Atherosclerosis, Dementia, and Alzheimer Disease in the Baltimore Longitudinal Study of Aging Cohort

Hillary Dolan, MA,[1] Barbara Crain, MD,[3] Juan Troncoso, MD,[3] Susan M. Resnick, PhD,[4] Alan B. Zonderman, PhD,[4] and Richard J. OBrien, MD, PhD[1,2]

Objective: Although it is now accepted that asymptomatic cerebral infarcts are an important cause of dementia in the elderly, the relationship between atherosclerosis per se and dementia is controversial. Specifically, it is unclear whether atherosclerosis can cause the neuritic plaques and neurofibrillary tangles that define Alzheimer neuropathology and whether atherosclerosis, a potentially reversible risk factor, can influence cognition independent of brain infarcts.

Methods: We examined the relationship between systemic atherosclerosis, Alzheimer type pathology, and dementia in autopsies from 200 participants in the Baltimore Longitudinal Study of Aging, a prospective study of the effect of aging on cognition, 175 of whom had complete body autopsies.

Results: Using a quantitative analysis of atherosclerosis in the aorta, heart, and intracranial vessels, we found no relationship between the degree of atherosclerosis in any of these systems and the degree of Alzheimer type brain pathology. However, we found that the presence of intracranial but not coronary or aortic atherosclerosis significantly increased the odds of dementia, independent of cerebral infarction. Given the large number of individuals with intracranial atherosclerosis in this cohort (136/200), the population attributable risk of dementia related to intracranial atherosclerosis (independent of infarction) is substantial and potentially reversible.

Interpretation: Atherosclerosis of the intracranial arteries is an independent and important risk factor for dementia, suggesting potentially reversible pathways unrelated to Alzheimer pathology and stroke through which vascular changes may influence dementia risk.

ANN NEUROL 2010;68:231–240

Cerebral infarction and Alzheimer disease (AD) are leading and independent causes of dementia in the elderly.[1–8] Systemic atherosclerosis has also been suggested to play a role in cognitive deterioration in the elderly[9,10] and several studies have proposed that systemic atherosclerosis can increase Alzheimer pathology directly, thus making Alzheimer pathology potentially remediable with the treatment of systemic atherosclerosis.[11–16] The effect of atherosclerosis on dementia has also been attributed to its relation to cerebral infarction[1,3,5,6,8] or to systemic or local factors that underlie both atherosclerosis and cognition.[10,17–19] Alternatively, atherosclerosis and AD pathology may reflect a common underlying process leading to a relationship between the 2 pathologies. Prospective cohorts with postmortem brain evaluations have been important in attempts to understand the etiology of dementia in the elderly. Such studies are uniquely able to investigate associations between cognitive changes during life and a variety of pathological findings at autopsy, including AD pathology, atherosclerosis, macroscopic and microscopic infarcts, and Lewy body pathology.[4] We report here the results of the Baltimore Longitudinal Study of Aging (BLSA) Autopsy Program, a prospective study of the effects of aging on cognition and dementia. The large number of subjects in this study with complete autopsies makes it an important resource for elucidating the contri-

Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/ana.22055

Received Oct 31, 2009, and in revised form Mar 30, 2010. Accepted for publication Apr 2, 2010.

Address correspondence to Dr OBrien, Mason F Lord Center Tower, Suite 5100, Johns Hopkins Bayview Medical Center, 5200 Eastern Ave, Baltimore MD 21224. E-mail: robrien@jhmi.edu

From the [1]Department of Neurology and [2]Department of Medicine, Johns Hopkins Bayview Medical Center; [3]Department of Pathology, Johns Hopkins University; and [4]National Institute on Aging, Intramural Research Program, Laboratory of Personality and Cognition, National Institutes of Health, Baltimore, MD.

© 2010 American Neurological Association

bution of systemic atherosclerosis to dementia and the mechanisms underlying these effects. We report that coronary, intracranial, and aortic atherosclerosis are not correlated with brain AD pathology, although intracranial atherosclerosis uniquely and significantly increases the odds of dementia independent of cerebral infarcts.

Subjects and Methods

Cohort

A total of 579 participants from the BLSA have agreed to postmortem brain exams. The rate of dementia and clinical stroke in the autopsy cohort is similar to that in the BLSA cohort as a whole.[20] As of January 2009, 216 subjects have died and underwent brain autopsy (88% autopsy rate). Of this group, we excluded 15 subjects who had other pathological explanations for cognitive impairment; 9 had both a clinical and a pathological diagnosis of Parkinson disease (subjects with Parkinson disease were specifically sought out for the autopsy cohort at its inception and are thus not representative of the cohort as a whole), 1 had a primary brain tumor, 1 had an inflammatory leukoencephalopathy, 1 had metastatic brain lesions, and 3 had hippocampal sclerosis combined with frontotemporal dementia. An additional participant was excluded because language deficits from a clinical stroke compromised assessment of cognition. These exclusions left 200 individuals for the present analysis (133 men, 67 women). Participants were predominantly white (94%), with a mean of 17.1 $\pm$ 3.9 (standard deviation [SD]) years of education. The mean age at death was 87.6 $\pm$ 7.1 years.

All participants in the present study were cognitively and neurologically normal at the time of entry into the BLSA and the autopsy cohort. They were assessed at baseline, within 18 months of death (mean of 8.7 $\pm$ 6.3 months prior to death), and periodically in between. The majority were seen annually after age 70 years, although approximately 25% of the cohort had gaps in their follow-up of several years duration. Using Fisher exact test, the percentages of subjects with dementia or any pathologic infarct did not differ significantly between the group with annual evaluations (n = 154) and those with less intense follow-up (n = 46). Studies of this cohort are conducted under the auspices of the Johns Hopkins and MedStar Research Institute institutional review boards, and all participants provided written informed consent.

