Trajectory of white matter hyperintensity burden preceding mild cognitive impairment

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ABSTRACT

Objective: To determine the time of acceleration in white matter hyperintensity (WMH) burden, a common indicator of cerebrovascular pathology, in relation to conversion to mild cognitive impairment (MCI) in the elderly.

Methods: A total of 181 cognitively intact elderly volunteers from the longitudinal, prospective, Oregon Brain Aging Study underwent yearly evaluations, including brain MRI, and cognitive testing. MRIs were analyzed for imaging markers of neurodegeneration: WMH and ventricular CSF (vCSF) volumes. The time before MCI, when the changes in WMH and vCSF burden accelerate, was assessed using a mixed-effects model with a change point for subjects who developed MCI during follow-up.

Results: During a follow-up duration of up to 19.6 years, 134 subjects converted to MCI. Acceleration in %WMH volume increase occurred 10.6 years before MCI onset. On average, the annual rate of change in %WMH increased an additional 3.3% after the change point. Acceleration in %vCSF volume increase occurred 3.7 years before the onset of MCI. Out of 63 subjects who converted to MCI and had autopsy, only 28.5% had Alzheimer disease (AD) as the sole etiology of their dementia, while almost just as many (24%) had both AD and significant ischemic cerebrovascular disease present.

Conclusions: Acceleration in WMH burden, a common indicator of cerebrovascular disease in the elderly, is a pathologic change that emerges early in the presymptomatic phase leading to MCI. Longitudinal changes in WMH may thus be useful in determining those at risk for cognitive impairment and for planning strategies for introducing disease-modifying therapies prior to dementia onset. *Neurology*® 2012;79:741-747

GLOSSARY

AD = Alzheimer disease; **CDR** = Clinical Dementia Rating; **CI** = confidence interval; **FLAIR** = fluid-attenuated inversion recovery; **HTN** = hypertension; **ICV** = intracranial volume; **LBD** = Lewy body disease; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **OBAS** = Oregon Brain Aging Study; **TE** = echo time; **TR** = repetition time; **VaD** = vascular dementia; **vCSF** = ventricular CSF; **WMH** = white matter hyperintensity.

Changes within the cerebral white matter, observed as hyperintensities (white matter hyperintensity [WMH]) on T2 and fluid-attenuated inversion recovery (FLAIR) brain MRI sequences, are extremely common in elderly individuals,¹⁻³ and are associated with ischemic cerebrovascular disease and loss of vascular integrity on neuropathologic examination.^{4,5} In cross-sectional studies, WMH lesions have been associated with poorer performance in multiple areas of cognition, including executive function, processing speed, memory, global cognition,⁶⁻⁸ and increased risk of mild cognitive impairment (MCI).⁹⁻¹¹ Increased accumulation of WMH volume over time has been shown to be greatest in those with higher baseline burden,¹¹⁻¹³ and is associated with cognitive decline^{3,12,14,15} and increased risk of dementia.¹⁶⁻¹⁸ Greater rates of WMH progression have been shown to be associated with the development of MCI, a poten-

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tial precursor of progressive dementia, and is a better predictor of cognitive impairment risk than baseline WMH burden.¹¹ Ventricular enlargement, another common MRI finding in older individuals, has been associated with cognitive decline, cerebrovascular disease, and dementia,^{19–21} and may partially be a reflection of brain atrophy or total white matter degeneration. Despite the evidence implicating white matter degeneration in hastening cognitive decline, the timing of the acceleration of known MRI markers of white matter degeneration, such as WMH change, relative to the transition to MCI has not been established. The objective of this study was to determine the timing of acceleration of WMH burden, a likely marker of cerebrovascular pathology, in relation to the emergence of cognitive impairment in the elderly. In addition, we aimed to compare the timing of WMH acceleration with that of ventricular CSF (vCSF) volume expansion, a likely marker of brain or total white matter degeneration, and hippocampal volume decline, a marker of neurodegenerative disease, in a population of well-characterized elderly.

