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White matter hyperintensities and cerebral amyloidosis: Necessary and sufficient for clinical expression of Alzheimer's disease?

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Abstract

Context—Current hypothetical models emphasize the importance of beta amyloid in Alzheimer's 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 (WMH) on MRI scans, may be a key factor that contributes independently to AD presentation.

Objective—To determine the impact of WMH and PIB PET-derived "amyloid positivity" on the clinical expression of AD.

Design—Baseline PIB-PET values were downloaded from the Alzheimer's Disease Neuroimaging (ADNI) database. Total WMH volume was derived on accompanying structural MRI data. We examined whether PIB "positivity" and total WMH predict diagnostic classification of patients with AD (n=20) and controls (n=21). A second analysis determined whether WMH discriminates 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 WMH, in addition to PIB

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status, can be used to predict future risk of AD among subjects with mild cognitive impairment (MCI; n=59).

Setting—The ADNI public database.

Outcome measures—Clinical AD diagnosis, WMH volume.

Results—PIB positivity and increased total WMH volume independently predicted AD diagnosis. Among PIB positive subjects, those diagnosed with AD had greater WMH volume than normal controls. Among MCI subjects, both WMH and PIB status at baseline conferred risk for future diagnosis of AD.

Conclusions—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 WMH are modifiable, these findings suggest intervention and prevention strategies for the clinical syndrome of AD.

Introduction

Current pathogenic models of Alzheimer's disease (AD) emphasize the precipitating role of cerebral beta amyloid deposition in a cascade of biological events that ultimately cause neurodegeneration and dementia[1]. The vast majority of studies that has examined the association between AD and beta amyloid measured at autopsy has confirmed an increase in beta amyloid among patients meeting clinical criteria. Amyloid plaques, along with neurofibrillary tangles, comprise one of the two pathological markers for the disease.

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[2–6]. However, also consistent with autopsy studies[7,8], 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[9–13]. Further, the amount of measurable amyloid deposition is a relatively weak correlate of symptom severity among individuals with AD or individuals at risk for AD[10,12,14–18]. Together, these findings suggest that beta amyloid is *necessary* but perhaps not *sufficient* to cause the syndrome associated with the disease.

Despite consistent observations linking vascular factors to AD[19,20], cerebrovascular disease is considered a distinct process that is not a core feature of the disease. In fact, recently re-formulated diagnostic criteria for AD treat evidence of cerebrovascular disease as an explicit exclusionary criterion[21]. Yet, a preponderance of literature suggests that severity of small vessel cerebrovascular disease is increased among individuals with AD and at risk for AD [22,23], reliably predicts who will develop AD in the future[24,25], and predicts rate of decline of cognitive symptoms among individuals with diagnosed AD[26]. 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 (WMH). It is unclear, however, whether WMH confer an increased risk for AD above-and-

beyond the risk conferred by amyloid beta. It is also unclear whether or how WMH interact with beta 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 WMH discriminates between individuals with prevalent AD and controls independently of the effects of beta 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 in order to inform treatment and preventive strategies and to determine prognosis. Thus, the second purpose of this study was to examine whether, among individuals who are "PIB positive," WMH severity discriminates between those who meet clinical criteria for AD and those who are classified as normal controls. Our final goal was to examine whether the severity of WMH provides prognostic information regarding individuals with mild cognitive impairment (MCI). To do so, we examined whether baseline information about WMH, in addition to PIB status, predicts future development of AD. By applying a threshold value to define high and low WMH burden derived from the second analysis to the MCI subjects, 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 (www.loni.ucla.edu/ADNI). 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 lessen the time and cost of clinical trials.

The Principal Investigator of this initiative is Michael Weiner, MD, VA Medical Center and University of California, San Francisco. ADNI is the result of efforts of many co-investigators from a range of academic institutions and private corporations, and subjects have been recruited from over 50 sites across the U.S. 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 controls (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 Table 1. The three groups were similar in age, sex distribution, and

modified Hachinski Ischemic Score[27]. The three groups differed, as expected, on the Mini Mental State Examination (MMSE). 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 (www.loni.ucla.edu\ADNI) that did not consider imaging data. All participants with AD met criteria for probable AD[28]. Individuals with MCI met standard research criteria for amnestic MCI, which included age between 55 and 90, a memory complaint, objective evidence of abnormal memory, Clinical Dementia Rating (CDR) score of 0.5, with a Memory Box score of at least 0.5, MMSE score between 24 and 30 (inclusive), general cognition preserved such that a diagnosis of AD could not be made, stable medication, and not depressed[29]. Recruitment and diagnostic procedures for ADNI have been reported previously[30]. Clinical data closest in time to the PET scan were used for diagnostic classification in the current study.