Neuropsychological and Risk Factor Evaluation

Evaluations included neuropsychological tests, neurological exam, interval medical history, medication review, and a structured informant and subject interview as described.[21] A diagnosis of diabetes or hypertension required both a documented history and the use of at least 1 medication for that condition over >1 visit. A diagnosis of coronary artery disease (CAD) required a history of myocardial infarction or CAD plus medication prescribed to treat CAD. Smoking history (any history of smoking) was obtained from a BLSA questionnaire obtained during yearly assessment. Apolipoprotein E (ApoE) genotype was obtained for 154 of the 200 subjects with brain autopsies and 133 of the 175 subjects with complete autopsies. Fasting total cholesterol levels were obtained, off medication, on entry into the study.

Diagnosis of Dementia

All participants were reviewed at a consensus conference at time of death or during life if their Blessed Information Memory Concentration score[22] was $\geq$3, if their informant or subject Clinical Dementia Rating[23] score was $\geq$0.5 or if the Dementia Questionaire[24] was abnormal. Diagnoses of dementia were based on Diagnostic and Statistical Manual of Mental Disorders, revised third edition criteria. The diagnosis of dementia required evidence of a progressive cognitive syndrome, including memory decline.

General Autopsies

At the time of death, subjects underwent either complete (n = 175) or brain-only autopsy (n = 25). Information about atherosclerosis in the heart, aorta, or brain was transcribed from the autopsy report by an assistant blinded to the purpose of the study and without information regarding the cognitive diagnosis, Consortium to Establish a Registry for Alzheimer's Disease (CERAD), or Braak scores. In grading atherosclerosis, we sought to divide the subjects into 3 groups, 1 with only minimal atherosclerosis (grade 1), 1 with severe atherosclerosis (grade 3), and 1 with an intermediate grade (grade 2). We defined severe atherosclerosis (grade 3) based on generally accepted criteria[25–27] and attempted to include at least 35 subjects in each group to provide statistical power. We had no limit on the number of subjects categorized as grade 1. Subjects were divided into atherosclerosis groups without knowledge of the end organ damage or risk factors against which the atherosclerosis would be correlated (brain or myocardial infarcts, abdominal aneurysms, hypertension, cholesterol), and without knowledge of Braak and CERAD scores. Although there was variability in the pathologists performing the general autopsies, which is a limitation of our analysis, we found no significant variation in atherosclerosis grade that was dependent on the performing pathologist.

Cardiac Atherosclerosis (n = 175)

For all complete autopsies, serial 3-to 5mm axial sections of all the major cardiac vessels along their length were taken and examined for atherosclerosis. Estimates of degree of stenosis were made visually by the performing pathologist. Old myocardial infarcts were diagnosed by the presence of discrete areas of fibrosis and replacement of muscular tissue. Coronary atherosclerosis was graded in the following 3 categories. Grade 1 (n = 41) included subjects who had no atherosclerotic plaques or atherosclerotic plaques and no stenosis beyond 20% in a single vessel. Grade 3 (n = 55) required >50% stenosis in 2 of 4 major cardiac vessels (left main, circumflex, left anterior descending coronary artery, right coronary artery). Grade 2 (n = 77) included subjects intermediate to grades 1 and 3 and consisted mainly of subjects with high grade (>50%) disease in 1 vessel or more diffuse but less obstructing disease.

Aortic Atherosclerosis (n = 175)

All aortas were opened longitudinally along their entire length (ascending, thoracic, and abdominal) and examined for the degree of atherosclerosis (confluent [extending circumferentially] or nonconfluent) and the presence of complexities, including ulcerations and protrusions. The presence of abdominal aneurysms was also noted. The presence of an aneurysm did not change the atherosclerosis grade. All subjects in the study had some degree of aortic atherosclerosis. A grade of 1 (n = 39) was assigned if atherosclerotic aortic plaques were not confluent (extending around the circumference of the aorta) and if plaque ulceration and protrusions were absent. Grade 3 (n = 69) required confluent plaques and either multifocal ulceration or protrusions. Grade 2 (n = 61) was intermediate, and for the most part included subjects with confluent areas of plaques but either no ulceration or 1 area of ulceration and minimal protrusions.

Intracranial Atherosclerosis (n = 200)

All subjects had an examination of the intracranial circulation including the circle of Willis, carotid siphon, distal internal carotid arteries, intracranial vertebral arteries, basilar artery, and proximal portions of the middle, anterior, and posterior cerebral arteries. We did not have data on the carotid bifurcation, as this was not included with the brain when it was removed from the body and was usually not described by the pathologist performing the autopsy. All vessels were inspected visually; areas of atherosclerosis were identified and then sectioned to determine the degree of stenosis (in most cases by visual estimation without measurement). Grade 1 intracranial atherosclerosis (n = 51) required no stenotic lesions (defined as ≥20%) in any vessel. Grade 3 (n = 47) required a stenosis of ≥40% in 2 vessels. Grade 2 (n = 71) was assigned for intermediate lesions, which for the most part included single-vessel disease or multiple low-grade stenoses. The extent and number of intracranial vessels that were examined in subjects with complete autopsies was identical to those examined in subjects with brain-only autopsies, as in both cases the vessels examined were those that came with the brain when it was removed from the skull.

Composite Atherosclerosis Grade (n = 175)

A composite atherosclerosis grade was generated by adding the grades of the 3 individual atherosclerosis scores (aortic, cardiac, and intracranial; range, 3–9) and then dividing them into 4 groups with similar numbers of subjects from minimal to severe systemic atherosclerosis. Grade 1 composite atherosclerosis had total atherosclerosis scores of 3 and 4 (n = 39), grade 2 had total atherosclerosis scores of 5 and 6 (n = 58), grade 3 had a total atherosclerosis score of 7 (n = 45), and grade 4 had total atherosclerosis scores of 8 and 9 (n = 37).