METHODS Subjects. The Oregon Brain Aging Study (OBAS) was initiated in 1989 at the National Institute on Aging's Layton Oregon Aging and Alzheimer's Disease Center consisting of community-dwelling, functionally independent elderly subjects.²² Between 1989 and 2005, 376 subjects were evaluated, and 305 subjects met inclusion criteria and were enrolled. A total of 293 of the 305 subjects were 65 years of age or older, and were included in this study. Initial entry criteria required subjects to be free of most comorbid illnesses. In order to include subjects who were more representative of the general population, entry criteria were modified in 2004 to include subjects with well-controlled, chronic medical conditions common with advanced age, such as hypertension and coronary artery disease. Attrition rates caused by loss to follow-up other than death were less than 1% per year. OBAS entry inclusion criteria included a score of 24 or greater on the Mini-Mental State Examination (MMSE)²³ and 0 on the Clinical Dementia Rating Scale (CDR).²⁴ Volunteers were solicited from retirement homes, senior citizens' organizations, and public relation activities. Those who had sought or planned to seek medical attention for memory problems were not enrolled. Each CDR was based on interviews with the participant and someone familiar with the participant who served as a collateral source as well as examination by a neurologist. A total of 181 subjects had *APOE* allele testing, detailed annual cognitive and neurologic assessments, and a brain MRI analyzed for WMH, hippocampal, and vCSF volumes.

Annual evaluations were performed by trained neurologists and geriatric nurse practitioners and included a medical history,

mental status examination, CDR score determination, and standardized neurologic examination. Semiannual evaluations that included CDR determination was also conducted. MCI was defined as being the first of 2 consecutive semiannual CDR scores of 0.5 or higher. Changes in subjects' general medical conditions were obtained yearly through patient report, and from 1996 on from a modified cumulative illness rating scale²⁵ administered yearly. Information regarding subjects' stroke risk factors at enrollment was obtained from a detailed medical history form. The clinical diagnosis of Alzheimer disease (AD), Lewy body disease (LBD), and vascular dementia (VaD) were based on National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association, McKeith, and California criteria, respectively.^{26–28} A subset of subjects ($n = 63$) had brain autopsy at the time of their death. Neuropathologic diagnosis of AD and VaD followed published criteria.^{28–31}

Standard protocol approvals, registration, and patient consents. All subjects signed written informed consent according to the policies of the Institutional Review Board of Oregon Health & Science University who approved the use of human subjects for this study.

MRI acquisition. The general procedures have been described previously.³² Briefly, MRI scans were performed with a 1.5 Tesla magnet. The protocol consists of slice thickness of 4 mm (no gap), 24 cm field of view with a 256×256 matrix (0.86 mm $\times$ 0.86 mm pixel size) and 0.5 repetitions per sequence. The brain was visualized in 2 planes using the following pulse sequences: 1) T1-weighted sagittal images centered in the midsagittal plane with the pituitary profile (including the infundibulum) and cerebellar vermis clearly delineated: repetition time (TR) = 600 msec, echo time (TE) = 20 msec images; 2) multiecho sequence T2-weighted (TR = 2,800 msec, TE = 80 msec) and proton density (TR = 2,800 msec, TE = 32 msec) coronal images perpendicular to the sagittal plane.

Image analysis. Image analysts evaluated each scan independently and were blind to subjects' cognitive or neurologic testing, demographic characteristics, and results from previous imaging. Image analysis software REGION is used to quantitatively assess regional brain volumes of interest.^{32,33} Briefly, recursive regression analysis of bifeature space based on relative tissue intensities was employed to separate tissue types on each coronal image. Pixel areas were summed for all slices and converted to volumetric measures by multiplying by the slice thickness for each of the following regions of interest: total WMH, vCSF, and hippocampal volumes. Intracranial volume was determined by automatically regressing for brain tissue, CSF, and WMH collectively against bone, creating a boundary along the inner table of the skull. Additional boundaries were manually traced along the tentorium cerebelli and the superior border of the superior colliculus, the pons, and the fourth ventricle. The pituitary, vessels in the sphenoidal area, and any sinuses that may have been included by the automatic regression were also manually excluded. Hippocampal bodies were determined by manually outlining the structures with a cursor directly on the computer display, as previously described.³³ Median number of MRIs per participant was 4 assessments. The intraclass correlation coefficient as a measure of reliability of volume determination was ≥ 0.95 for all regions except for WMH volume, which was 0.85.

