Cognitive impairment risk

White matter hyperintensity progression matters

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ABSTRACT

Objective: To determine whether white matter hyperintensity (WMH) progression rate is a better predictor of cognitive impairment risk than baseline WMH volume in healthy elderly individuals.

Method: Ninety-eight cognitively intact elderly subjects were followed in the Oregon Brain Aging Study. Forty-nine had at least 3 brain MRIs and annual cognitive and neurologic assessments until diagnosed with persistent cognitive impairment (PCI). Brain, ventricular CSF (vCSF), intracranial volume (ICV), hippocampus, total WMH, periventricular (PV) WMH, and subcortical WMH volumes were measured. Cox proportional hazards survival analyses were used to assess cognitive impairment risk.

Results: After adjusting for age, apolipoprotein E4 status, incident hypertension, ICV, entry Mini-Mental State Examination, baseline hippocampus, and both baseline vCSF volume and rate of vCSF volume change, increased progression of total WMH volume (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.3–2.7, $p = 0.0007$) and PV WMH volume (HR 1.94, 95% CI 1.3–3.1, $p = 0.001$) conferred higher risk of PCI, whereas baseline WMH volumes did not. Every 1 mL/y increase in PV WMH volume was associated with a 94% increased risk of PCI.

Conclusion: Progression of total and periventricular (PV) white matter hyperintensity (WMH) volumes are better predictors of persistent cognitive impairment (PCI) than baseline WMH burden. Greater PV WMH burden progression is associated with the development of PCI, a potential precursor to Alzheimer or vascular dementia. Identification of factors that decrease WMH accumulation over time is needed to maintain cognitive health in our growing elderly population. *Neurology*® 2009;73:120–125

GLOSSARY

AD = Alzheimer disease; **CDR** = Dementia Rating Scale; **CI** = confidence interval; **HR** = hazard ratio; **HS** = hippocampal sclerosis; **HTN** = hypertension; **ICV** = intracranial volume; **MCI** = mild cognitive impairment; **MMSE** = Mini-Mental State Examination; **NA** = not applicable; **NS** = not significant; **PCI** = persistent cognitive impairment; **PV** = periventricular; **SES** = socioeconomic status; **TE** = echo time; **TR** = repetition time; **vCSF** = ventricular CSF; **vol** = volume; **WMH** = white matter hyperintensity.

White matter changes seen as white matter hyperintensities (WMHs) on T2-weighted MRI are commonly observed on brain imaging of elderly individuals[1] and are associated with cognitive changes[2-5] and conversion to mild cognitive impairment (MCI).[6] It has been shown that such white matter change is likely to progress over time,[7-9] with increased rate of progression in those with greater baseline WMH burden.[7,8,10] A few longitudinal volumetric MRI studies have shown detrimental effects of total WMH progression on verbal IQ, memory, and executive function.[11-13] One previous study showed more specific regional consequences of periventricular (PV) white matter progression on worsening executive function testing,[14] whereas another volumetric study showed that progression of PV WMH is associated with onset of dementia in depressed elderly subjects.[15] Most previous longitudinal studies calculated rates of WMH change from scans obtained from all subjects regardless of whether they had converted to

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cognitive impairment, thus increasing the chance of introducing confounding effects on CNS structural changes from non–WMH-related neurodegenerative disease (i.e., hippocampal or brain volume decline known to be associated with Alzheimer disease [AD]).

One recent study has shown that increased total baseline WMH burden is associated with onset of MCI.[6] Few, if any, however, have studied the effects of WMH progression on the onset of mild cognitive symptoms, which in some cases precedes conversion to dementia, particularly in those with greater baseline and PV WMH burden.[16] The objective of this study was to compare the regional effects of baseline WMH burden with *rates* of WMH volume change over time in cognitively intact elderly individuals on the risk of eventual cognitive impairment.

