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Coronary Artery Disease is Associated with Cognitive Decline Independent of MRI Changes in Cognitively Normal Elderly

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Abstract

BACKGROUND/OBJECTIVES—White matter hyperintensities (WMH) and silent brain infarcts (SBI) have been associated with both vascular factors and cognitive decline. We examined among cognitively normal elderly, whether vascular factors predict cognitive decline and whether these associations are mediated by MRI measures of subclinical vascular brain injury.

DESIGN—Prospective multi-site longitudinal study of subcortical ischemic vascular diseases

SETTING—Memory and aging centers in California

PARTICIPANTS—We studied 74 participants who were cognitively normal at entry and received at least 2 neuropsychological evaluations and 2 MRI exams over an average follow-up of 6.9 years.

MEASUREMENTS—Item response theory was used to create composite scores of global, verbal memory, and executive functioning. Volumetric MRI measures included WMH, SBI, hippocampus, and cortical gray matter (CGM). We used linear mixed effects models to examine the associations between vascular factors, MRI measures, and cognitive scores.

RESULTS—History of coronary artery disease (CAD) was associated with greater declines in global, verbal memory, and executive cognition. The CAD associations remained after controlling for changes in WMH, SBI, hippocampal and CGM volumes.

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CONCLUSION—History of CAD may be a surrogate marker for clinically significant atherosclerosis which also affects the brain. Structural MRI measures of WMH and SBI do not fully capture the potential adverse effects of atherosclerosis on the brain. Future longitudinal studies of cognition should incorporate direct measures of atherosclerosis in cerebral arteries, as well as more sensitive neuroimaging measures.

Keywords

cognitively normal elderly; coronary artery disease; cognitive decline; MRI

INTRODUCTION

Risk factors for atherosclerotic cerebrovascular disease (CVD) such as hypertension, hyperlipidemia, diabetes mellitus, and obesity are highly prevalent in older Americans.¹⁻² These potentially modifiable conditions are associated with the development and progression of cognitive impairment and incident dementia.³⁻⁵ Among community-dwelling adults, hypertension, diabetes mellitus, and hyperlipidemia are associated with worse cognitive function in both cross-sectional⁶⁻⁹ and longitudinal studies.⁷ A history of coronary artery disease (CAD) has also been associated with cognitive decline.¹⁰⁻¹¹

Evidence of subclinical vascular brain injury, including white matter hyperintensities (WMH) and silent brain infarct (SBI), have been associated with vascular factors and cognitive decline in community-based epidemiologic studies.¹²⁻¹⁵ It has been hypothesized that WMH and SBI mediate the relationship between vascular factors and cognitive decline.¹⁶⁻¹⁸ In the Framingham Offspring study, a stroke risk profile correlated with brain atrophy;¹³ severe WMH and SBI predicted risk of incident stroke, incident dementia, and mortality, independent of vascular risk factors.¹² In the Rotterdam Scan Study, 3-year progression of WMH and incident SBI were associated with decline in overall cognitive function, especially information processing speed.¹⁴ In the Cardiovascular Health Study, worsening of WMH grade during 5-year follow-up was associated with decline in the modified Mini-Mental State Exam (MMSE) and the digit symbol substitution test.¹⁵ These studies however have been limited by the traditional cognitive and semi-quantitative MRI measures.

In the Ischemic Vascular Dementia (IVD) program project, we followed subjects using psychometrically-matched measures of global, memory and executive function and volumetric MRI measures. The current analyses focus on participants who were cognitively and functionally intact at baseline. We have previously reported that, in cognitively normal elderly, hippocampal atrophy was associated with decline in episodic memory performance, whereas decreased cortical gray matter (CGM) and increased WMH were independently associated with executive decline.¹⁶⁻¹⁸ The objectives of the present analyses were to 1) examine the associations between vascular factors ascertained at baseline and changes in cognitive function over an average of 6.9 years; and 2) determine the extent to which observed associations were mediated by longitudinal changes in volumetric MRI measures, including WMH, SBI, hippocampal volume (HV), and CGM.

METHODS

Study Participants

Our study sample was drawn from a multi-center longitudinal study designed to examine the contributions of subcortical ischemic vascular disease to cognitive impairment and dementia (total n=720). All participants received a comprehensive clinical evaluation.¹⁹ Exclusion criteria included age < 55, non-English-speaking, cortical strokes, severe illnesses other than

CVD or dementia, or medications likely to affect cognition. At study entry, 282 out of 720 participants had initial CDR=0. During the longitudinal follow-up, 237 participants had at least 2 consecutive neuropsychological tests. Of these, 74 had at least 2 MRI completed during the longitudinal follow-up. Our analysis sample therefore consisted of 74 cognitively normal participants meeting the following criteria: (a) cognitively intact, (b) a Clinical Dementia Rating (CDR) score of 0 at initial testing, (c) at least 2 consecutive neuropsychological tests, and (d) at least 2 MRIs completed during longitudinal follow-up. Written informed consent was obtained from all participants following the protocols approved by the institutional review boards at each participating institution.

