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Carotid Atherosclerosis and 10-year Changes in Cognitive Function

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Abstract

Background—Carotid atherosclerosis has been suggested to be involved in cognitive decline.

Methods—The Epidemiology of Hearing Loss Study is a longitudinal study of aging among Beaver Dam residents, WI. In 1998–2000, carotid intima-media thickness (IMT) and plaque were measured by ultrasound; cognitive function was measured by the Mini-Mental State Examination (MMSE). Follow-up examinations were conducted in 2003–2005 and 2009–2010. Incidence of cognitive impairment was defined as a MMSE score <24 or reported physician-diagnosed dementia during the follow-up. In the last examination, five additional cognitive tests were added. The associations of carotid atherosclerosis with incident cognitive impairment and cognitive test performance ten years later were evaluated.

Results—A total of 1651 participants (mean age 66.8 years, 41% men) without cognitive impairment at baseline were included in the incidence analysis. IMT was associated with incidence of cognitive impairment after multiple adjustments (hazard ratio: 1.09, p=0.02 for each 0.1 mm increase in IMT). A total of 1311 participants with atherosclerosis data at baseline had the additional cognitive tests 10 years later. Larger IMT was associated with longer time to complete the Trail-Making Test-part B after multiple adjustments (0.1 mm IMT: 2.3 seconds longer, p=0.02). Plaque was not associated with incident cognitive impairment or cognitive test performance 10 years later.

Conclusions—In this population-based longitudinal study, carotid IMT was associated with a higher risk of developing cognitive impairment during the 10-year follow-up, and was associated with poorer performance in a test of executive function 10 years later.

Keywords

Carotid atherosclerosis; cognitive impairment; longitudinal; population-based; epidemiology

1. Introduction

Dementia is an important public health problem, and cardiovascular risk factors have been suggested to have important roles in cognitive decline and dementias including Alzheimer's

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disease [1]. Subclinical CVD, atherosclerosis, may be involved in cognitive decline through chronic cerebral hypo-perfusion and cerebrovascular disease [1–4]. However current studies have not been consistent on this association [5–11], and there is a lack of large population-based longitudinal studies. It is also not clear whether atherosclerosis preferentially affects specific cognitive domains. Studies with multiple cognitive tests have reported different results on the association of atherosclerosis with specific cognitive domains [6–11]. Evaluating the role of atherosclerosis in cognitive decline in specific domains is helpful to understand the etiology of dementia, and to develop specific preventive strategies in the future. The aim of our population-based cohort study was to investigate the association of atherosclerosis measured by carotid ultrasound with decline in cognitive function during a ten year period.

2. Methods

2.1 Study population

The Epidemiology of Hearing Loss Study (EHLS) is a longitudinal study of aging among residents of Beaver Dam, WI [12]. In 1989–90, the Beaver Dam town residents aged 43–84 years were invited to participate in the Beaver Dam Eye Study (BDES) [13]. Survivors were invited to participate in the EHLS study which was conducted concurrently with the BDES 5-year follow-up examination (1993–1995). A total of 3,753 adults were examined (average age: 65.8 years, 57.7% women), and they were re-examined every 5 years.

Carotid atherosclerosis and cognitive function were first measured in the EHLS five-year follow-up examination (1998–2000); this examination forms the baseline for the current manuscript. A total of 2,042 (73%) participants at this examination had carotid ultrasound data. Ultrasounds were not obtained on participants unable to come to the central site, unable to lie on the table, or when the sonographer was unavailable.

The study was approved by the University of Wisconsin-Madison Health Sciences Institutional Review Board, and all participants provided informed consent.

2.2 Measurements

Carotid atherosclerosis—Carotid atherosclerosis was assessed using a Biosound AU4 (Indianapolis, IN, USA) with a 7.5 MHZ probe (LA13A) based on a slight modification of the Atherosclerosis Risk in Communities (ARIC) protocol [14–16]. Carotid intima-media thickness (IMT) and presence of plaque were measured using a modification of the ARIC protocol. The IMT was measured on the left and right sides of the near and far walls of the common carotid artery (CCA), the bifurcation and the internal carotid artery (ICA). The mean IMT of the measurements from the 12 sites was used as carotid IMT in our analyses.