Quantification of WMH using REGION. Using REGION's sampling tools, the analyst selects representative, unambiguous pixels of WMH (as well as brain tissue, fluid, and bone) from the

multiecho sequence display. A regression model including the proton density and T2 intensities and location of each pixel differentiates tissue types. WMH is distinguished from brain tissue and fluid based on higher signal on both the proton density and T2 images.

Statistical analysis. t Tests for continuous variables, Pearson χ^2 , or Fisher exact tests for categorical variables, if appropriate, were used to determine differences in demographic, clinical, and MRI characteristics at baseline between those who converted to MCI and those who did not. Time before MCI when the change in WMH and vCSF volumes accelerates was assessed using a mixed-effects model with a change point³⁴ for subjects who developed MCI during the follow-up period. The location of the change point relative to the timing of MCI conversion was estimated by maximum likelihood using the SAS procedure NLMIXED (SAS Institute, Cary, NC). The inclusion of a change point in the mixed-effects model allows the rates of change to differ before and after the change point. The point of change in the coefficients is relative to the timing of MCI onset, as opposed to age. Each individual could have different age slopes (random effects), but the model assumes that the timing of the change point relative to MCI onset is common across all subjects. All 134 subjects who converted to MCI during the follow-up were included in the change point analyses using all available information in the framework of a mixed-effects model. Separate mixed-effects models were fit with the change point at fixed 1-month intervals up to 15 years before MCI conversion. The model with the highest likelihood was used to summarize the results. We tested whether there was acceleration in the rate of change in outcomes relative to MCI conversion by calculating a 95% confidence interval (CI) around the parameter on the change point term, using a likelihood ratio approach.³⁴ The significance of the other terms in the mixed-effects model was determined using a Wald test statistic.³⁵ Standard errors for the parameter estimates were calculated using the conditional variance as proposed previously.³⁴ WMH and vCSF were log (base e) transformed to address the skewed distributions. Analyses were adjusted for variables that have frequently been associated with increased dementia risk. These included age, gender, *APOE* $\epsilon 4$ allele (having at least one $\epsilon 4$ allele vs none), baseline hippocampal volume (for outcomes of WMH and vCSF), and the presence vs absence of the following cerebrovascular risk factors: history of stroke/TIA, hypertension (HTN), diabetes, and smoking. Cerebrovascular risk factors were coded as being present if they existed either prior to entry into the study or if they occurred at any time point during follow-up. In order to adjust for baseline differences in head size, analyses were also adjusted for intracranial volume. The higher order term of time (age) was included if the inclusion improved the model fitness indicated by the Bayesian Information Criteria. Age was centered at 80 to reduce correlations among the higher order terms. Statistical significance was taken as $p = 0.05$.

RESULTS A total of 184 OBAS participants had at least 1 MRI assessment during the follow-up. Among them, 3 subjects were excluded from the current analysis because their WMH value was at or greater than 5 standard deviations from the mean WMH volume based on the entire distribution of WMH among the OBAS participants. No outlier was identified for vCSF volume. The remaining 181 subjects were used in the analysis.

During a follow-up duration of up to 19.6 years, 134 subjects out of 181 converted to MCI, with an average age at conversion being 89.9 years. Mean duration of follow-up and subject characteristics in converters and nonconverters are presented in table 1. On average, subjects who converted to MCI during the follow-up period were older at baseline, and were followed for a longer period of time. More nonconverters had a history of smoking and HTN than converters. A total of 114 of the 189 MCI subjects died during the study follow-up. MCI subjects who died during follow-up were significantly older at entry and at last follow-up. After adjusting for age, there was no significant difference in baseline WMH or vCSF volumes ($p > 0.05$, multivariate regressions). There was no significant difference in mortality between converters and nonconverters with HTN (Fisher exact test, $p = 0.27$).

