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Reconsidering harbingers of dementia: progression of parietal lobe white matter hyperintensities predicts Alzheimer's disease incidence

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ABSTRACT

Accumulating evidence implicates small vessel cerebrovascular disease, visualized as white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging, in the pathogenesis and diagnosis of Alzheimer's disease (AD). Cross-sectional volumetric measures of WMH, particularly in the parietal lobes, are associated with increased risk of AD. In the present study, we sought to determine whether the longitudinal regional progression of WMH predicts incident AD above-and-beyond traditional radiological markers of neurodegeneration (i.e., hippocampal atrophy and cortical thickness). Three hundred three nondemented older adults (mean age = 79.24 ± 5.29) received high-resolution magnetic resonance imaging at baseline and then again 4.6 years (standard deviation = 1.01) later. Over the follow-up interval 26 participants progressed to AD. Using structural equation modeling, we calculated latent difference scores of parietal and nonparietal WMH, hippocampus volumes, and cortical thickness values in AD-related regions. Within the structural equation modeling framework, we determined whether baseline or change scores or both predicted AD conversion, while controlling for several time-invariant relevant variables. Smaller baseline hippocampus volume, change in hippocampus volume (i.e., atrophy), higher baseline parietal lobe WMH, and increasing parietal lobe WMH volume but not WMH in other regions or measures of cortical thickness, independently predicted progression to AD. The findings provide strong evidence that regionally accumulating WMH predict AD onset in addition to hallmark neurodegenerative changes typically associated with AD.

1. Introduction

Alzheimer's disease (AD) is one of the most pernicious public health issues affecting older adults. There are currently no effective interventions that prevent the disease or fundamentally alter its clinical course. Alzheimer's disease has been described and defined historically as a mixed-pathologic condition, comprising intercellular accumulation of fibrillar forms of the beta-amyloid protein and intracellular deposition of neurofibrillary tangles (Rothschild, 1934). Recent evidence, however, implicates small vessel cerebrovascular disease as an additional important feature of the disease, contributing at least additively, but possibly in a synergistic or primary manner, to disease pathogenesis (Brickman, 2013; Brickman et al., 2009).

In addition to microhemorrhages and lacunar infarcts, small vessel cerebrovascular disease is best visualized as increased signal or white matter hyperintensities (WMH) on T2-weighted magnetic resonance imaging (MRI). White matter hyperintensity volume is associated with risk of AD, the diagnosis of AD, and rate of cognitive decline among individuals with AD (Brickman et al., 2008a, 2012; Luchsinger et al., 2009; Meier et al., 2012; Provenzano et al., 2013). The regional distribution of WMH is also important, in terms of

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clinical outcome. In our previous work, increased parietal lobe distribution of WMH was specifically associated with risk of AD (Brickman et al., 2012), whereas more anterior distribution appeared to be nonspecific and associated with mortality (Wiegman et al., 2013). To examine the causal impact of regionally-distributed cerebrovascular disease and its specificity, we determined whether longitudinal progression of parietal lobe WMH predicts incident AD in addition to hippocampal atrophy and cortical thickness, measures of AD-related neurodegeneration (Whitwell et al., 2008), in a large cohort of community-dwelling older adults. We hypothesized that both markers of AD-related neurodegeneration and progression of WMH in the parietal lobes would predict incident AD.

2. Methods

2.1. Participants

Participants came from the Washington Heights Inwood Columbia Aging Project, an ongoing longitudinal study of cognitive aging and dementia. Participants were initially recruited at 2 time points, in 1992 and 1999 (Tang et al., 2001) and are evaluated approximately every 24 months. Beginning in 2004, active participants (n = 2776) who were nondemented at their preceding visit were invited to participate in an MRI study (Brickman et al., 2008b). Seven hundred sixty-nine participants underwent MRI scanning. They were about 1 year older, more likely to be women, and more likely to be African American than the 407 study members who were eligible for MRI scanning but refused participation (Brickman et al., 2008b). Approximately 4.5 years following their initial scan, individuals who were nondemented at the time of their first MRI scan (n = 717) were invited to return for a second MRI scan; 303 participants had available baseline and follow-up MRI data (see Table 1 for baseline characteristics). Individuals with follow-up MRI data were younger at baseline (79.27 ± 5.29 vs. 80.64 ± 5.66, $t(715) = 3.29$, $p = 0.001$) but were similar in terms of sex ($\chi^2(1) = 0.778$, $p = 0.378$) and race/ethnicity ($\chi^2(3) = 5.94$, $p = 0.115$) distributions, than individuals for whom a second MRI scan was not conducted. The study was approved by our Institutional Review Board, and all participants gave written informed consent.