Baseline Clinical Data

Participant age, gender, ethnicity, and years of education were obtained at baseline using standardized structured questionnaires. Height, weight, and blood pressure were measured and body mass index (BMI) was calculated as weight (kilograms) / height (meters)². Blood pressure was measured twice in a seated position.

Cognitive Assessment

A battery of standardized neuropsychological tests was administered every other year for participants less than 80 years old and every year for participants at least 80 years old.^{16, 20-21} Measures of global cognition, verbal memory, and executive function were created using item response theory as previously described.²²⁻²³ Briefly, scale development used 400 elderly individuals with cognitive function ranging from normal to demented. Donor items for the global cognition scale came from the first two learning trials of the Memory Assessment Scale (MAS) List Learning Test, Wechsler Memory Scale-Revised Digit Span total raw score, letter fluency (FAS), and animal category fluency. Items selected for this scale met two criteria: 1) they broadly measured cognition; 2) they were robustly sensitive to individual differences across a broad cognitive spectrum from normal to demented. The global measure was directly validated against the Mattis Dementia Rating Scale. While highly correlated with the Mattis, the global measure had better reliability across the full spectrum of cognitive ability and psychometric characteristics that were matched to the memory and executive Scales.²² The verbal memory scale combined short delayed free recall, short delayed cued recall, and immediate recall on learning trials 1 and 3. Donor scales for the Executive Function scale were the Initiation-Perseveration subscale of the Mattis Dementia Rating Scale, the FAS verbal fluency test, Digit Span backward, and Spatial Span backward. Each scale was transformed to a mean of 100 and a standard deviation of 15. The normal distribution of each scale offers important advantages for statistical analysis particularly for longitudinal studies.

MRI Image Acquisition and Identification of SBI

Detailed image acquisition and segmentation methods have been described elsewhere.¹⁹⁻²¹ The MRI measures of interest were number of SBI and volumetric measures of WMH, HV, and CGM, obtained on a standard 1.5 Tesla Vision Siemens System (Siemens, Islen, NJ). SBI were defined as discrete gray and white matter hyperintensities >2 mm in diameter and WMH were defined as hyperintense regions on proton density MRI. Hippocampal boundaries were defined using the protocol described by Watson including the hippocampus proper, dentate gyrus, subiculum, fimbria, and alveus.^{21, 24}

Vascular Assessment

Six markers of vascular risk or disease were assessed at baseline: hypertension, hyperlipidemia, diabetes, obesity, CAD, and CVD, obtained using the Minimum Uniform Dataset (MUDS) of the California Alzheimer's Disease Centers Program. Hypertension was

defined by the presence of: systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, self-reported history of hypertension, or current use of antihypertensive medications. Hyperlipidemia and diabetes mellitus included self-reported history or current medication treatment. Obesity was defined as a BMI ≥ 30 kg/m². CAD was defined by self-reported history of myocardial infarction (MI), coronary artery bypass graft (CABG), coronary angioplasty, or positive exercise stress test. CVD was defined by history of carotid endarterectomy, stroke, or transient ischemic attack.

Statistical Analysis

We used linear mixed effects models to investigate the associations between vascular factors and the global, verbal memory, and executive scores. An indicator variable for the presence/absence of each vascular factor was modeled as a fixed effect, while time (in years) since the first neuropsychological testing was included as a random effect. An interaction term of risk-factor-by-time tested whether the annual rate of change in a cognitive measure differed by the presence of each vascular factor. All models controlled for age at the first neuropsychological testing, gender, education, and the interaction of these variables with follow-up time. Separate models were fitted for each vascular factor and cognitive measure.

To examine whether the associations between vascular factors and cognition were mediated by WMH or SBI, baseline levels and changes in MRI measures were added in the multivariate models as covariates. Changes in each MRI measure were calculated as the difference between last and initial measures. Only vascular factors significantly related to cognitive changes at $p < 0.05$ were tested. Model regression coefficients were annual rates of change in cognitive measures by the presence of vascular factor or per unit change in MRI measures. Because the scale of measurement for HV was so small, the rate of change in cognitive scores for HV was expressed per SD of HV (0.028% of intracranial volume (ICV)). The rate of change in cognitive scores for WMH and CGM were expressed per unit percentage of ICV. All statistical testing was performed at a two-sided 5% level of significance and used Statistical Analysis System version 9.1 software (SAS Institute, Cary, NC). Analyses with mixed effects models used SAS PROC MIXED.