Brain Pathology

Postmortem examination of all brains was performed at Johns Hopkins by a neuropathologist; neuritic plaques and neurofibrillary tangles were assessed as described.[8] Macroscopic infarcts were assessed on the basis of visual inspection of 1cm coronal slices of both hemispheres. Microscopic infarcts were determined from 1.5cm hematoxylin and eosin–stained sections obtained from the middle frontal, superior and middle temporal, parietal, occipital, cingulate, orbitofrontal, basal forebrain, and entorhinal cortex, as well as the hippocampus, basal ganglia, amygdala, thalamus, midbrain, pons, medulla, and cerebellum. Infarcts judged acute or subacute, based on macroscopic and microscopic features, were not included in this analysis. Ninety of the 200 subjects had at least 1 old (cavitary) brain macroscopic or microscopic infarct. AD pathology was examined on silver stains and graded according to CERAD and Braak criteria.[28,29] For CERAD scoring, we determined both the maximum neuritic plaque score seen in all 4 cortical regions examined (peak CERAD score) and the mean of the peak scores in each of the 4 cortical regions examined (mean CERAD score). In addition, we generated a composite AD pathology score by summing the CERAD and Braak scores in equal measure. CERAD scores were assigned to 3 groups with 1 = zero or mild neuritic plaques, 2 = moderate neuritic plaques, and 3 = frequent neuritic plaques. Braak scores were divided into 3 groups with 1 = Braak stages 0, I, and II; 2 = Braak stages III and IV; and 3 = Braak stages V and VI. The sum of the modified Braak and CERAD scores yielded a composite score ranging from 2 to 6. The composite AD pathology score has been shown to correlate closely with cognitive status in this cohort.[8] Cerebral white matter ratings were not included in this analysis.

Statistics

Potential predictors of dementia were analyzed using univariate and stepwise multivariate logistic regression with dementia as the dependent variable. All models included age at death and sex as covariates. Age was examined as both a continuous variable and categorized in quartiles or tertiles without any difference in the results. Comparisons of mean AD pathology scores in different atherosclerosis groups were performed using a 1-way analysis of variance (ANOVA). Nonparametric correlations between discrete vascular risk factors and atherosclerosis and between atherosclerosis grades and AD pathology were made using Spearman rank correlation and ordinal regression. Ordinal regression analyses were adjusted for age and sex. Power analyses using G*Power software demonstrated an 80% certainty of excluding 1-way effects (increasing atherosclerosis leading to increasing AD pathology scores) of ≥30% both in the ANOVA (group 1 vs group 3) and the Spearman rank test.

Results

Atherosclerosis Grades Correlate with End Organ Damage

Blinded atherosclerosis grades in each of the 3 vascular systems correlated with accepted atherosclerotic endpoints (Fig 1). After adjusting for age, sex, hypertension, and the presence of diabetes, a unit increase in the cardiac atherosclerotic grade was associated with a 6.1-(3.3-to 11.2-) fold increase in the odds of a myocardial infarction. Increasing aortic atherosclerosis grades were associated with a 3.0-(1.3-to 7.1-) fold increase in the odds of an abdom-

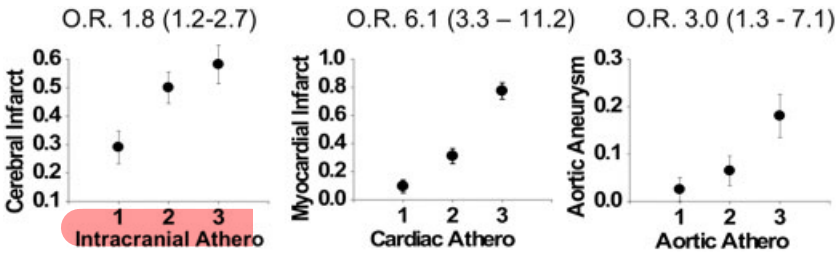

FIGURE 1: Relationship between regional atherosclerosis (Athero) and regional vascular endpoints. Intracranial, cardiac, and aortic atherosclerosis grades are plotted ± standard error against the rate of any coincident cerebral infarct, myocardial infarct, or aortic aneurysm being present (respectively) in the same autopsy specimen. All relationships are significant at the 0.01 level using logistic regression. The odds ratio (O.R.) indicates the increase in odds of the indicated outcome with a step increase in the regional atherosclerosis grade, adjusting for age and sex. Relationships with intracranial atherosclerosis are based on 200 autopsies, whereas aortic and cardiac atherosclerosis are based on 175 autopsies.

inal aortic aneurysm per unit increase in aortic atherosclerosis grade, whereas increasing intracranial atherosclerosis was associated with a 1.8-(1.2-to 2.7-) fold increase in the odds of a cerebral infarct per unit increase whether analyzed in the 175 subjects with complete autopsies or the 200 subjects with complete or brain-only autopsies. Interestingly, only aortic atherosclerosis showed a significant relationship with baseline cholesterol (rho = 0.26; p = 0.001; Spearman rank test) and smoking history (rho = 0.20; p = 0.01). There was also a significant correlation between the degree of atherosclerosis in 1 vascular bed with the degree of atherosclerosis in another (mean rho = 0.25; p = 0.001; Spearman rank test). It should be noted that although we corrected for age at death in all our analyses, there was no statistical difference in the mean age of death between groups with minimal and maximal atherosclerosis grades.

Atherosclerosis Grades Do Not Correlate with AD Pathology

To examine the association between atherosclerosis and Alzheimer pathology, we plotted intracranial, aortic, coronary, and composite atherosclerosis grades against peak CERAD score, mean CERAD score, Braak score, and composite AD pathology score (Fig 2). Using ANOVA or ordinal regression, adjusting for age at death and sex, or an unadjusted Spearman rank test (Table 1), there were no significant relationships between any AD pathology score and any atherosclerosis grade. The lack of significant associations was observed in analyses of AD pathology scores in subjects with mild, moderate, and severe atherosclerosis (grades 1–3) and in comparisons of subjects with mild versus severe atherosclerosis (grade 1 vs grade 3; see Table 1). Moreover, there was no relationship between AD pathology scores and atherosclerotic outcomes such as stroke (below) and the presence of a myocardial infarction on autopsy (not shown). The presence of an ApoE4 allele had no effect on systemic atherosclerosis or on the relationship between atherosclerosis and AD pathology (not shown), although the number of ApoE4-positive subjects with total body autopsies in this cohort was small (35/133).