The presence of plaque was evaluated at six sites (CCA, ICA and the bifurcation, both sides). Changes in the wall shape (protrusion into the lumen), texture (walls echoing brighter than adjacent boundaries), and thickness (≥ 1.5 mm) were considered. Plaque was considered present if, in the presence of acoustic shadowing, one of these wall characteristics was present or, in the absence of acoustic shadowing, two wall characteristics were observed. The number of sites (left and right CCA, ICA, and bifurcation) with plaque was categorized: 0, 1–3 and 4–6 sites.

The reproducibility of IMT and plaque assessment was good. The mean inter-grader difference in IMT was 0.03 mm; and for plaque, the kappa coefficient was 0.76 and percent agreement was 90% [17].

Cognitive function tests—The Mini Mental State Examination (MMSE), a test of general cognitive function [18] was included in the 1998–2000 examination and repeated in 2003–2005 and 2009–2010. Cognitive impairment was defined as a score of MMSE <24 (out of 30) or a self or proxy report of physician-diagnosed dementia. At the last visit (2009–2010) additional tests of cognitive function were added. Trail Making Test- part A and part B (TMT-A and TMT-B) are tests of executive function, attention and speed, which require the participant to connect 25 consecutive targets as quickly as possible within five minutes [19]. In TMT-A, the targets are all numbers (1, 2, 3, etc.), and in TMT-B, the targets are numbers alternating with letters (1, A, 2, B, etc.). The score for each task was the time (seconds) taken to complete the test; a score of 301 was given if the subject had not completed the test within the allowed time. The Digit Symbol Substitution Test (DSST) is a test of psychomotor speed and sustained attention, which requires the participant to translate digits (1–9) to symbols using a key at the top of the sheet as quickly as possible [20]. The score was the total number of correct symbols that the participant filled in within the 90 seconds. Rey Auditory Verbal Learning Test (AVLT) is a list-learning test of memory [19]. The Rey AVLT was modified in our study due to limited exam time with four learning trials instead of five. In the test, a 15-word list was read to the participant, and he/she was asked to recall as many words as possible. After three repeated trials, an interruption word list was read, and the participant was asked to recall the interruption word list. Then the participant was immediately asked to recall the original 15-word list again. The total number of words recalled from the original 15-word list (all 4 trials summed) was used as the score. The Verbal Fluency Test (VFT) measures spontaneous production of words under restricted search conditions [21]. The participant was asked to give as many words beginning with letter F, A and S as possible in one minute. The score of VFT was the total number of words given by the participant. Higher test scores reflect better cognitive function except for the TMT-A and TMT-B where higher scores (longer times) are worse.

Covariates—Age, sex, education, and lifestyle factors were self-reported through questionnaires. Participants were asked to bring their current medications to the examinations and the information was recorded. Heavy drinking was defined as ever having 4 or more drinks daily. Physical activity was defined as current exercise at least once a week long enough to sweat. The Short Form Health Survey (SF-36) was administered, and the mental health score was calculated. Height (m) and weight (kilograms) were measured. Seated blood pressure was measured using the Hypertension Detection and Follow-up Program protocol [22]. Hypertension was defined as measured systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg or current use of antihypertensive medications. Blood samples were drawn, and glycated hemoglobin A1C was determined using affinity chromatography (Isolab, Akron, OH). Total and HDL cholesterol were measured using reflectance spectrophotometry. APOE genotyping was performed at the Center for Applied Genomics, the Children's Hospital of Philadelphia among a subgroup of participants. CVD history was defined as self-reported physician-diagnosed angina, myocardial infarction or stroke. Diabetes was defined as self-reported physician-diagnosed diabetes mellitus, or hemoglobin A1C ≥ 6.5%, or suspected diagnosis with current medications for diabetes. Some of the covariate data were obtained during the concurrent BDES examinations.

2.3 Statistical analyses

All the analyses were conducted with SAS 9.2 (SAS Institute Inc., Cary, NC, USA). The association between carotid atherosclerosis and incident cognitive impairment was assessed using Cox proportional hazard models. The event was defined as the first occurrence of a MMSE score <24 or reported dementia diagnosis during the follow-up. Because age is a strong determinant of the outcome, age was used as the time scale as recommended [23].