Neuroimaging

PIB PET—Data from [(11)C]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[31] 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 extant literature[32], a threshold value of 1.50 was chosen to define "PIB positivity," or showing evidence of significant amyloid deposition. Of the 41 scans from AD patients and controls, 28 (68%) were classified as PIB positive; 11 of these 28 were clinically defined as normal controls 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 *versus* a PIB negative PET scan. A greater proportion of individuals diagnosed with AD were PIB positive than those with MCI, who, in turn were more likely to be PIB positive than controls (Table 1).

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 multi-modal fuzzy logic classification for voxel labeling[33]. Briefly, the implementation of our approach is similar to work by Admiraal-Behloul and colleagues [34] but was modified to quantify WMH without fluid attenuated inverse recovery (FLAIR) T2-weighted images (as is the case for ADNI-1). Ours is a two-stage automatic segmentation method comprising an adaptive and a reasoning stage. White matter hyperintensities appear as increased signal on T2-weighted and PD images. On T1-weighted images the intensity values for these voxels falls within the intensity distribution of grey matter tissue, despite their propensity for appearing within the white matter.

During the adaptive stage, first T1-weighted, T2-weighted, and PD images are brain extracted and bias field corrected with FMRIB Software Library[35]. The T1-weighted image is 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 FLAIR images from a community-based study of over 750 older adults[36,37] and Montreal Neurological Institute grey matter templates are registered into the T2-weighted/PD space. T1-weighted, T2-weighted, and PD images are segmented into their linguistic variables (dark, medium, bright) using a hidden Markov Random Field Model[38].

A Fuzzy Inference System[39,40] is used for the reasoning stage. The system evaluates each voxel and labels it as WMH or non-WMH depending on the combination of linguistic variables. Finally, thresholding, erosion/dilation, and small cluster removal are applied to remove artifacts. The total WMH volume is 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 with AD had significantly greater WMH volumes than subjects with MCI or controls (Table 1).

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 control, 1=AD) as the dependent variable. The model was re-run with a WMH by PIB positivity interaction term. Next, the analyses was 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 cut-off that best separated the two groups with the highest specificity and sensitivity.

This WMH volume cutoff score was forward applied to the subject with MCI to derive four PIB/WMH groups: PIB negative/low WMH, PIB negative/high WMH, PIB positive/low WMH, and PIB positive/high WMH. Participants in ADNI are re-evaluated every 6 months. We examined differences in the proportion of subjects with MCI who “converted” to AD over the follow-up period with Chi-Squared analysis. To see additionally whether WMH increased risk for future development of AD among MCI patients, we performed a logistic regression analysis, with final diagnosis (0=remained non-demented, 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 non-demented) and age as additional predictors/covariates.

Results

Baseline assessment of participants classified as NC or AD

There were 28 (68%) participants classified as PIB positive, of whom 17 met clinical criteria for AD, and 13 participants classified as PIB negative, of whom 3 met criteria for AD ($\chi^2(1)=5.03$, p=0.025). 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=0.167); however when we examined the relationship between cortical PIB uptake values and total WMH volume among all participants (including MCI), there was a significant negative association between the two (*r*s(100)=-0.203, p=0.042).

Results from the logistic regression model (overall model $\chi^2(3)=16.69$, p=0.001), showed that higher WMH volume (β=0.247, p=0.015) and PIB positivity (β=1.881, p=0.049) were each independently associated with AD diagnosis. Age was not associated with diagnosis (β=−0.022, p=0.559). When the model was re-run with a WMH by PIB positivity interaction term, that variable was not associated significantly with diagnosis (β=0.163, p=0.450).