To investigate local relationships between atherosclerosis and AD pathology, we performed 2 additional analyses. In the first, we compared the superior and middle temporal gyrus (SMTG) CERAD scores in subjects with ≥50% stenoses of the ipsilateral distal internal carotid or proximal middle cerebral artery (n = 27) with SMTG CERAD scores in subjects with minimal intracranial atherosclerosis (n = 51). No difference was seen in the SMTG CERAD score distal to these severe ipsilateral stenoses (1.4 ± 1.2) compared to the SMTG CERAD score in subjects with minimal intracranial atherosclerosis (mean ± SD, 1.5 ± 1.1; odds ratio, 1.0; 95% confidence interval, 0.7–1.3). Second, SMTG CERAD scores were no different in subjects with ipsilateral middle cerebral artery territory infarcts (1.5 ± 1.2; n= 37) and no history of atrial fibrillation or congestive heart failure (to isolate the effect of atherosclerosis) than in subjects with minimal intracranial atherosclerosis, no cerebral infarcts, and no history of atrial fibrillation or congestive heart failure (1.4 ± 1.1; n = 41).

Intracranial Atherosclerosis Correlates with Dementia Independent of Brain Infarcts

Despite the lack of relation between atherosclerosis and AD pathology, we observed a relation between intracranial atherosclerosis and dementia that was independent of the presence of cerebral infarcts. As shown in Figure 3 and Table 2, increasing intracranial, but not aortic or cardiac, atherosclerosis significantly increased the odds for dementia. Univariate odds for dementia increased by a factor of 2.0 per unit increase in intracranial atherosclerosis grade and increased by a factor of 2.7 for any intracranial atherosclerosis grade other than 1. The magnitude of the effect was not changed by including age, sex, AD

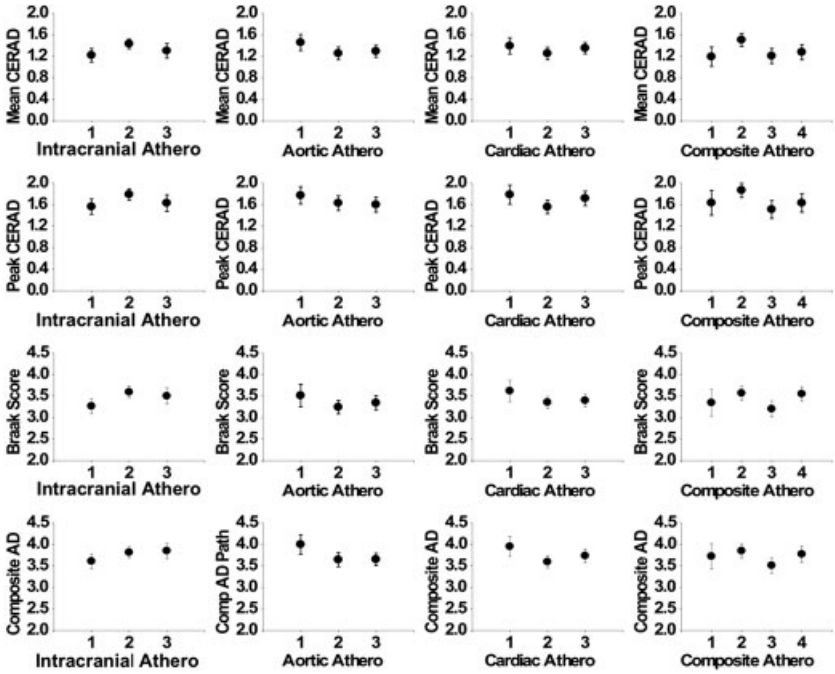

FIGURE 2: The relationship between atherosclerosis (Athero) and Alzheimer disease (AD) pathology. Multiple indicators of cerebral AD pathology are plotted against the degree of intracranial, cardiac, aortic (graded on a 3-point scale), and composite atherosclerosis (graded on a 4-point scale) ± standard error. None of the relationships is significant. Associations with intracranial atherosclerosis include data from 200 autopsies, and associations with aortic and cardiac atherosclerosis include data from 175 autopsies. CERAD = Consortium to Establish a Registry for Alzheimer's Disease.

pathology, stroke risk factors, and, most importantly, the presence of cerebral infarcts (including microscopic infarcts) as covariates (Table 3). To further verify that the effect of intracranial atherosclerosis on dementia was independent of infarction, we analyzed the data from the 110 subjects without any cerebral infarcts (see Table 3) and found the same result.

Given the large number of individuals in our cohort with intracranial atherosclerosis grades >1 (136/200), the population attributable risk of dementia related to intracranial atherosclerosis (independent of infarction) is substantial, in spite of the relatively modest odds ratio. The rate of dementia in subjects with atherosclerosis above grade 1 is 82/136; in subjects with grade 1 intracranial atherosclerosis, it is 22/64. Given the total incidence of dementia in the cohort (104/200), the percent of dementia that is attributable to intracranial atherosclerosis, independent of cerebral infarcts, in this cohort is 34%. Looking at the same data using a multivariate logistic regression model (Table 4), a intracranial atherosclerosis grade >1, a composite AD pathology score >3, and any brain infarct were each independent predictors of dementia. Although AD pathology was associated with the largest increase in the odds of dementia, intracranial atherosclerosis was still associated with a substantial increase in the odds of dementia, with a significantly higher population at risk than either stroke or high AD pathology score.

Discussion

Relationship between Atherosclerosis and AD

Using a series of 200 autopsies from prospectively followed subjects in the Baltimore Longitudinal Study of Aging, 175 of whom had total body autopsies, we have found that the presence of intracranial atherosclerosis uniquely increased the odds of dementia independent of Alzheimer pathology or cerebral infarcts. There was no significant relationship between systemic or localized atherosclerosis and brain AD pathology. The etiologic role of atherosclerosis in the development of AD pathology[12,13] and the relationship between atherosclerosis and dementia independent of its association with stroke[1–8] have been controversial. Clinical studies of the association of atherosclerosis risk factors and dementia have shown positive associations between dementia and carotid atherosclerosis, ankle-brachial blood pressure ratio, cardiovascular risk factors, and electrocardiographic abnormalities.[10,17–19]

Two studies have looked at the relationship between ultrasound-visualized atherosclerosis and dementia in vivo. The Rotterdam study[17] found a correlation between carotid atherosclerosis, determined by ultrasound, and the diagnosis of AD. Another group[30] found an association between atherosclerosis in the circle of Willis (measured by transcranial Doppler) and the diagnosis of Alzheimer dementia. These studies are important but limited by