RESULTS

A total of 74 participants (36 men, 38 women) were included in the present analysis, with a mean age at study entry of 73.8 years (range 58-88), and 88% Caucasian (Table 1). The mean education level was 15.4 years (range 8-24). The mean duration of follow-up was 6.9 years (SD 2.5, range 1-11). Twenty participants (27%) had evidence of SBI on the baseline MRI. Eight participants (11%) had CAD: 2 MI, 3 CABG, 2 coronary angioplasty, and 1 positive exercise stress test. Among the original sample of 237 cognitively intact participants (95 men, 142 women) with at least 2 neuropsychological tests, mean age at study entry was 71.2 years (range 55-88). Seventy-six percent of participants were Caucasian. The mean education level was 15.3 years (range 5-24). The mean duration of follow-up was 6.6 years (SD 3.1, range 1-12). Forty-nine participants (20.7%) had evidence of SBI on the baseline MRI and 26 (11%) had CAD. In sum, our study sample of 74 participants with at least 2 MRI was representative of the sample of 237 cognitively intact participants with longitudinal follow-up.

Table 2 presents the multivariate linear mixed effects model for each of the three cognitive measures. CAD was associated with decline in all cognitive measures. No significant associations were observed for other vascular factors. Lower baseline HV was associated with greater decline in verbal memory ($p = 0.01$). Increases in WMH were associated with greater decline in global and executive function.

Table 3 displays the multivariate associations of CAD, baseline levels and changes in MRI measures with longitudinal changes in cognitive measures controlling for age, gender, and years of education. The beta represents annual rate of change in composite cognitive measures by the presence of vascular factors or per unit change in MRI measures. Associations between CAD and decline in global, verbal memory, and executive scores remained after controlling for MRI changes, age, gender, and education (Model 5). Higher HV at baseline showed an independent effect on longitudinal decline in verbal memory ($p = 0.004$). Increases in WMH ($p = 0.002$) and decreases in HV ($p = 0.002$) were independently associated with greater decline in executive score over time. No significant associations were observed for baseline levels and changes in CGM.

DISCUSSION

The major finding of this study is that history of CAD predicts greater declines in global, verbal memory, and executive cognition in community-dwelling elders who were cognitively intact at baseline, with the majority remaining normal after a mean follow-up of 6.9 years (77% with CDR = 0 at the end of follow-up). Longitudinal changes in WMH, SBI, and HV were correlated with cognitive measures, consistent with previous findings reported in middle-aged adults and cognitively normal elderly.^{12, 14} The association between CAD and cognitive decline persisted after adjustment for both baseline levels and changes in WMH, SBI, HV, and CGM. Thus, WMH and SBI found on proton density MRI do not fully explain the relationship between CAD and cognitive decline. It is well recognized, however, that in other types of subcortical ischemic vascular disease (e.g., CADASIL), diffusion tensor imaging studies provide more sensitive measures (e.g., mean diffusivity) of microstructural changes than WMH.²⁵⁻²⁶

In this sample of cognitively normal elderly with longitudinal follow-up, CAD proved to be a stronger predictor of cognitive decline than vascular risk factors (e.g., hypertension, hyperlipidemia). The stronger association between cognitive decline and CAD (versus other vascular factors) has been recognized in the literature, and is consistent with the notion that CAD represents a specific sign of more advanced, symptomatic, end-organ disease. In a prospective longitudinal study of 395 participants with an average age of 64.4 years, 326 patients with CAD showed significantly greater decline on global cognition over 72 months, compared to 69 heart healthy participants without CAD.²⁷ Moreover, comparable severity of decline was found among patients with CAD who has been treated surgically on-pump CABG ($n = 152$), off-pump CABG ($n = 75$) or non-surgically ($n = 99$). Therefore, late cognitive decline after CABG is not specific to the use of cardiopulmonary bypass²⁷ but may be related to the effects of underlying atherosclerosis. Our study extends these findings by demonstrating associations between CAD with verbal memory and executive functioning, in addition to global cognition.