Participants who did not return for follow-up were censored at their age of their last examination. Models were adjusted for baseline age, sex and education. Other potential confounders from baseline were added one by one, and were retained in the final multivariable model if they were found to change the estimates of the atherosclerosis variables moderately or were statistically significant. The proportionality assumption was examined and no significant violation of this assumption was found.

Linear regression was used to determine the association of baseline IMT and plaque to the 10-yr change in MMSE score, adjusting for age, sex, and education. Logistic regression was used to determine the odds ratio (OR) for IMT and cognitive impairment at five and 10 years of follow-up.

The association of atherosclerosis and other cognitive test performance at the 10-year examination was assessed with ordinary linear regression. Individual test scores were analyzed adjusting for baseline age, sex and education; other potential confounders were included if their inclusion resulted in a moderate change in the estimates of the atherosclerosis variables, or were statistically significant. Because the scores of TMT-A and TMT-B are right-censored (truncated at 301 s), Tobit analyses were done additionally as sensitivity analysis [24]. Because the results were not different, they were not reported here.

2.4 Analytic subsets

Participants with carotid ultrasound data who were not cognitively impaired were included in the analyses of the incidence of cognitive impairment and change in MMSE score. At baseline, among the 2042 participants with carotid ultrasound data, 1885 participants were free of cognitive impairment and1651 of these had follow-up cognitive tests (1618 were re-examined at the 5-year follow-up and 1287 at the 10-year follow-up). The primary reason for loss to follow-up of the 234 participants without follow-up data was death (83%). Those without follow-up were older (74 years vs. 67 years, $p<.0001$), had larger carotid IMT (mean: 0.99 mm vs. 0.86 mm, $p<.0001$), and had higher prevalence of comorbidities (CVD: 25% vs. 12%, $p<.0001$, and diabetes: 21% vs. 12%, $p<.0001$) compared to those with follow-up data.

Participants with carotid ultrasound data at baseline, regardless of cognitive status, who had data on any of the additional cognitive tests at the 10-year examination were included in the linear regression analyses (n=1311). There were 731 participants with baseline carotid ultrasound data who did not have cognitive tests at the 10-year examination and the primary reason for missing follow-up data was death (76%). These 731 participants were older (74 years vs. 65 years, $p<.0001$), had larger carotid IMT (0.97 mm vs. 0.84 mm, $p<.0001$), and had higher baseline prevalence of cognitive impairment (13.2% vs. 2.4%, $p<.0001$) compared to those with cognitive data at the 10-year follow-up.

3. Results

3.1 Carotid atherosclerosis and cumulative incidence of cognitive impairment during the 10-year follow-up

At baseline, the mean age of the participants included in this analysis (n=1651) was 66.8 years, and 40.8% were men; 52% of them had a plaque score 1 (1–3 sites with plaque), and 14% of participants had a plaque score 2 (4–6 sites with plaque), and the mean IMT was 0.86 mm (sd: 0.21, range: 0.50–2.27). Other characteristics of these participants are shown in Table 1. The average length of follow-up was 9.2 years (range: 3–13 years), and the total follow-up was 15,413 person-years. There were 144 persons with incident cognitive impairment (77 cases after five years, and an additional 67 cases by 10 years), and the

cumulative incidence was 9.3 per 1000 person-years. Among these 144 cases, 128 were based upon a MMSE score < 24, and 16 were based on reported diagnosis of dementia.

Adjusting for baseline age, sex, and education, a 0.1 mm increase in baseline IMT was associated with a hazard ratio (HR) of 1.09 (95% CI: 1.02–1.17, p=0.02) of incident cognitive impairment during the 10-years of follow-up; this association remained when adjusting for hypertension, hemoglobin A1C, HDL cholesterol, smoking, heavy drinking and SF-36 mental score (HR: 1.09, 95% CI: 1.01–1.18, p=0.02).

We repeated our analyses using logistic regression to analyze the associations between IMT and cognitive impairment at the five and ten year follow-up examinations. The age-sex-education-adjusted OR for IMT (0.1 mm) was 1.07 (95%CI: 0.97–1.19, p=0.19) at five years and 1.13 (95% CI: 1.02–1.26, p=0.02) at ten years.