TABLE 1: The Relationship between Systemic Atherosclerosis and Alzheimer Pathology

Analysis	Peak CERAD	Mean CERAD	Braak Score	Composite AD Score
ANOVA, corrected for age and sex, *p*				
Intracranial atherosclerosis	0.52	0.48	0.74	0.77
Intracranial atherosclerosis, grade 1 vs grade 3	0.72	0.69	0.83	0.49
Cardiac atherosclerosis	0.41	0.59	0.33	0.26
Cardiac atherosclerosis, grade 1 vs grade 3	0.76	0.99	0.32	0.39
Aortic atherosclerosis	0.71	0.67	0.32	0.43
Aortic atherosclerosis, grade 1 vs grade 3	0.44	0.39	0.20	0.24
Composite atherosclerosis	0.28	0.17	0.30	0.48
Composite atherosclerosis, grade 1 vs grade 4	0.69	0.62	0.71	0.88
Ordinal regression, corrected for age and sex, odds ratio (95% CI)				
Intracranial atherosclerosis	1.0 (0.7–1.5)	1.1 (0.8–1.6)	1.1 (0.8–1.5)	1.1 (0.8–1.6)
Intracranial atherosclerosis, grade 1 vs grade 3	1.1 (0.6–2.2)	1.2 (0.6–2.4)	1.0 (0.6–2.1)	1.2 (0.6–2.3)
Cardiac atherosclerosis	0.9 (0.6–1.4)	1.0 (0.7–1.3)	0.9 (0.6–1.3)	0.9 (0.6–1.3)
Cardiac atherosclerosis, grade 1 vs grade 3	0.8 (0.4–1.7)	0.9 (0.5–1.9)	0.8 (0.4–1.7)	0.8 (0.4–1.6)
Aortic atherosclerosis	0.9 (0.6–1.2)	0.9 (0.6–1.2)	0.8 (0.6–1.2)	0.9 (0.6–1.2)
Aortic atherosclerosis, grade 1 vs grade 3	0.8 (0.4–1.6)	0.8 (0.4–1.4)	0.8 (0.4–1.4)	0.8 (0.4–1.4)
Composite atherosclerosis	0.9 (0.7–1.2)	1.0 (0.7–1.3)	1.0 (0.8–1.3)	1.0 (0.7–1.3)
Composite atherosclerosis, grade 1 vs grade 4	1.1 (0.5–2.7)	1.1 (0.8–1.5)	1.2 (0.6–2.3)	1.1 (0.5–2.8)
Spearman rank test, rho (*p*)				
Intracranial atherosclerosis	0.03 (0.68)	0.06 (0.39)	0.09 (0.24)	0.08 (0.32)
Intracranial atherosclerosis, grade 1 vs grade 3	0.02 (0.84)	0.07 (0.43)	0.09 (0.34)	0.08 (0.38)
Cardiac atherosclerosis	−0.03 (0.69)	−0.01 (0.93)	−0.01 (0.93)	−0.04 (0.62)
Cardiac atherosclerosis, grade 1 vs grade 3	−0.04 (0.69)	0.00 (0.98)	−0.02 (0.83)	−0.06 (0.58)
Aortic atherosclerosis	−0.06 (0.42)	−0.05 (0.46)	−0.06 (0.40)	−0.06 (0.40)
Aortic atherosclerosis, grade 1 vs grade 3	−0.08 (0.35)	−0.09 (0.33)	−0.10 (0.26)	−0.10 (0.29)
Composite atherosclerosis	−0.05 (0.51)	−0.01 (0.85)	0.02 (0.78)	−0.01 (0.85)
Composite atherosclerosis, grade 1 vs grade 4	0.01 (0.91)	0.08 (0.48)	0.11 (0.37)	0.03 (0.77)

The significance of the relationship between increasing intracranial, cardiac, aortic, and composite atherosclerosis grades and 4 measures of Alzheimer pathology was tested using several parametric and nonparametric tests. We compared the entire spectrum of atherosclerosis for each vascular bed against the AD pathology endpoints, or simply compared the group with minimal atherosclerosis in each vascular bed against the group with the maximal atherosclerosis in each vascular bed (grade 1 vs grade 3 in the case of intracranial, aortic, and cardiac atherosclerosis, or grade 1 vs grade 4 in the case of composite atherosclerosis). The intracranial atherosclerosis data are from 200 autopsies; the aortic and cardiac data are from 175. Spearman rank test was not corrected for age and sex, whereas ordinal regression and ANOVA were. None of the relationships are significant.
CERAD = Consortium to Establish a Registry for Alzheimer's Disease; AD = Alzheimer disease; ANOVA = analysis of variance; CI = confidence interval.

their inability to exclude stroke, increasing AD pathology, or other mechanisms as the proximate cause of the increased rate of dementia in subjects with intracranial atherosclerosis.

Autopsy studies[14–16] have found an association between circle of Willis atherosclerosis and AD in retrospective convenience samples of postmortem autopsies. However, because these studies were not prospective and lacked cognitively normal older subjects with AD pathology, who are common in most prospective studies of the elderly,[31] they were not able to determine whether the increased atherosclerosis in subjects with AD was due to

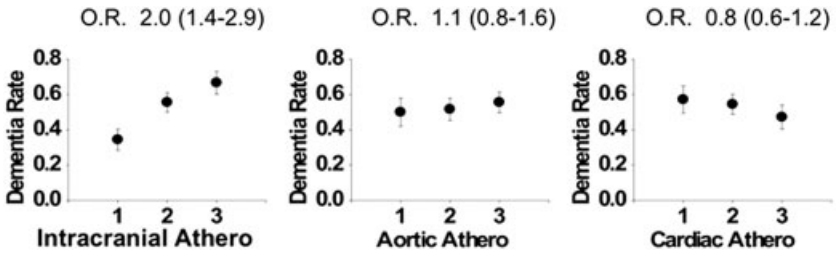

FIGURE 3: The relationship between atherosclerosis (Athero) and dementia. Intracranial, cardiac, and aortic atherosclerosis grades are plotted ± standard error against the dementia rate for subjects with those grades. The odds ratio (O.R.) refers to the increase in odds of dementia for a step increase in the regional atherosclerosis grade, adjusting for age and sex. Associations with intracranial atherosclerosis include data from 200 autopsies, whereas associations with aortic and cardiac atherosclerosis include data from 175 autopsies.