METHODS

Subjects. Ninety-eight subjects aged 65 years or older underwent baseline brain MRI, ApoE allele testing, and detailed annual cognitive and neurologic assessments as part of an ongoing longitudinal study of brain aging and cognition (Oregon Brain Aging Study).[17,18] Entry inclusion criteria included a score of 24 or greater on the Mini-Mental State Examination (MMSE)[19] and a 0 on the Clinical Dementia Rating Scale (CDR).[20] At entry, subjects were community-dwelling, functionally independent adults, free of comorbid conditions commonly associated with cognitive decline (e.g., stroke, heart disease, cancer, diabetes, neurologic disorders), and were not taking medications that affect cognition. Volunteers were solicited from retirement homes, senior citizens' organizations, and public relation activities. Those who showed evidence of questionable dementia by CDR >0, had an MMSE score <24, or 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. Elders who showed evidence of clinical depression were not enrolled. Participants who developed health problems were retained in the project. All subjects had total WMH volumes analyzed. In addition, WMH volumes were regionally defined as being subcortical or periventricular. Forty-nine subjects had 3 or more MRIs analyzed for total, PV, and subcortical WMH volumes corresponding with a cognitive and motor evaluation before conversion to persistent cognitive impairment (PCI). As defined previously, subjects were considered to have PCI if they had 2 consecutive semiannual CDR scores of 0.5 or greater and did not convert back to normal cognition (defined as having 2 or more consecutive CDR scores of 0 during the duration of their follow-up).[21] For subjects who converted to PCI, neurologic and MRI data were used from the last visit before their conversion. All subjects signed written informed consent, and approval from the Institutional Review Board of Oregon Health & Science University was obtained. Information regarding subjects' cardiac risk factors at enrollment was obtained from a detailed medical history form. Changes in subjects' general medical conditions were obtained yearly through patient report, and from 1996 on, from a modified cumulative illness rating scale[22] administered yearly. A subset of subjects agreed to brain autopsy at the time of their death. Neuropathologic diagnosis of AD and vascular dementia followed published criteria.[23-26]

MRI acquisition. The general procedures have been described previously.[27] Briefly, MRI scans were performed with a 1.5-T magnet. The protocol consists of slice thickness of 4 mm (no gap), 24-cm field of view with a 256 × 256 matrix (0.86 × 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. The coronal plane is determined by a line drawn from the lowest point of the splenium to the lowest point of the genu of the corpus callosum on the midsagittal image.

Image analysis. Image analysts evaluated each scan independently and were blind to subjects' cognitive or neurologic testing, demographic characteristics, and results from previous imaging. The image analysis software REGION is used to quantitatively assess regional brain volumes of interest.[27,28] Briefly, recursive regression analysis of bifeature space based on relative tissue intensities was used 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: PV WMH, subcortical WMH, total WMH (PV plus subcortical WMH), brain volume, ventricular cerebral spinal fluid (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.[28] Rates of change of outcomes were determined by calculating the slope obtained from the regression line created by all available data points from scans performed before the onset of conversion. 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. Areas of high signal that immediately abut ventricular fluid as visualized on the coronal image are considered periventricular. WMH bounded by brain tissue on all sides is considered subcortical. Areas of infarct were determined separately from WMH volumes based on whether they had clean or sharp edges and were relatively dark on proton density images.

Table 1 Baseline subject and MRI characteristics

	All (n = 49)	Cognitively intact (n = 25)	Became cognitively impaired (n = 24)	*p* Value
Age at entry, y	84.1 (6.2)	83.1 (7.5)	85.0 (4.5)	0.30
Duration of follow-up, y	10.7 (3.2)	10.0 (3.7)	11.5 (2.6)	0.11
MMSE at entry	27.9 (1.8)	28.0 (1.8)	27.8 (1.8)	0.62
ApoE 4+	10	2	8	0.04
% Female	53	48	58	0.57
Education, y	14.5 (2.7)	14.4 (2.7)	14.5 (2.7)	0.90
SES at entry	46.7 (12.7)	45.6 (10.1)	47.8 (15.1)	0.55
% Hypertension at entry	0	0	0	NA
% Diabetes at entry	0	0	0	NA
% Stroke or TIA at entry	0	0	0	NA
% Smoking history	16	16	16.7	1.00
Baseline ICV, mL	1,160.4 (129.8)	1,164.9 (122.6)	1,155.7 (138.6)	0.81
Baseline brain vol, mL	906.0 (97.6)	918.9 (100.1)	892.6 (95.2)	0.35
Baseline vCSF vol, mL	38.5 (15.4)	36.5 (14.6)	40.6 (16.2)	0.36
Baseline hippocampal vol, mL	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)	0.93
Baseline total WMH vol, mL	7.5 (7.2)	5.6 (5.3)	9.6 (8.4)	0.05
Baseline PV WMH vol	6.3 (5.6)	5.1 (4.7)	7.5 (6.3)	0.15
Baseline subcortical WMH vol, mL	1.3 (2.0)	0.5 (0.7)	2.1 (2.5)	0.003