To our knowledge, this is the first study to examine the degree to which associations between CAD and cognitive decline are mediated by WMH and SBI. A meta-analysis of 23 studies in non-demented adults demonstrated that WMH are associated cross-sectionally with reduced global and executive cognition.²⁸ Longitudinal increase in WMH grade has been linked to cognitive decline in non-demented older adults.^{15-16, 29-30} Progression of WMH is significantly correlated with hypertension, but not with diabetes mellitus, or carotid intima-media thickness.¹⁴ Our findings suggest that WMH measured on structural MRI is not a sensitive marker for CAD-associated cognitive decline and more sensitive measures of cerebral microstructural change such as diffusion tensor imaging should be considered in the future.

Strengths of our study include: 1) a prospective longitudinal study of well-characterized elderly participants who were cognitively normal at baseline; 2) use of psychometric measures with linear measurement properties covering an array of cognitive domains;²² and 3) use of longitudinal and volumetric MRI measures of subclinical vascular brain injury rather than semi-quantitative ratings.¹⁶

There are also several limitations to the present study. (1) Medical history was based on self report without medical record documentation. This may have lead to misclassification of vascular conditions with likely bias towards the null hypothesis. (2) We did not collect data on duration or severity of cardiovascular disease that may substantially affect cognitive function longitudinally. (3) Low prevalence of diabetes and absence of laboratory measures (e.g., fasting glucose, insulin, and lipids) limit informativeness of this study for diabetes mellitus. (4) Our findings may represent false positive associations, although to minimize multiple comparisons, we limited our hypothesis tests to vascular factors and the results were robust after controlling for confounders. (5) Lastly, the relatively high mean years of education (15.4) in our sample may limit the generalizability of our results to the general elderly population.

In summary, this study confirms associations between CAD and cognitive decline, but highlights that these associations are not fully explained by MRI-measured WMH and SBI. If we propose that CAD is a surrogate marker of clinically significant atherosclerosis affecting the brain, future longitudinal studies of cognition should consider utilizing measures of atherosclerosis in cerebral arteries and more sensitive neuroimaging measures of microstructural changes in the brain.

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Table 1**Sample Demographics and Baseline Clinical Characteristics and Cognitive Measures**

Characteristics	N = 74
Female, no. (%)	38 (51.3)
Caucasian, no. (%)	65 (87.8)
Age at initial test, mean $\pm$ SD	73.8 $\pm$ 7.0
Years of education, mean $\pm$ SD	15.4 $\pm$ 3.0
Span of years tested, mean $\pm$ SD	6.9 $\pm$ 2.5
Number of tests, median (range)	5 (2, 10)
Average initial cognitive performance	
Global	101.0 $\pm$ 14.7
Verbal Memory	106.3 $\pm$ 15.3
Executive	98.9 $\pm$ 13.3
MMSE	29.1 $\pm$ 1.3
Presence of vascular factor, no. (%)	
Hypertension	51 (68.9)
Hyperlipidemia	28 (37.8)
Diabetes	8 (10.8)
Obesity (N=67)	19 (28)
Coronary artery disease	8 (10.8)
Cerebrovascular disease	3 (4.0)
Baseline key MRI measures	
Silent Brain Infarct, no. (%)	20 (27.0)
White Matter Hyperintensities (% ICV)	0.6 $\pm$ 0.7
White Matter Hyperintensities (cc)	7.6 $\pm$ 8.4
Hippocampal Volume (% ICV)	0.3 $\pm$ 0.04
Cortical Gray Matter (% ICV)	39.4 $\pm$ 2.2

ICV = intracranial volume.

Table 2

Multivariate Linear Mixed Effects Models of the Associations between Vascular Factors and Cognitive Decline (N=74)