an effect of atherosclerosis on AD pathology or was simply due to an additive effect of 2 independent pathologies (Alzheimer pathology and atherosclerosis) on cognition. In addition, none of these studies controlled for microscopic infarcts, a significant cause of dementia in several prospective cohorts.[6,8,32,33] Although our data suggest that variations in atherosclerosis as seen in our cohort are not related to variations in AD pathology, we cannot exclude the possibility that extreme levels of atherosclerosis are related to increases in AD pathology scores in some cases.

TABLE 2: Relationship between Systemic Atherosclerosis and Dementia: Odds of Dementia per Step Increase in Atherosclerosis Grade

Atherosclerosis Type	Univariate Analysis
Intracranial atherosclerosis (n = 200)	2.0 (1.4–2.9)
Intracranial atherosclerosis (1 vs 2 + 3; n = 200)	2.9 (1.5–5.3)
Cardiac atherosclerosis (n = 175)	0.8 (0.6–1.2)
Aortic atherosclerosis (n = 175)	1.1 (0.8–1.6)
Intracranial atherosclerosis (n = 175)	1.9 (1.2–3.1)

A univariate logistic regression analysis examined the relationship between atherosclerosis in different vascular beds and dementia. For intracranial, aortic, and cardiac atherosclerosis, we calculated the increasing odds of dementia per step increase in atherosclerosis grade (1–3). For intracranial atherosclerosis, we also determined the increase in the odds of dementia for any grade >1 (1 vs 2 + 3). The intracranial atherosclerosis data were analyzed both in the 175 subjects who had complete autopsies and in the 200 who had either complete or brain–only autopsies.

Presence of Intracranial Atherosclerosis Increases the Odds of Dementia but Does Not Affect AD Pathology

Our data are consistent with reports showing a relationship between atherosclerosis and dementia,[34] and extend those results in several important ways. First, the relationship appears to be due to the atherosclerosis itself. Adjusting for diabetes, smoking, hypertension, and cholesterol did not influence our findings. We were not able to adjust for homocysteine levels, but suspect this is unrelated,

TABLE 3: Relationship between Systemic Atherosclerosis and Dementia: Odds of Dementia per Step Increase in Intracranial Atherosclerosis Grade

Covariates, n = 200	Multivariate Analysis
Age, sex	1.9 (1.3–2.8)
Age, sex, DM, HTN	2.0 (1.3–3.0)
Age, sex, DM, HTN, any brain infarct	1.9 (1.3–2.8)
Age, sex, DM, HTN, CVA, chol, smoking	1.8 (1.2–3.0)
Age, sex, DM, HTN, any cortical infarct	1.9 (1.2–3.0)
Age, sex, DM, HTN, CVA, AD pathology	2.0 (1.4–3.4)
Subjects with no infarcts (n = 110)	1.9 (1.1–3.9)

The odds of dementia per step increase in intracranial atherosclerosis grade was calculated using the indicated factors as covariates. In the subjects with no infarcts (n = 110), the odds of dementia due to intracranial atherosclerosis was corrected for age, sex, DM, HTN, and AD pathology.
DM = diabetes mellitus; HTN = hypertension; CVA = cerebrovascular accident; chol = high cholesterol; AD = Alzheimer disease.

TABLE 4: Relationship between Systemic Atherosclerosis and Dementia: Logistic Regression Model Using the Indicated Threshold Variables

Multivariate Model, n = 200	Odds of Dementia	Number at Risk
Any cerebral infarct	3.4 (1.7–6.8)	90
Composite AD pathology score >3	6.0 (3.0–12)	115
Intracranial atherosclerosis >1	2.7 (1.3–5.7)	135

as homocysteine is related to generalized atherosclerosis, not specifically to intracranial atherosclerosis.[35] Second, atherosclerosis and dementia are related only for intracranial atherosclerosis, but not for cardiac or aortic atherosclerosis. This implies that the effect of atherosclerosis on cognition is local and not mediated by more systemic underlying processes that might be common to atherosclerosis in all vascular beds. Atherosclerosis in the intracranial circulation is likely to have significant differences from atherosclerosis in other beds, as the prevalence of intracranial atherosclerosis shows a poor correlation with atherosclerosis at the carotid bifurcation[36,37] and in the coronary arteries.[38,39] Indeed, in our own cohort, the correlation between the severity of intracranial atherosclerosis and the severity of coronary and aortic atherosclerosis was only 25%, implying some degree of heterogeneity between atherosclerosis in these vascular beds, as was also demonstrated in the CAPRIE study.[39] Understanding the mechanisms for these heterogeneities and the unique risk factors for intracranial atherosclerosis are important future research endeavors.

Two possible explanations, a priori, for the unique association between intracranial atherosclerosis and dementia would be through an effect on the number of brain infarcts or an increase in AD pathology. However, we found neither of these enticing possibilities was the explanation for our results, although both AD pathology and infarcts are independent and powerful predictors of dementia in this cohort.[8] We observed no significant association between atherosclerosis in any vascular bed and measures of AD pathology such as Braak, CERAD, or composite AD pathology score. Furthermore, we did not find that the presence of an ApoE4 allele influenced this relationship. This result is similar to that found by Itoh and colleagues,[40] who found no association between AD pathology and aortic, cardiac, or intracranial atherosclerosis in a convenience sample of autopsies from elderly subjects, but differs from that of Beeri and colleagues,[41] who found a relationship between neuritic plaques and coronary atherosclerosis (mostly in ApoE4 carriers) in a retrospective convenience sample of 99 brains, 36 of whom were ApoE4 positive. We offer the prospective nature of our cohort, and its larger total numbers, as an important addition to this debate.