2.2. Diagnostic procedures

Participants underwent in-person evaluation at each follow-up visit, including full medical and neurologic examination and neuropsychological testing in English or Spanish. The neuropsychological battery included measures of memory, orientation, language, abstract reasoning, and visuospatial functioning (Stern et al., 1992), which measured equivalent traits across the 2 language groups represented in the study population (Siedlecki et al., 2010). The diagnosis of dementia was established via review of all available clinical information (not including radiological data), medical evaluation and was based on standard research criteria (American Psychiatric Association, 1987). Following each clinical evaluation, a consensus conference, including at least 1 physician and 1 neuropsychologist, reviewed available data to assign a research diagnosis. First, a diagnosis of dementia was made (American Psychiatric Association, 1987) and then the etiology was determined based on research criteria for probable or possible AD (McKhann et al., 1984), Lewy body dementia (McKeith et al., 1999), vascular dementia (Roman et al., 1993), and other dementias. In the case of vascular dementia, history of stroke, and its contribution to the dementia syndrome was determined via medical history and evaluation. History of heart disease, clinical stroke, hypertension, and diabetes was ascertained by self-report, supplemented by physical examination. These 4 dichotomous variables were summed to create a single vascular risk summary score (Brickman et al., 2008b).

Table 1
Sample characteristics

	Total sample (N = 303)	pAD patients (N = 26)	Nondemented individuals (N = 261)
Age, mean y (SD)	79.24 (5.29)	81.88 (5.74)[a]	79.00 (5.14)
Sex, % female	69.0	84.6	67.4
Race and/or ethnicity			
Black, %	37.3	26.9	38.3
Hispanic, %	33.0	61.5[a]	29.1
White, %	29.7	11.6	32.6
Education, mean y (SD)	11.14 (4.83)	8.65 (5.18)[a]	11.69 (4.57)
Recruitment year			
1992, %	18.5	15.4	18.4
1999, %	81.5	84.6	81.6
Years between scans, mean (SD)	4.61 (1.01)	4.46 (0.76)	4.63 (1.03)
Years in follow-up, mean (SD)	5.53 (1.66)	5.85 (0.96)	5.48 (1.71)
ICV, mean cm^3 (SD)	1305.11 (154.67)	1276.97 (138.72)	1309.81 (154.98)
APOE e4 allele			
Yes, %	26.8	34.6	25.3
No, %	73.2	65.4	74.7
Vascular risk summary score, mean (SD) number of items endorsed	1.15 (0.88)	1.04 (0.77)	1.16 (0.89)
WMH volume, mean cm^3 (SD)			
Frontal	3.83 (5.87)	4.08 (6.98)	3.81 (5.76)
Temporal	0.38 (0.56)	0.42 (0.08)	0.38 (0.58)
Parietal	2.69 (3.90)	3.67 (4.71)	2.60 (3.82)
Occipital	0.80 (0.90)	1.01 (0.98)	0.77 (0.90)

Total sample also includes individuals who progressed to a dementia other than probable AD (N = 16).
Key: pAD, probable Alzheimer's disease; ICV, intracranial volume; SD, standard deviation.
[a] Significant difference between pAD patients and those who remained nondemented ($p < 0.05$).

Participants were classified as incident AD versus those who remained nondemented throughout the follow-up, based on whether they met diagnostic criteria for probable AD at any point following the initial MRI scan, over a 5.5-year follow-up period. Descriptive statistics for the 2 groups are displayed in Table 1. Cases were older, more likely to be Hispanic, and had lower educational levels than those who remained nondemented but were similar in terms of sex, year of recruitment, time interval between MRI scans, number of years of follow-up after the initial MRI scan, total cranial volume, and APOE-ε4 allele status.

2.3. MRI protocol

MRI scan acquisition took place on the same 1.5 T Philips Intera scanner at the 2 time points, using the identical acquisition sequences (Brickman et al., 2008b). T1-weighted (repetition time = 20 ms, echo time = 2.1 ms, field of view 240 cm, 256 × 160 matrix, 1.3 mm slice thickness) and T2-weighted fluid attenuated inversion recovery (FLAIR; repetition time = 11,000 ms, echo time = 144.0 ms, inversion time = 2800, field of view 25 cm, 2 nex, 256 × 192 matrix with 3 mm slice thickness) images were acquired in the axial orientation. Regional WMH volumes were derived as described previously (Brickman et al., 2009, 2011, 2012). Briefly, FLAIR images were skull stripped and a Gaussian curve was fit to map the voxel intensity values. Voxels falling above 2.0 standard deviation of the image mean were labeled as WMH. Labeled images were inspected visually and corrected in the case of labeling commission or omission errors. To derive WMH volumes in the frontal,