Data are mean (SD).
MMSE = Mini-Mental State Examination; SES = socioeconomic status (Hollingshead, 1975)[41]; NA = not applicable; ICV = intracranial volume; vol = volume; vCSF = ventricular CSF; WMH = white matter hyperintensity; PV = periventricular.

Statistical analysis. Longitudinal clinical data and coded MRI data were exported from a dedicated database into the statistical program JMP (SAS Institute, Cary, NC). MRI regions and clinical outcomes of interest were examined as continuous variables. Change in MRI outcome measures over time was determined from the calculated slope of a regression line created from 3 or more time points for each subject. *T* tests for continuous variables and Fisher exact tests for categorical variables were used to determine differences in subject and MRI characteristics between those who converted to PCI and those who did not. Survival analyses (Cox proportional hazards) were used to determine associations between baseline brain volumes and rates of brain volume change over time with risk of PCI. Analyses were adjusted for age, intracranial volume, baseline MMSE, baseline hippocampal volume, and ApoE-4 status. When rate of volume change was included as a covariate, we also controlled for the baseline volume of that variable. Proportionality assumptions were examined through visual inspection of survival curves ($-\ln(-\ln S(t))$) as well as statistical assessments for all variables.[29]

Table 2 Rates of MRI volume change

	Total (n = 49)	Cognitively intact (n = 25)	Became cognitively impaired (n = 24)	*p* Value
Time between first and last precognitive impairment scan	5.6 (3.4)	6.3 (3.4)	4.9 (3.2)	0.13
Brain volume slope, mL/y	−3.9 (7.1)	−3.9 (6.5)	−4.0 (7.8)	0.97
vCSF volume slope, mL/y	1.6 (1.5)	1.5 (1.5)	1.7 (1.5)	0.61
Hippocampal slope, mL/y	−0.02 (0.04)	−0.02 (0.03)	−0.02 (0.05)	0.92
Total WMH slope, mL/y	1.6 (1.9)	0.8 (1.1)	2.4 (2.2)	0.004
PV WMH slope, mL/y	1.3 (1.6)	0.7 (1.1)	2.0 (1.9)	0.003
Subcortical WMH slope, mL/y	0.2 (0.4)	0.2 (0.4)	0.3 (0.4)	0.32

Data are mean (SD).
vCSF = ventricular CSF; WMH = white matter hyperintensity; PV = periventricular.

RESULTS Ninety-eight participants were followed up to 15.8 years (average 9.5 years), during which time 53 subjects developed PCI. Two percent of subjects had a diagnosis of hypertension (HTN) at entry into the study. Over the total duration of follow-up, 32% had an HTN diagnosis. Subjects who eventually converted to PCI were more likely to have at least 1 ApoE-4 allele present ($\chi^2 = 6.8$, $p = 0.009$). Forty-nine subjects had 3 or more scans from which rates of volumetric change was calculated. These subjects did not differ in entry age, sex, socioeconomic status, education, ApoE-4 status, cerebrovascular risk factor status (presence of HTN, diabetes, TIA, stroke, or smoking history), or baseline MMSE from those without 3 or more scans. Baseline subject and MRI characteristics for subjects with longitudinal data are presented in table 1. Of the 49 subjects with multiple scans, 24 developed PCI. The average time between first and last precognitive impairment scan was 5.6 years. Longitudinal MRI characteristics are presented in table 2. Subjects who converted to PCI had greater progression of total and PV WMH burden over time.