Although intracranial atherosclerosis was related to the presence of cerebral infarcts, this effect did not account for the magnitude of the observed effect of atherosclerosis on dementia risk. Although it is likely that some microscopic strokes were unaccounted for in our postmortem analysis, accounting for the presence of any infarct (microscopic or macroscopic) did not affect the association of intracranial atherosclerosis and dementia risk, making it unlikely that unidentified microscopic infarcts were the cause of the association between intracranial atherosclerosis and dementia, although we did not rigorously exclude a role for watershed infarcts in this association.

Intracranial Atherosclerosis and Dementia

Because intracranial atherosclerosis appears to be additive to, yet independent of, AD pathology in the etiology of dementia in the elderly, the question of its mechanism of action deserves consideration. As detailed in our prior work,[8] cerebral infarcts are a significant cause of dementia in the BLSA cohort. Our current study, however, suggests that there is an additional association between intracranial atherosclerosis and cognition that is independent of cerebral infarctions. Our results are similar to those recently described in a cohort of subjects selected on the basis of significant preexisting cerebrovascular disease, where pathological measures of intracranial atherosclerosis were predictors of gray matter volume independent of AD pathology, and are similar to a recent retrospective pathologic study suggesting that circle of Willis atherosclerosis is significantly related to dementia.[34] Our results extend these observations to a larger, more generalizable, prospective cohort and emphasize the specific role of intracranial atherosclerosis in clinical dementia outcomes.[42]

Possible explanations for the association between intracranial atherosclerosis and dementia include a common mechanism that results in intracranial atherosclerosis and cerebral dysfunction, such as oxidative stress,[43,44] white matter disease,[45] toxic yet soluble amyloid species,[46,47] or the expression of inflammatory mediators within blood vessels or brain parenchyma, including the receptor for advanced glycation end products.[48–50] Alternatively, large-vessel intracranial atherosclerosis could be a marker for dysfunction of small cerebral vessels and their endothelium that might be the proximate cause of cognitive deterioration, either through disruption of the communication between neurons and blood vessels (the neurovascular unit) that underlies activity-induced vasodilata-

tion,[51–53] or through disruption of the blood-brain barrier.[54] Clearly this deserves further investigation, as these represent processes that can be prevented.

Limitations of Current Study

Although our study is prospective, our participants are not generalizable to the entire population; the majority are Caucasian and well educated. However, the relative uniformity of the sample lends strength in isolating particular interactions. Moreover, we had no data on carotid bifurcation atherosclerosis, which would have added strength to this study. Finally, because our sample size is limited, small effects of severe atherosclerosis on AD pathology cannot be excluded. This analysis might have been facilitated if we had available more quantitative counts of plaque and tangle density. Nevertheless, our study indicates that intracranial atherosclerosis, which is potentially preventable and whose number 1 risk factor is hypertension,[55] is significantly associated with the burden of dementia in the United States, independent of its effect on cerebral infarcts.

Acknowledgment

Supported by National Institute on Aging grant P50 AG05146 RO, JT, the Burroughs Wellcome Fund for Translational Research 1005227 RO, and the Intramural Research Program, National Institute on Aging SR, AZ, NIH.

Potential Conflicts of Interest

Nothing to report.

References

1. Snowdon DA, Greiner LH, Mortimer JA, et al. Brain infarction and the clinical expression of Alzheimer disease. The Nun Study. JAMA 1997;277:813–817.
2. Schneider JA, Wilson RS, Cochran EJ, et al. Relation of cerebral infarctions to dementia and cognitive function in older persons. Neurology 2003;60:1082–1088.
3. Schneider JA, Wilson RS, Bienias JL, et al. Cerebral infarctions and the likelihood of dementia from Alzheimer disease pathology. Neurology 2004;62:1148–1155.
4. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. Ann Neurol 2007;69:2197–2204.
5. Esiri MM, Nagy Z, Smith MZ, et al. Cerebrovascular disease and threshold for dementia in the early stages of Alzheimer's disease. Lancet 1999;354:919–920.
6. White L, Petrovitch H, Hardman J, et al. Cerebrovascular pathology and dementia in autopsied Honolulu-Asia Aging Study participants. Ann N Y Acad Sci 2002;977:9–23.
7. Sonnen JA, Larson EB, Crane PK, et al. Pathological correlates of dementia in a longitudinal, population-based sample of aging. Ann Neurol 2007;62:406–413.
8. Troncoso JC, Zonderman AB, Resnick SM, et al. Effect of infarcts on dementia in the Baltimore longitudinal study of aging. Ann Neurol 2008;64:168–176.
9. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? Neurology 2009;72:368–374.
10. Exel EV, Gussekloo J, Houx P, et al. Atherosclerosis and cognitive impairment are linked in the elderly. The Leiden 85-plus Study. Atherosclerosis 2002;165:353–359.
11. Sparks DL. Coronary artery disease, hypertension, ApoE, and cholesterol: a link to Alzheimer's disease? Ann N Y Acad Sci 1997;826:128–146.
12. Casserly I, Topol E. Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins. Lancet 2004;363:1139–1146.
13. de la Torre JC. Is Alzheimer's disease a neurodegenerative or a vascular disorder? Data, dogma, and dialectics. Lancet Neurol 2004;3:184–190.
14. Roher AE, Esh C, Rahman A, et al. Atherosclerosis of cerebral arteries in Alzheimer disease. Stroke 2004;35:2623–2627.
15. Honig LS, Kukull W, Mayeux R. Atherosclerosis and AD: analysis of data from the US National Alzheimer's Coordinating Center. Neurology 2005;64:494–500.
16. Roher AE, Esh C, Kokjohn TA, et al. Circle of Willis atherosclerosis is a risk factor for sporadic Alzheimer's disease. Arterioscler Thromb Vasc Biol 2003;23:2055–2062.
17. Hofman A, Ott A, Breteler MMB, et al. Atherosclerosis, apolipoprotein E, and prevalence of dementia and Alzheimer's disease in the Rotterdam Study. Lancet 1997;349:151–154.
18. Laurin D, Masaki KH, White LR, Launer LJ. Ankle-to-brachial index and dementia: The Honolulu-Asia Aging Study. Circulation 2007;116:2269–2274.
19. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease in the cardiovascular health study cohort. J Am Geriatr Soc 2005;53:1101–1107.
20. Gamaldo A, Resnick S, Kilada S, et al. The interaction between stroke and Alzheimer pathology on dementia in the Baltimore Longitudinal Study of Aging. Neurology 2006;67:1363–1369.
21. Kawas C, Gray S, Brookmeyer R, et al. Age-specific incidence rates of Alzheimer's disease: the Baltimore Longitudinal Study of Aging. Neurology 2004;54:2072–2077.
22. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 1968; 114:797–811.
23. Morris JC. Clinical Dementia Rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. Int Psychogeriatr 1997;9(suppl 1):173–176.
24. Kawas C, Segal J, Stewart WF, et al. A validation study of the Dementia Questionnaire. Arch Neurol 1994;51:901–906.
25. Creager M, Dzau VJ, Loscalzo J. Vascular medicine: a companion to Braunwald's heart disease. Philadelphia, PA: Saunders, 2006.
26. Libby P, Bonow R, Mann D, Zipes D. Braunwald's heart disease: a textbook of cardiovascular medicine. Philadelphia, PA: Saunders, 2007.
27. Kim JS, Caplan LR, Wong L. Intracranial atherosclerosis. Hoboken, NJ: Wiley-Blackwell, 2008.
28. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991;41:479–486.
29. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. Acta Neuropathol 1991;82:239–259.