Change point models were run using the MCI converters ($n = 134$) (table 2). We used natural log transformed (base e) WMH and vCSF as outcomes due to their skewed distributions. The following mixed-effects models with change points were each controlled for baseline intracranial volume (ICV), hippocampal volume (for nonhippocampal outcomes), *APOE* $\epsilon 4$ allele status, and the presence of the following cerebrovascular risk factors: history of stroke/TIA, HTN, diabetes, and smoking. Power of age effect was also included since it was found significant.

Change point analysis for WMH volume. Acceleration in WMH volume increase occurred 10.6 years (95% CI 5.16–unknown) before the onset of MCI. Before that change point, WMH increased by 6.5% of the previous value annually ($e^{0.0628} = 1.065$) ($p < 0.0001$), but after the change point, WMH increased by additional 3.3% of the previous value annually ($e^{0.0323} = 1.033$) ($p = 0.04$) (figure).

Change point analysis for vCSF volume. Acceleration in vCSF volume expansion occurred 3.66 years (95% CI 0.75–5.58) before the onset of MCI. Before that change point, vCSF increased by 4.1% annually ($e^{0.0408} = 1.041$) ($p < 0.0001$), but after the change point, this increase accelerated by an additional 0.8% annually ($e^{0.008} = 1.008$) ($p = 0.01$).

Change point analysis for hippocampal volume. Hippocampal volumes were normally distributed, and were therefore not log transformed. The change point model for hippocampal volume did not converge ($p > 0.05$).

Clinical and pathologic diagnosis of MCI converters. A total of 58 of the 134 MCI converters eventually transitioned to dementia. Of those 58 subjects, the most common dementia diagnosis obtained during the most recent clinical evaluation was probable or

Table 1 Subject characteristics

	Converters (n = 134), mean (SD); range	Nonconverters (n = 47), mean (SD); range	p Value ^a
Age at entry, y	84.8 (5.9); 65.8-102.9	82.10 (8.1); 65.2-97.4	<0.037
Mean follow-up, y	10.1 (4.1); 0.5-19.6	6.9 (4.4); 0.8-18.6	<0.001
Median no. MRI assessments	4.0; 1-15	2.0; 1-10	<0.001
Education, y	14.2 (2.7); 8-20	14.2 (2.4); 7-19	0.96
% Female	61.2	70.2	0.26
% APOE ε4+	20.9	12.8	0.22
% Ever smoked	25.4	44.7	0.01
% Diabetes	4.3	3.7	0.87 ^b
% Stroke or TIA	17.9	21.3	0.61
% Hypertension during follow-up	60.5	95.7	<0.001
% Hypertension at baseline	27.0	11.0	0.68
% Baseline WMH volume [(cc WMH/cc ICV) × 100]	0.89 (0.89); 0-4.10	0.76 (1.11); 0-5.17	0.43
% Baseline vCSF volume [(cc vCSF/cc ICV) × 100]	3.82 (1.59); 1.12-9.22	3.73(1.85); 1.15-10.76	0.42
% Baseline hippocampal volume [(cc vCSF/cc ICV) × 100]	0.111 (0.019); 0.046-0.155	0.116 (0.017); 0.084-0.152	0.11

Abbreviations: ICV = intracranial volume; vCSF = ventricular CSF; WMH = white matter hyperintensity.

^a Based on Wilcoxon rank sum test for continuous variables and Pearson χ^2 test for categorical variables unless specified otherwise.

^b Fisher exact test.

possible AD (44/58), followed by VaD or mixed AD/VaD (11/58). Out of 90 converters who died during the follow-up period, brain autopsy evaluations were available for 70% (63/90) of those subjects. There was no difference in age, sex, education, *APOE4* status, baseline MMSE, or duration of follow-up between those with and without brain autopsy. Of those with pathology available, 63% (40/

63) met neuropathologic criteria for AD following published criteria.³⁰ Of those subjects, only 45% (18/40) had AD pathology as the sole etiology of their dementia, with almost just as many subjects (15/40) having a significant amount of coexisting vascular pathology, characterized by discrete medium or large vessel strokes, multiple lacunes, or a high number of microinfarcts observed in hematoxylin-eosin sections of neocortex, basal ganglia, and thalamus³¹ (tables 3 and 4).