Baseline subject characteristics and risk of PCI. Subject characteristics were individually entered into a Cox proportional hazards survival regression adjusted for age. Sex, education, socioeconomic status, a history of HTN, stroke or TIA, and smoking were not associated with cognitive decline. The absence of any ApoE-4 allele (hazard ratio [HR] 0.61, 95% confidence interval [CI] 0.45–0.84, $p = 0.003$) conferred a lower risk of PCI.

Baseline MRI volumes and risk of PCI (n = 98). Baseline MRI volumes (cubic centimeters) were individually entered into a Cox proportional hazards survival regression adjusted for age, incident HTN, ICV, MMSE at entry, and ApoE-4 status. Because a larger baseline hippocampal volume conferred a lower risk of cognitive impairment (HR 0.11, 95% CI 0.02–0.73, $p = 0.02$), all other analyses were also adjusted for baseline hippocampal volume. Greater baseline PV WMH (HR 1.06, 95% CI 1.01–1.10, $p = 0.02$) and total WMH (HR 1.04, 95% CI 1.00–1.07, $p = 0.03$), and vCSF (HR 1.02, 95% CI 1.00–1.04, $p = 0.04$) conferred a higher risk of cognitive impairment. Brain volume at baseline was not associated with cognitive decline. After adjusting for baseline

Table 3 Proportional hazards regression model of persistent cognitive impairment (n = 49)

	Model 1: Total WMH progression			Model 2: PV WMH progression		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Age at entry	1.2	1.0–1.4	0.01	1.22	1.1–1.4	0.007
MMSE at entry	0.89	0.7–1.2	NS	0.82	0.6–1.1	NS
Incipient HTN (0)	1.44	0.8–2.7	NS	1.53	0.9–2.9	NS
ApoE 4 status (0)	0.54	0.3–1.0	0.05	0.64	0.3–1.2	NS
Baseline ICV, mL	1.0	1.0–1.0	NS	1.0	1.0–1.0	NS
Baseline hippocampal vol, mL	0.16	0.008–2.8	NS	0.24	0.01–4.1	NS
Baseline vCSF	0.97	0.9–1.0	NS	0.98	0.9–1.02	NS
Baseline total WMH vol, mL	0.94	0.8–1.1	NS			
Baseline PV WMH vol, mL				0.92	0.8–1.04	NS
Total WMH slope, mL/y	1.84	1.3–2.7	0.0007			
PV WMH slope, mL/y				1.94	1.3–3.1	0.001
vCSF slope, mL/y	1.79	1.2–2.8	0.007	1.80	1.2–2.8	0.006

WMH = white matter hyperintensity; PV = periventricular; HR = hazard ratio; CI = confidence interval; MMSE = Mini-Mental State Examination; NS = not significant; HTN = hypertension; ICV = intracranial volume; vol = volume; vCSF = ventricular CSF.

vCSF volume, higher PV WMH (HR 1.04, 95% CI 1.00–1.09, $p = 0.078$) remained a relatively weak predictor of PCI, whereas total WMH volume was no longer significant.

Rates of MRI volume change and risk of PCI (n = 49). Rates of MRI volume change were individually entered into a Cox proportional hazards survival regression adjusted for age, incident HTN, ICV, MMSE at entry, baseline hippocampal and vCSF volume, ApoE-4 status, and baseline MRI volume for each region of interest. Because vCSF volume increase over time conferred a higher risk of PCI (HR 1.69, 95% CI 1.10–2.68, $p = 0.02$), all other analyses were also adjusted for vCSF slope. Greater rates of total WMH and PV WMH increase were associated with a higher risk of cognitive impairment (table 3). No relationship was observed between brain volume change or subcortical WMH volume change and cognitive decline.

