WMHs and clinical AD among individuals without a significant medical history also suggests that WMHs may reflect pathologic changes that are not restricted to small-vessel cerebrovascular disease. For example, WMHs may to some degree point to underlying inflammatory changes or vascular forms of β-amyloid itself.\(^8\) This latter possibility would suggest a mechanistic link between WMHs and primary AD pathology, but careful clinicopathologic correlates studies are needed.

Other authors have reported significant associations between WMH severity and amyloid burden measured in cerebrospinal fluid.\(^4\) Here, we did not see a reliable difference between PIB-positive and PIB-negative individuals in overall WMH burden, which may be explained partially by the small sample size. Indeed, when we examined the association between cortical PIB uptake values and WMH volume in all participants, there was a reliable negative relationship between them. Despite the modest relationship between the two, both fa-
tors (ie, WMH burden and PIB positivity) were important in the prediction of AD diagnosis. It will be important to determine to what degree the two are truly independent pathologic processes. In the analyses that incorporated longitudinal data, it is clear that PIB status is a primary discriminator between those who ultimately convert to AD (Figure 4); however, it is noteworthy that even among PIB-negative participants with MCI, having a high burden of WMHs was associated with an increased risk for AD at follow-up. Future longitudinal analyses with larger samples will be necessary to examine the progression of amyloid deposition and WMHs, as well as their interaction as they relate to future incidence of AD.

The ADNI study was designed to comprise subjects with characteristics that would parallel those in clinical trials. Therefore, it is not necessarily reflective of the overall population. Participants in the ADNI are very carefully and systematically evaluated and excluded if they have significant vascular disease histories, increasing confidence in observation about the involvement of WMHs in AD. Amyloid imaging studies, particularly those that consider other cerebral structural and functional factors, are very limited; to our knowledge, this study is the first examination of the independent associations of β-amyloid and WMHs with AD. Thus, these observations are preliminary and replication in larger samples would be necessary for verification. Future work is needed to determine the pathologic underpinnings of WMHs. Regardless of mechanistic associations between WMHs and AD pathology, it is becoming clear from studies such as this one and others that vascular factors are quite important in the pathogenesis of the AD phenotype, which suggests clinical strategies for disease prevention and treatment.

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