Table 2 Results of change point mixed-effects model analysis^a

MRI characteristic	MCI converters (n = 134), (SE) p value
White matter hyperintensities	
Annual change in log transformed (base e) WMH	0.062 (0.015) <0.000
Rate of annual change before change point	6.5% ($e^{0.0628} = 1.065$)
Additional change in log transformed (base e) WMH	0.032 (0.016) 0.04
Additional rate of annual change after change point	3.3% ($e^{0.0323} = 1.033$)
Change point in relation to MCI diagnosis, y	10.58 (95% CI 5.16-unknown ^b)
Ventricular CSF volume	
Annual change in log transformed (base e) WMH	0.0408 (0.002) <0.0001
Rate of annual change before change point	4.1% ($e^{0.0408} = 1.041$)
Additional change in log transformed (base e) WMH	0.008 (0.003) <0.01
Additional rate of annual change after change point	0.8% ($e^{0.008} = 1.008$)
Change point in relation to MCI diagnosis, y	3.66 (95% CI 0.75-5.58)

Abbreviations: CI = confidence interval; ICV = intracranial volume; MCI = mild cognitive impairment; WMH = white matter hyperintensity.

^a All models are controlling for baseline ICV, baseline hippocampal volumes, *APOE4* status, and cerebrovascular risk factors.

^b Unknown based on available information owing to left censoring.

DISCUSSION WMH acceleration, a probable representation of underlying cerebrovascular pathology, has been shown previously to result in progressive cognitive decline³ that eventually reaches a threshold of MCI.¹¹ Results from this study show that WMH burden acceleration predates the onset of MCI by many years, and occurs prior to changes in the acceleration of vCSF volume. The mean time before MCI conversion in which there was acceleration of WMH increase was 10.6 years. The upper limit of the CI could not be observed in our current data possibly because the maximum follow-up duration observed before MCI conversion was too short to observe the upper limit in the change point (i.e., left censoring).

The pathologic correlates of WMH change are variable, and include demyelination, axonal loss, dilated perivascular spaces, and spongiosis.³⁶ There is a general consensus that much of the MRI white matter change is derived from ischemia occurring sec-

Figure Median WMH volume trajectory over time, using the results of the change point models and assuming MCI onset would occur at age 90 (mean age of MCI onset among our study cohort)

CI = confidence interval; MCI = mild cognitive impairment; WMH = white matter hyperintensity.

ondary to disease of the arteriole supplying the white matter⁴ and as a result of a loss of vascular integrity resulting in disruption of the blood–brain barrier.⁵ The clinical diagnosis of probable AD was applied to this cohort using rigorous standardized diagnostic criteria in an academic setting, and the clinical diagnosis of probable AD was the most common dementia diagnosis given. Pathologically, however, there were almost as many subjects with vascular pathology coincident with AD lesions as there were with subjects who had AD pathology as their sole cause of dementia. This type of finding has been observed in other longitudinal aging studies in which pathologic examination of the cohort was obtained,³⁷ indicating a likely pivotal and under-recognized role of cerebro-

vascular disease in the subsequent clinical manifestation of Alzheimer dementia.

Age-related decreases in vascular density, with increased arteriolar tortuosity and venous collagenosis resulting in loss of deep white matter cerebral blood flow, independent of arteriosclerotic changes, have been described. Others report a nonvascular etiology, such as breakdown of the ependyma or age-related myelin loss, to smooth or regular periventricular WMH capping. It is possible that age-related white matter integrity disruption, independent of or in concert with small vessel ischemic disease, results in a decreased threshold of susceptibility to the detrimental effects of β -amyloid deposits and other classic AD-associated pathologies.

Alternatively, the acceleration in WMH burden 10.6 years prior to MCI conversion may represent axonal degeneration secondary to concurrent cortical β -amyloid deposition. This rationale is supported by prior studies estimating a temporal lag of approximately 10 years between the deposition of $A\beta$ and the clinical syndrome of AD.³⁸ Previous studies examining regional effects of WMH change have shown greater posterior periventricular and corpus callosum splenium WMH burden in subjects with AD compared with controls.³⁹ This, along with other studies showing decreased structural integrity of white matter in those with AD that was not explained by the presence of vascular risk factors,⁴⁰ suggest that neurodegeneration is likely to contribute to the etiology of WMH change in the elderly. Ventricular volume change was seen closer to the onset of cognitive change, and thus may be reflective of more clinically relevant neuronal loss. We did not find acceleration in hippocampal volume loss prior to MCI conversion in this study. It is possible that hippocampal atrophy occurs in a more constant rate over time, or that the implementation of other methods of measurement (i.e., including medial temporal lobe structures) may confer increased sensitivity to changes in regional brain volumes known to be affected early in AD.