Adjusting for age, sex and education, plaque was not significantly associated with incident cognitive impairment, the HRs were 1.10 (95% CI: 0.72–1.70, p=0.65) for those with plaque in 1–3 sites and 1.26 (95% CI: 0.76–2.11, p=0.37) for those with plaque in 4–6 sites compared to those without plaque. Results were not changed in multivariable models (data not shown).

On average, MMSE scores declined by 0.32 points during the ten years of follow-up. Adjusting for age, sex and education, every 0.1 mm increase in baseline IMT was associated with a 0.07 decrease in MMSE score by the 10-yr follow-up examination (p = .04). There were no significant associations between baseline plaque and 10-year change in MMSE score.

3.2 Carotid atherosclerosis and cognitive test scores at the 10-year follow-up examination

The distribution of the cognitive test scores among the 1,311 participants included in these analyses is shown in Table 2. Adjusting for age, sex and education, IMT was associated with scores on the TMT-A, TMT-B, and DSST but not with AVLT and VFT. The effects were attenuated but the association with TMT-B remained significant after further adjustments (Table 3).

Plaque was associated with TMT-A and TMT-B after adjusting for age, sex and education, but these associations were attenuated and lost significance in multivariable models; no significant associations were found between plaque and other cognitive function test scores (Table 4).

The TMT-A score was subtracted from the TMT-B score and the difference was modeled as the outcome in a multivariable model containing the same covariates as the final model for TMT-B. For every 0.1 mm increase in baseline IMT, this executive function measure increased (worsened) by 1.97 seconds (p = 0.02). Omitting one participant who had a high mean baseline IMT but a fast time increased this association to 2.17 seconds (p = .01). No association was found with baseline plaque.

4. Discussion

Previously we reported that larger carotid IMT was correlated with lower MMSE score at baseline [25]. In this longitudinal study, we found that larger carotid IMT was associated with higher risk of incident cognitive impairment during the 10-year follow-up, and associated with a greater 10-yr decline in MMSE score. Although the effect size was small, it remained significant in the multivariable model, which supported the hypothesis that atherosclerosis is involved in cognitive decline. In the few population-based longitudinal

studies, the association of atherosclerosis and cognitive function has been inconsistent [9–10, 26–27]. The ARIC study did not find associations between IMT and cognitive tests in longitudinal analyses with six years of follow-up, similar to our findings at five but not ten years of follow-up [9]. The Cardiovascular Health Study found that stenosis but not the IMT measured in the left common carotid artery was associated with cognitive impairment and decline [26]. But the other two studies found that larger IMT was associated with cognitive decline on multiple tests [10, 27]. Different age ranges in study populations, choice of cognitive function tests, lengths of follow-up and controlling of various confounders may contribute to the discrepant results. Our study results add further evidence that carotid IMT is associated with long-term cognitive decline.

Our finding that carotid IMT was associated with TMT-B score, and the difference between TMT-B and TMT-A, strengthens the evidence of a link between atherosclerosis and cognitive decline. However, no association was found between IMT and TMT-A or DSST, which are also tests of executive and psychomotor function. This may be related to the different properties of these tests. The TMT-B is more intellectually difficult than the TMT-A; and the DSST is relatively unaffected by intellectual ability, memory, and learning compared to TMT-B [19]. As shown in our data, the TMT-B score had more variability, and thus may better capture the range of cognitive function.

We did not find associations between carotid atherosclerosis and memory or language fluency. These findings were consistent with some cross-sectional studies, which reported that carotid IMT was associated with the attention-executive-psychomotor domain but not with memory or language fluency domains [6–8, 11]. Therefore it was suggested that frontal-subcortical circuits of the brain which support executive cognitive function may be particularly vulnerable to ischemic injury caused by atherosclerosis [8]. But two longitudinal studies found that IMT was associated with memory and language fluency as well [10, 27]. In addition, the Rotterdam study found that carotid IMT was associated with dementia, especially with Alzheimer's disease (memory deficit is a prominent symptom of this disorder) [28]. Therefore it could be that other domains of cognitive function such as memory and language fluency would also be affected by hypo-perfusion and ischemia over time, and longitudinal studies are more powerful designs to detect such associations.