	Global Cognition *	Verbal Memory *	Executive Function *
Hypertension	-0.88 ± 0.55; 0.11	-0.31 ± 0.68; 0.65	-0.38 ± 0.43; 0.38
Hyperlipidemia	0.4 ± 0.6; 0.51	0.09 ± 0.74; 0.91	-0.01 ± 0.46; 0.98
Diabetes	0.83 ± 1; 0.41	2.05 ± 1.22; 0.09	-0.51 ± 0.77; 0.5
Obesity	0.21 ± 0.67; 0.75	-0.31 ± 0.83; 0.71	-0.81 ± 0.47; 0.09
Cerebrovascular disease	-0.06 ± 0.77; 0.94	-0.35 ± 0.94; 0.71	0.16 ± 0.6; 0.79
Coronary artery disease	-2.52 ± 0.89; 0.005	-2.42 ± 1.11; 0.03	-1.38 ± 0.7; 0.049
Baseline			
Silent Brain Infarct	-0.01 ± 0.23; 0.97	-0.24 ± 0.29; 0.4	-0.24 ± 0.18; 0.17
WMH (% ICV)	-0.34 ± 0.41; 0.4	-0.13 ± 0.5; 0.8	0.01 ± 0.32; 0.98
HV (0.028% ICV)	0.01 ± 0.2; 0.96	0.61 ± 0.24; 0.01	0.11 ± 0.16; 0.5
CGM (% ICV)	-0.02 ± 0.14; 0.91	0.02 ± 0.16; 0.89	-0.03 ± 0.11; 0.77
Changes in			
Silent Brain Infarct	-0.31 ± 0.16; 0.06	-0.12 ± 0.21; 0.55	-0.18 ± 0.13; 0.16
WMH (% ICV)	-1.88 ± 0.88; 0.033	-2.08 ± 1.1; 0.06	-2.46 ± 0.65; <0.001
HV (0.028% ICV)	0.72 ± 0.28; 0.01	0.48 ± 0.35; 0.17	0.69 ± 0.21; 0.001
CGM (% ICV)	0.1 ± 0.09; 0.23	0.16 ± 0.11; 0.14	0.09 ± 0.07; 0.19

β represents annual rate of change in composite cognitive measures by the presence of vascular factors or per unit change in MRI measures; all models were adjusted for age, gender, and years of education.

WMH = white matter hyperintensities; HV = hippocampal volume; CGM = cortical gray matter; ICV = intracranial volume.

*
β ± SE; p-value

Table 3

Multivariate Linear Mixed Effects Models of the Associations between Vascular Factors, MRI measures, and Cognitive Decline (N = 74)

Model	Independent Variables	Global Cognition *	Verbal Memory *	Executive Function *
1	CAD [†]	-2.56 ± 0.88; 0.004	-2.55 ± 1.12; 0.024	-1.49 ± 0.67; 0.026
	Baseline WMH	-0.17 ± 0.39; 0.67	0.06 ± 0.49; 0.9	0.2 ± 0.29; 0.49
	Change in WMH	-1.91 ± 0.86; 0.028	-2.18 ± 1.1; 0.049	-2.56 ± 0.65; <0.001
2	CAD	-2.55 ± 0.85; 0.003	-2.38 ± 1.13; 0.036	-1.35 ± 0.67; 0.046
	Baseline SBI	-0.14 ± 0.23; 0.56	-0.24 ± 0.3; 0.42	-0.33 ± 0.18; 0.07
	Change in SBI	-0.39 ± 0.17; 0.021	-0.23 ± 0.22; 0.28	-0.31 ± 0.13; 0.019
3	CAD	-2.53 ± 0.86; 0.004	-2.47 ± 1.06; 0.021	-1.41 ± 0.66; 0.035
	Baseline HV	0.09 ± 0.19; 0.63	0.66 ± 0.23; 0.004	0.17 ± 0.15; 0.24
	Change in HV	0.74 ± 0.27; 0.007	0.57 ± 0.33; 0.08	0.72 ± 0.21; 0.001
4	CAD	-2.43 ± 0.9; 0.007	-2.23 ± 1.12; 0.048	-1.27 ± 0.71; 0.08
	Baseline CGM	0.06 ± 0.15; 0.68	0.14 ± 0.18; 0.42	0.03 ± 0.11; 0.82
	Change in CGM	0.09 ± 0.1; 0.34	0.17 ± 0.12; 0.14	0.08 ± 0.07; 0.27
5	CAD	-2.69 ± 0.85; 0.002	-2.52 ± 1.06; 0.019	-1.51 ± 0.65; 0.02
	Change in WMH	-1.27 ± 0.87; 0.15	-1.63 ± 1.09; 0.14	-2.03 ± 0.66; 0.002
	Change in SBI	-0.24 ± 0.16; 0.14		-0.07 ± 0.12; 0.56
	Baseline HV		0.68 ± 0.23; 0.004	
	Change in HV	0.53 ± 0.28; 0.06	0.45 ± 0.34; 0.19	0.49 ± 0.21; 0.02

β represents annual rate of change in composite cognitive measures by the presence of vascular factors or per unit change in MRI measures; all models were adjusted for age, gender, and years of education.

CAD = coronary artery disease; SBI = silent brain infarct; WMH = white matter hyperintensities; HV = hippocampal volume; CGM = cortical gray matter.

* β (SE); p-value

[†] CAD was defined by a self-reported history of myocardial infarction, coronary artery bypass graft (CABG), coronary angioplasty, or positive exercise stress test