Restricting the analysis to individuals who were PIB positive only, increased WMH volume was also associated with AD diagnosis (β=0.335, p=0.05; overall model $\chi^2(3)=9.516$, p=0.002). 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 cut at 1.25cm^3 total WMH volume yields a sensitivity and specificity of AD classification of 83% and 64% respectively.

Longitudinal analyses with subjects with MCI

Subjects with MCI were followed for a mean (SD) of 29.73 (12.75) and 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 (37%) of MCI participants converted to AD during the follow-up interval. Those who converted and those who remained non-demented were similar in age at baseline ($F(1,58)=0.010$, p=0.920) and sex distribution ($\chi^2(1)=0.028$, p=0.866). The 59 participants with MCI were divided into the four PIB/WMH groups described above: 7 (11.9%) were in the PIB negative/low WMH group; 11 (18.6%) were in the PIB negative/high WMH group; 17 (28.8%) were in the PIB positive/low WMH group, and 24 (40.7%) were in the PIB positive/high WMH group. These groups did not differ in age ($F(3,58)=1.334$, p=0.273) or sex distribution ($\chi^2(3)=3.87$, p=0.275). When we compared the proportion of MCI patients who converted to AD across these groups, there was a significant linear-by-linear association ($\chi^2(1)=4.679$, p=0.031), such that the proportion of patients who converted increased monotonically across the groups (see Figure 4). Results from the logistic regression analysis (overall model $\chi^2(3)=14.083$, p=0.003 showed that PIB/WMH group (β=0.636, p=0.048) and time interval between baseline and diagnostic visit or last assessment (β=−0.078, p=0.006), but not age (β=−0.025, p=0.557) was associated with future diagnosis of AD.

Comment

When comparing AD patients and controls, we found that the severity of white matter hyperintensities and amyloidosis, in the form of PIB positivity, are independently associated with AD diagnosis. Among individuals with amyloidosis, WMH volume discriminates between those with clinical AD and normal controls 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 beta amyloid deposition as a precipitating pathological feature of the disease[1]. Consideration of findings from both *in vivo* beta 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[9,10,12,13]. These observations suggest that amyloidosis is necessary but not sufficient to cause dementia due to AD. Our findings suggest that WMH contribute to AD presentation in addition to beta amyloid *and* that WMH 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(e.g.,[41–46]). 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[47]. In the context of AD, the severity of WMH has been shown to be related to risk of incidence and course of disease progression[24,26]. However, despite consistent observations of their involvement with AD, WMH are typically thought to reflect rarefaction of white matter secondary to small vessel occlusive disease[48], which is thought to be a pathogenic pathway distinct from AD. The association between WMH and AD has most consistently been reported among community-based studies[24], 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, WMH still emerged as a significant factor in the presentation of the disease, adding even more clinical significance to our observations. The association between WMH and clinical AD among individuals without a significant medical history also suggests that WMH may reflect pathological changes that are not restricted to small vessel cerebrovascular disease. For example, WMH may to some degree point to underlying inflammatory changes or vascular forms of beta amyloid itself[49]. This latter possibility would suggest a mechanistic link between WMH and "primary" AD pathology, but careful clinicopathological correlates studies are needed.

Other authors have reported significant associations between WMH severity and amyloid burden measured in cerebrospinal fluid[50]. 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 the two. Despite the modest relationship between the two, both factors (i.e., 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 pathological 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 (see Figure 4), but it is noteworthy that even among PIB negative MCI participants, having a high burden of WMH was associated with increased risk for AD at follow-up. Future longitudinal analyses with larger samples will be necessary to examine progression of amyloid deposition and WMH and 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. It is therefore not necessarily reflective of the overall population. Participants in ADNI are very carefully and systematically evaluated and excluded if they