The null associations with cognitive function tests may also be partly related to the fact that the carotid ultrasound examination was done 10 years prior to the cognitive function tests. Participants who had larger IMT and poor cognitive function at the baseline examination were more likely to have died and less likely to attend the examination 10 years later, therefore the loss-to-follow-up might bias results toward the null. Future longitudinal follow-up studies are needed to reveal whether atherosclerosis is associated with declines in specific cognitive domains, and whether some cognitive domains decline earlier or faster than others under cerebral hypo-perfusion due to atherosclerosis.

In contrast to IMT, plaque was not associated with cognitive impairment or poorer function in our study. Plaque might not be as sensitive a predictor as IMT in our older population as the prevalence of plaque was high in this cohort; the continuous measure of IMT may have more precision than our plaque score. Carotid plaque probably has a different pathogenesis than IMT thickening; it was more related to myocardial infarction and coronary heart disease, while IMT strongly predicted stroke [28]. IMT may be marking the effects of long-term chronic hypertension on cognition. In addition, adults with unstable plaque are particularly at high risk for cerebrovascular events, and we were unable to differentiate unstable from stable plaque in this study. Our results are consistent with the idea that atherosclerosis risk has a continuous rather than threshold effect [10].

There may be several possible biological mechanisms for the association between carotid atherosclerosis and cognitive function. Carotid atherosclerosis contributes to cerebrovascular events. Carotid plaque, especially unstable plaque may peel off and cause cerebral emboli, and result in stroke, which may directly cause vascular dementia [3]. Secondly, carotid atherosclerosis may increase risk of silent stroke among those without clinical stroke, and these silent strokes, although not clinically manifest, may damage the brain and cause cognitive impairment [2]. Thirdly, chronic cerebral hypo-perfusion and ischemia caused by carotid atherosclerosis may directly increase the vulnerability of the neurons, and destabilize neurons and synapses [29–30].

Our study had several strengths. First, it was a large population-based cohort study with long term follow-up, and carotid atherosclerosis was measured using standardized protocols. Secondly, multiple cognitive function tests were administered. Finally, multiple traditional CVD risk factors were collected and adjusted for as potential confounders to minimize residual confounding. Our study also had limitations. Since the study was among older adults, loss to follow-up due to mortality is unavoidable with a long-term follow-up. In the incidence analyses, because those who did not come back for follow-up exams were older and less healthy, the result was likely to be biased toward the null. Secondly, because some of those who had physical limitations did not have data on carotid atherosclerosis, our results may not be applicable to the less healthy elderly participants with physical limitations. Thirdly, although multiple CVD risk factors have been controlled for, residual confounding may still exist due to insufficient control or even over-controlling.

In summary, our population-based study found that carotid IMT was associated with higher risk of incident cognitive impairment in a 10-year follow-up. Carotid IMT was associated with one test of executive-psychomotor function measured 10 years later. Our findings support the hypothesis that carotid atherosclerosis is associated with cognitive dysfunction. Future longitudinal studies with multiple cognitive function tests and dynamic measures of cerebral perfusion are needed to better understand this association.

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Highlights

1. Carotid atherosclerosis and cognitive function were measured in a cohort in WI.
2. Larger IMT was associated with higher risk of incident cognitive impairment.
3. Larger IMT was associated longer time to complete trail making test-part B.
4. Plaques were not associated incident cognitive impairment or other tests scores.
5. Carotid IMT may be involved in cognitive decline with aging.

Table 1

Baseline characteristics of the 1651 participants at risk for incidence of cognitive impairment.

Characteristic	**n**	**%**		
Education (years)	1650			
<12		13.1		
12		49.4		
13–15		17.4		
16+		20.1		
Physical activity (%)	1630	44.8		
APOE 4 carrier (%)	1435	14.8		
Smokers	1630			
--current		10.7		
--past		42.0		
Heavy drinker	1630			
--current		1.3		
--past		12.3		
Taking NSAIDs	1630	46.4		
Hypertension	1651	56.8		
Taking Anti-hypertensive meds.	1651	41.1		
Taking statins	1630	20.8		
History of CVD	1631	12.5		
Diabetes mellitus	1630	11.7		
Characteristic	n	Mean	sd	Range
BMI (kg/m^2)	1622	30.1	5.9	16–80.2
Total cholesterol (mg/dl)	1643	214.1	38.4	109–370
HDL cholesterol (mg/dl)	1603	51.2	16.7	13–130
Hemoglobin A1C (%)	1613	5.4	0.8	3.5–12.5
SF-36 mental score	1641	55.6	7.1	16.9–72.3

Table 2

Distribution of cognitive test scores at the 10-year follow-up (2008–2010) among those with baseline ultrasound data (N=1311).