Brain pathology. Of the 53 converters, 42 died during the follow-up period. Brain autopsy evaluations were available for 71% (30/42) of those subjects. There was no difference in age, sex, socioeconomic status, ApoE 4 status, baseline MMSE, or duration of follow-up between those with and without brain autopsy. Of those with pathology available, 70% (21/30) had a pathologic diagnosis of AD. Fifteen of these 21 AD subjects also had evidence of vascular disease, 1 had hippocampal sclerosis (HS), 1 had concurrent Lewy body disease, and 3 had a mixed AD/vascular dementia. Thirteen percent (4/30) had pathology consistent with vascular dementia, with 1 also having HS. Seven percent (2/30) had mixed pathology of HS, some AD pathology, and vascular disease, and 10 percent (3/30) had mild microvascular ischemic injury with moderate arteriolosclerosis.

DISCUSSION Results from this study show that greater total and PV WMH burden predicts PCI in healthy elderly people. In addition, this is one of the first studies to demonstrate that progression of total and PV WMH volumes are more robust predictors of cognitive impairment than baseline WMH burden. In those with brain autopsy available, AD pathology was the most common diagnosis. However, evidence of cerebrovascular disease was seen in almost all cases. The high prevalence of vascular disease among other types of pathology has been reported by others.[30-32] Because it is thought that AD pathology may precede the onset of cognitive symptoms by years,[33] it is possible that total and PV WMH progression is an early imaging manifestation of neuronal degeneration in those who have underlying AD pathology and are destined to develop the disease. Alternatively, the effects of cerebrovascular disease may promote Aβ aggregation or plaque formation and cognitive decline in early or mild AD, as has been suggested by others.[34-37] In this study, subcortical WMH progression was not associated with PCI. The total amount of subcortical WMH volume was small (<0.3% of brain), however, and likely reflective of the healthy nature of this cohort. It is possible that other subject populations with more cerebrovascular risk factors would have greater total subcortical WMH progression with subsequently increased impact on cognitive health. Alternatively, there may be a regional significance of PV WMH progression in

conferring greater cerebrovascular injury or in being a specific indicator of neuronal vulnerability when compared with progression of subcortical lesions.

Limitations of the study include generalizing results to other populations, given that our subjects had few cerebrovascular risk factors at entry, and—perhaps related to this—the small volume of subcortical WMH. On the other hand, 48% had acquired at least 1 vascular risk factor (HTN, diabetes, stroke, or TIA) by the mean follow-up period of the cohort. This suggests that if vascular risk factors are important for subcortical WMH development, their effect results from sustained risk factor exposure for many years. A strength of this study is use of the designation of persistent cognitive decline as an endpoint which helped ensure that individuals had enduring meaningful change. We chose to use the term PCI rather than other definitions of mild cognitive decline (e.g., cognitive impairment nondemented, vascular cognitive impairment, or various forms of MCI) to capture the full spectrum of early and mild cognitive symptoms before the onset of dementia in those showing a temporal pattern of decline likely to be reflective of true cognitive change. A PCI diagnosis has the additional advantage of being relatively easily replicated by other population- and community-based studies in which detailed neuropsychological testing may not be readily available. Other strengths of this study include the relatively long follow-up period and availability of pathologic data on some of the subjects. In addition, rates of volumetric change were created from a minimum of 3 time points, a method that is likely to reduce the amount of variability inherent in longitudinal measures. MRI volumetric slopes were determined from the scan before conversion for those who became cognitively impaired, thus reducing potential confounding effects from neurodegenerative disease. It is possible that cognitive effects from progressive ischemic brain injury may be more apparent during this time period, before the onset of overt dementia. This hypothesis is supported by pathologic studies that show reduced cognitive repercussions of certain types of cerebrovascular lesions after the spectrum of AD pathology is taken into account.[32,38,39] While prior studies have shown that concomitant vascular lesions do not affect rates of cognitive decline in those with AD,[40] results from this study suggest that the total burden and rate of accumulation of such WMH lesions may have a more significant impact on the development of cognitive decline before a clinical diagnosis of AD.

Total and PV WMH progression in cognitively intact elderly individuals confers increased risk of eventual cognitive impairment in relatively healthy elderly individuals. Specifically, every 1-mL/year increase in PV WMH increases risk of PCI by 94%. Identifying those vulnerable to such progression may be important so that those at risk for cognitive decline can be targeted for early intervention and treatment trials.

AUTHOR CONTRIBUTIONS

Statistical analyses were performed by L.C. Silbert.

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