have significant vascular disease histories, increasing confidence in observation about the involvement of WMH in AD. Amyloid imaging studies, particularly those that consider other cerebral structural and functional factors are very limited and this study is the first examination to our knowledge of the independent associations of beta amyloid and WMH with AD. These observations are thus preliminary and replication in larger samples would be necessary for verification. Future work is needs to determine the pathological underpinnings of WMH. Regardless of mechanistic associations between WMH 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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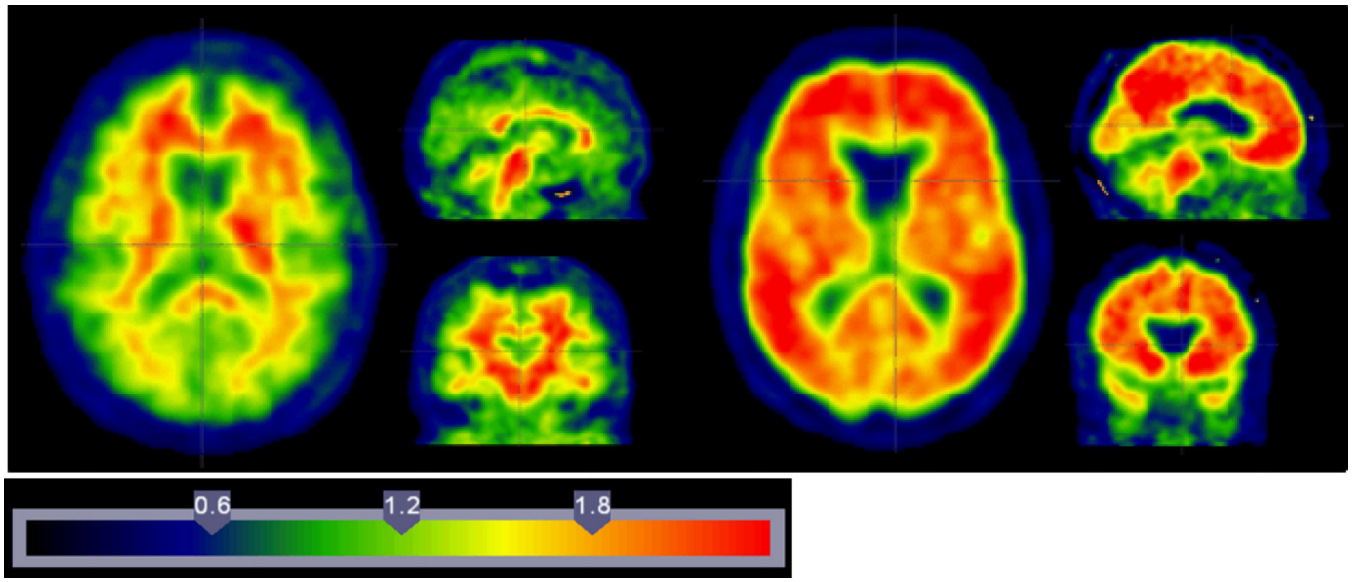

Figure 1.

Left: Example of a PIB negative scan. Right: 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. Color bar displays scale for uptake values.

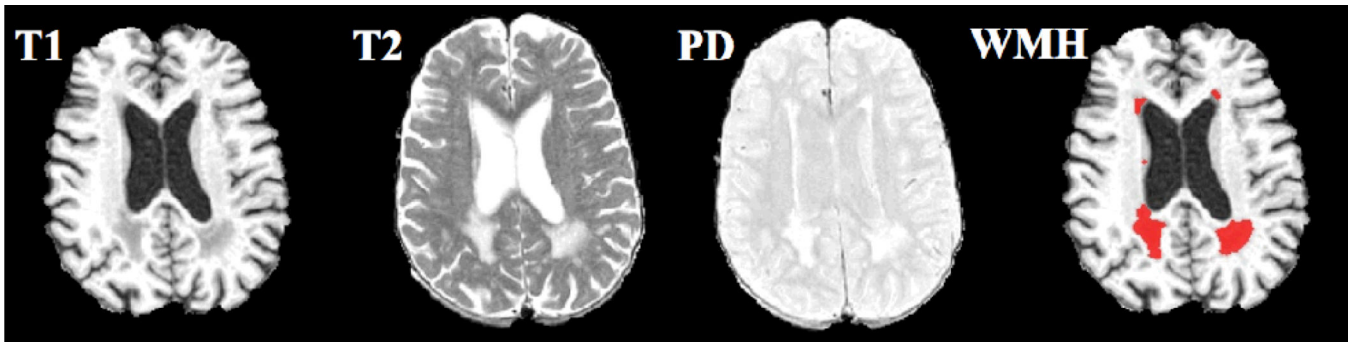

Figure 2.
Example of WMH segmentation on a single ADNI participant.