Test	n	Mean (sd)	Range
TMT-A* (seconds)	1232	48.2 (31.6)	15–301
TMT-B* (seconds)	1189	128.1 (67.5)	35–301
DSST (count)	1210	40.8 (12.1)	3–75
AVLT (count)	1206	24.2 (7.8)	1–53
VFT (count)	1245	32.6 (11.9)	3–79

* Five participants and 73 participants were who unable to complete the tests within 5 minutes were assigned a score of 301 seconds for TMT-A and TMT-B, respectively. Numbers vary by test due to missing data.

Table 3

Associations of baseline carotid IMT (0.1 mm) with cognitive test scores at the 10-year follow-up examination.

	Age-sex-education adjusted model				Multivariable model			
	n	coef.	se	p	n	coef.	se	p
TMT-A[1]	1232	0.96	0.44	0.03	1185	0.74	0.46	0.11
TMT-B[2]	1189	2.96	0.94	0.002	1153	2.27	0.98	0.02
DSST[3]	1210	−0.36	0.16	0.03	1160	−0.12	0.17	0.47
AVLT[4]	1206	−0.03	0.10	0.77	1143	0.03	0.11	0.82
VFT[5]	1245	0.03	0.17	0.87	1199	0.11	0.18	0.56

Multivariable models are further adjusted for

[1] hemoglobin A1C, SF-36 mental score, antihypertensive medications;

[2] BMI, antihypertensive medications, heavy drinking, SF-36 mental score;

[3] BMI, hemoglobin A1C, hypertension, smoking, SF-36 mental score;

[4] hemoglobin A1C, HDL cholesterol, smoking;

[5] hemoglobin A1C, heavy drinking, SF-36 mental score.

Table 4

Associations of baseline plaque with cognitive test scores at the 10-year follow-up examination.

	Age-sex-education adjusted model				Multivariable model			
	n	**Coef.**	**se**	**p**	**n**	**Coef.**	**se**	**p**
TMT-A[1]	1210				1134			
Plaque: 1–3 sites vs. 0		−0.19	1.76	0.92		−1.03	1.86	0.58
Plaque: 4–6 sites vs. 0		6.51	2.85	0.02		4.67	3.01	0.12
TMT-B[2]	1168				1133			
Plaque: 1–3 sites vs. 0		4.71	3.68	0.20		0.88	3.84	0.82
Plaque: 4–6 sites vs. 0		12.82	6.06	0.03		7.81	6.31	0.22
DSST[3]	1188				1140			
Plaque: 1–3 sites vs. 0		−0.60	0.63	0.34		0.18	0.65	0.78
Plaque: 4–6 sites vs. 0		−1.75	1.03	0.09		−0.50	1.07	0.64
AVLT[4]	1185				1110			
Plaque: 1–3 sites vs. 0		0.02	0.42	0.97		0.27	0.44	0.54
Plaque: 4–6 sites vs. 0		0.38	0.68	0.58		0.92	0.71	0.20
VFT[5]	1223				1203			
Plaque: 1–3 sites vs. 0		1.02	0.70	0.14		01.02	0.73	0.16
Plaque: 4–6 sites vs. 0		0.12	1.13	0.92		0.04	1.18	0.98

Multivariable models are further adjusted for

[1] HDL cholesterol, hemoglobin A1C, SF-mental score, and antihypertensive medications;

[2] antihypertensive medications, smoking, heavy drinking, BMI, SF-36 mental score;

[3] antihypertensive medications, BMI, smoking, hemoglobin A1C, and SF-36 mental score;

[4] antihypertensive medications, hemoglobin A1C, HDL cholesterol, BMI, NSAIDs, and SF-36 mental score;

[5] antihypertensive medications, and smoking.