30. Roher AE, Garami Z, Alexandrov AV, et al. Interaction of cardiovascular disease and neurodegeneration: transcranial Doppler ultrasonography and Alzheimer's disease. Neurol Res 2006;28: 672–678.

31. Driscoll I, Resnick SM, Troncoso JC, et al. Impact of Alzheimer's pathology on cognitive trajectories in nondemented elderly. Ann Neurol 2006;60:688–695.

32. Suter O-C, Sunthorn T, Kraftsik R, et al. Cerebral hypoperfusion generates cortical watershed microinfarcts in Alzheimer disease. Stroke 2002;33:1986–1992.

33. Miklossy J. Cerebral hypoperfusion induces cortical watershed microinfarcts which may further aggravate cognitive decline in Alzheimer's disease. Neurol Res 2003;25:605–610.

34. Beach TG, Wilson JR, Sue LI, et al. Circle of Willis atherosclerosis: association with Alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta Neuropathol 2007;113: 13–21.

35. Milani R, Lavie C. Homocysteine: the Rubik's cube of cardiovascular risk factors. Mayo Clin Proc 2008;83:1200–1202.

36. Suwanwela NC, Chutinetr A. Risk factors for atherosclerosis of cervicocerebral arteries: intracranial versus extracranial. Neuroepidemiology 2003;22:37–40.

37. Seo WK, Yong HS, Koh SB, et al. Correlation of coronary artery atherosclerosis with atherosclerosis of the intracranial cerebral artery and the extracranial carotid artery. Eur Neurol 2008;59: 292–298.

38. Bae HJ, Yoon BW, Kang DW, et al. Correlation of coronary and cerebral atherosclerosis: difference between extracranial and intracranial arteries. Cerebrovasc Dis 2006;21:112–119.

39. Ouriel K. Peripheral arterial disease. Lancet 2001;358:1257–1264.

40. Itoh Y, Yamada M, Sodeyama N, et al. Atherosclerosis is not implicated in association of APOE ε4with AD. Neurology 1999; 53:236–238.

41. Beeri MS, Rapp M, Silverman JM, et al. Coronary artery disease is associated with AD neuropathology in APOE 4 carriers. Neurology 2006;66:1399–1404.

42. Jagust WJ, Zheng L, Harvey DJ, et al. Neuropathological basis of magnetic resonance images in aging and dementia. Ann Neurol 2008;63:72–80.

43. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840–844.

44. D'Armiento FP, Bianchi A, de Nigris F, et al. Age-related effects on atherogenesis and scavenger enzymes of intracranial and extracranial arteries in men without classic risk factors for atherosclerosis. Stroke 2001;32:2472–2479.

45. Frisoni GB, Galluzzi S, Pantoni L, Filippi M. The effect of white matter lesions on cognition in the elderly—small but detectable. Nat Clin Pract Neurol 2007;3:620–627.

46. Wen Y, Yu WH, Maloney B, et al. Transcriptional regulation of beta-secretase by p25/cdk5 leads to enhanced amyloidogenic processing. Neuron 2008;57:680–690.

47. Walsh DM, Klyubin I, Fadeeva JV, et al. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 2002;416:535–539.

48. Arenillas JF, Alvarez-Sabín J. Basic mechanisms in intracranial large-artery atherosclerosis: advances and challenges. Cerebrovasc Dis 2005;20(suppl 2):75–83.

49. Hoshi T, Kitagawa K, Yamagami H, et al. Relation between interleukin-6 level and subclinical intracranial large-artery atherosclerosis. Atherosclerosis 2008;197:326–332.

50. Maczurek A, Shanmugam K, Munch G. Inflammation and the redox-sensitive AGE-RAGE pathway as a therapeutic target in Alzheimer's disease. Ann N Y Acad Sci 2008;1126:147–151.

51. Wollner L, McCarthy ST, Soper NDW, Macy DJ. Failure of cerebral autoregulation as a cause of brain dysfunction in the elderly. Br Med J 1979;1:1117–1118.

52. Benarroch EE. Neurovascular unit dysfunction: a vascular component of Alzheimer disease? Neurology 2007;68:1730–1732.

53. van Dijk EJ, Prins ND, Vrooman HA, et al. Progression of cerebral small vessel disease in relation to risk factors and cognitive consequences: Rotterdam Scan Study. Stroke 2008;39: 2712–2719.

54. Bell RD, Zlokovic BV. Neurovascular mechanisms and blood-brain barrier disorder in Alzheimer's disease. Acta Neuropathol 2009; 118:103–113.

55. Aboyans V, Lacroix P, Criqui MH. Large and small vessels atherosclerosis: similarities and differences. Prog Cardiovasc Dis 2007;50:112–125.