There were a larger percentage of subjects with a history of hypertension in nonconverters, which may be explained by underdiagnoses (and subsequent under treatment) of HTN in the MCI group. Alternatively, HTN in older age may be protective against decreased cerebral perfusion and related cognitive decline. Our population was a volunteer cohort that was relatively healthy; generalization requires confirmation in other populations. However, the data provided from this very old population are among the few addressing this pathology in this age group, making it highly relevant to the increasing large number of those of advanced age in the current population of elderly.

Table 3 Pathologic diagnosis of converters

	Percent of subjects (n = 63)
AD	28.5
Mixed AD/vascular disease	24.0
Alzheimer pathology	16.0
VaD	11.0
Mixed Alzheimer/Lewy body disease	5.0
Mixed hippocampal sclerosis + AD, VaD, or both	5.0
LBD	3.0
Hippocampal sclerosis	3.0
Mixed AD/LBD/VaD	1.5
LBD/VaD	1.5
Vascular pathology	1.5

Abbreviations: AD = Alzheimer disease; LBD = Lewy body dementia; VaD = vascular dementia.

Table 4 Alzheimer and vascular pathology among AD and VaD pathologic diagnostic groups

Pathologic diagnosis	No.	Braak stage, mean (SD)	Subcortical microvascular lesions, mean (SD)	Atherosclerosis, mean (SD)
AD	18	4.67 ^a (1.14)	0.41 (0.62)	1.53 (0.80)
Mixed AD/vascular disease	15	4.63 ^a (1.15)	2.33 ^b (1.18)	2.28 ^b (0.93)
Alzheimer pathology	10	2.60 (1.17)	0.60 (0.84)	1.30 (0.67)
VaD	7	3.17 (1.35)	2.14 ^b (1/21)	1.57 (0.53)
Overall group comparisons ^c		$p = 0.0006$	$p = 0.0001$	$p = 0.02$

Abbreviations: AD = Alzheimer disease; VaD = vascular dementia.

^a Wilcoxon-Mann-Whitney pairwise comparison tests: significantly greater than Alzheimer pathology and VaD.

^b Wilcoxon-Mann-Whitney pairwise comparison tests: significantly greater than AD and Alzheimer pathology ($p < 0.05$).

^c Using Kruskal-Wallis test.

Acceleration of WMH burden, a common indicator of small vessel ischemic disease in the elderly and possible reflection of early cortical A β deposition, is a pathologic change that emerges early in the presymptomatic phase leading to MCI. WMH acceleration may directly result in cognitive decline years later, or increase susceptibility to the detrimental effects of underlying Alzheimer pathology. Tracking longitudinal changes in WMH may be useful in determining those at different levels of risk for cognitive impairment and for planning strategies for introducing disease-modifying therapies prior to dementia onset.

AUTHOR CONTRIBUTIONS

Dr. Silbert is the primary author. Dr. Dodge performed the data analysis for this manuscript and made a substantive contribution in revising the manuscript for intellectual content. Mr. Perkins, Ms. Sherbakov, and Mr. Lhana assisted in the design and conceptualization of the study. In addition, they made a substantive contribution in revising the manuscript for intellectual content. Dr. Erten-Lyons made a substantive contribution in revising the manuscript for intellectual content. Dr. Woltjer performed neuropathological assessment of subjects, and made a substantive contribution in revising the manuscript for intellectual content. Dr. Shinto made a substantive contribution in revising the manuscript for intellectual content. Dr. Kaye assisted in the design and conceptualization of the study. In addition, he made a substantive contribution in revising the manuscript for intellectual content. Drs. Dodge and Silbert conducted the statistical analyses for this study.

DISCLOSURE

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