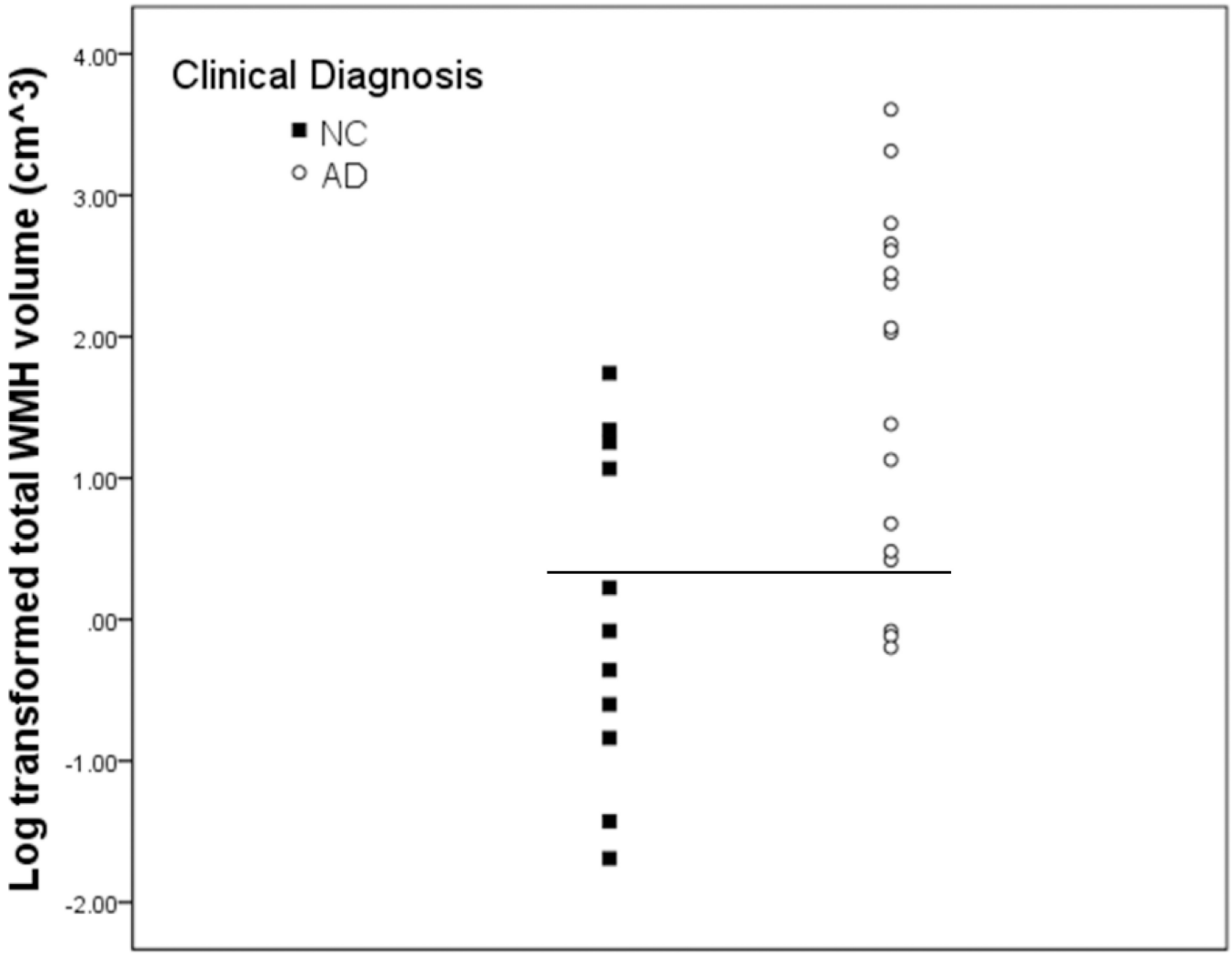

Figure 3.

Distribution of WMH volume among PIB positive participants as a function of clinical diagnosis. For illustration, data are presented in log transformed units. At a cut score of 0.22 log-transformed units (~1.25cm^3 raw units) of WMH volume (solid line), there is 83% sensitivity and 64% specificity for diagnostic classification.

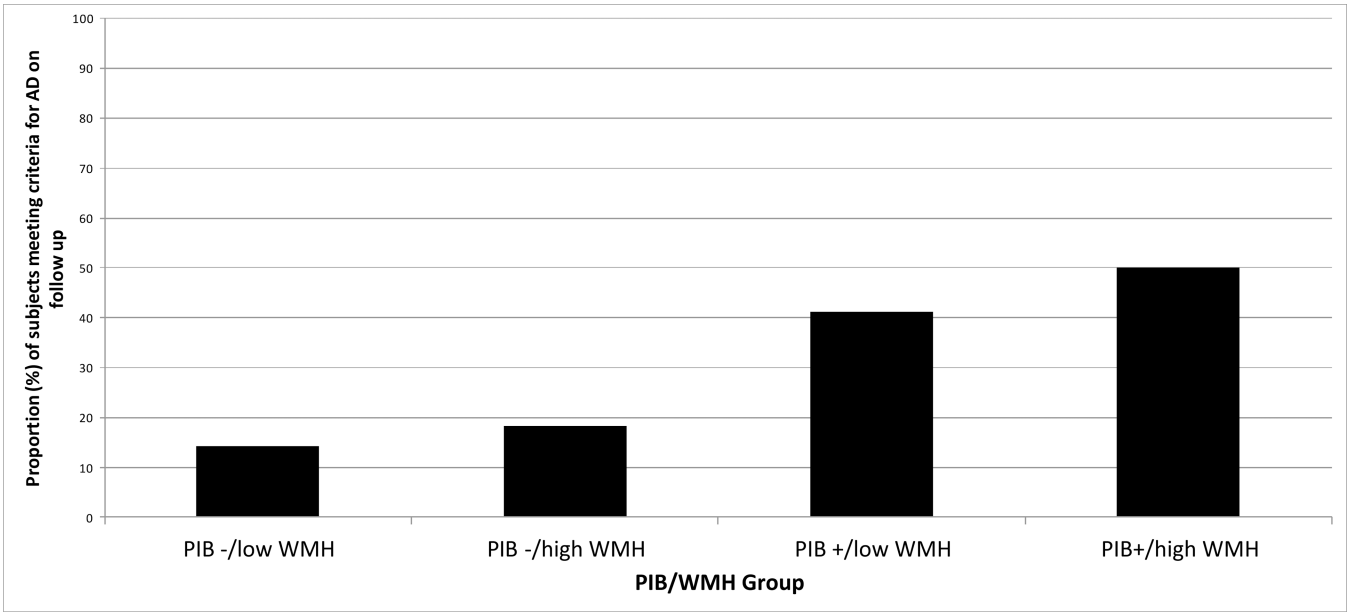

Figure 4.

Proportion of MCI subjects who converted to AD over the follow-up period as a function of the PIB/WMH group.

Table 1

	NC	MCI	AD	STATISTIC
N	21	59	20	
Age (mean ± SD years)	76.2 ± 5.97	75.72 ± 7.86	73.00 ± 8.55	F=1,90, p=0.309
% Women	38	31	40	χ^2=0.798, p=0.671
MMSE (mean ± SD)	28.71 ± 1.35	27.22 ± 1.95	21.20 ± 4.28	F=55.87, p<0.001, NC > MCI > AD
Modified Hachinski (mean ± SD)	0.67 ± 0.80	0.67 ± 0.66	0.70 ± 0.57	F=0.020, p=0.980
Percentage of PIB+ individuals	52%	70%	85%	X^2=5.09, p=0.024 (linear)
Cortical PIB uptake values (mean ± SD)	1.59 ± 0.36	1.81 ± 0.411	1.82 ± 0.35	F=2.87, p=0.061
Total WMH volume (mean ± SD cm^3)	2.26 ± 2.80	4.07 ± 5.78	9.34 ± 9.84	F(2, 98)=7.158, p=0.001, (NC = MCI)<AD