Title

Cerebral Atherosclerosis Is Associated With Cystic Infarcts and Microinfarcts but Not Alzheimer Pathologic Changes

Journal

Stroke, 44(10)

ISSN

0039-2499

Authors

Zheng, Ling
Vinters, Harry V
Mack, Wendy J
et al.

Publication Date

2013-10-01

DOI

10.1161/strokeaha.113.001945

Peer reviewed

Published in final edited form as:
Stroke. 2013 October ; 44(10): 2835–2841. doi:10.1161/STROKEAHA.113.001945.

Cerebral Atherosclerosis is Associated with Cystic Infarcts and Microinfarcts, but not Alzheimer Pathologic Changes

Ling Zheng, PhD[1], **Harry V. Vinters, MD**[2], **Wendy J. Mack, PhD**[1], **Chris Zarow, PhD**[1], **William G. Ellis, MD**[3], and **Helena C. Chui, MD**[1]

[1]Keck School of Medicine, University of Southern California, Los Angeles, CA

[2]University of California Los Angeles, Los Angeles, CA

[3]University of California Los Angeles, Los Angeles, CA

Abstract

Background and Purpose—Some studies have reported associations between intracranial atherosclerosis and Alzheimer disease (AD) pathology. We aimed to correlate severity of cerebral atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy (CAA) with neurofibrillary tangles, neuritic plaques, and cerebral infarcts.

Methods—This autopsy study (n = 163) was drawn from a longitudinal study of subcortical ischemic vascular disease, AD, and normal aging. Multivariable logistic regression models were used to test associations among the 3 forms of cerebrovascular disease and the presence of ischemic and neurodegenerative brain lesions. Apolipoprotein E genotype was included as a covariate in these multivariable models.

Results—Cerebral atherosclerosis was positively associated with microinfarcts (odds ratio (OR) = 2.3; 95% confidence interval (CI) = 1.2–4.4) and cystic infarcts (OR = 2.0, 95%CI = 1.0–4.2), but not AD pathology. Arteriolosclerosis showed a positive correlation with lacunar infarcts (OR = 2.0, 95%CI = 1.0–4.2), but not AD pathology. CAA was inversely associated with lacunar infarcts (OR = 0.6, 95%CI = 0.41–1.1), but positively associated with Braak & Braak stage (OR = 1.5, 95%CI = 1.1–2.1) and CERAD plaque score (OR = 1.5, 95%CI = 1.1–2.2).

Conclusions—Microinfarcts, which have been correlated with severity of cognitive impairment, were most strongly associated with atherosclerosis. Possible pathogenetic mechanisms include artery-to-artery emboli, especially micro-emboli that may include atheroemboli or platelet-fibrin emboli. Arteriolosclerosis was positively, while CAA was negatively correlated with lacunar infarcts, which might prove helpful in clinical differentiation of arteriolosclerotic from CAA-related vascular brain injury.

Keywords

Atherosclerosis; Alzheimer; Microinfarct; Infarct

Corresponding Author: Helena C. Chui, M.D., Professor and Chair, Department of Neurology, USC Keck School of Medicine, 1540 Alcazar St., CHP215, Los Angeles, CA 90033, Phone (323) 442-7686, chui@usc.edu.

DISCLOSURES

The authors have no financial or any other kind of personal conflicts with this paper.

INTRODUCTION

The three most prevalent forms of late-life cerebrovascular disease (CVD) are atherosclerosis, arteriolosclerosis, and cerebral amyloid angiopathy (CAA). CVD is a well-established risk factor for ischemic vascular brain injury - regions of encephalomalacia which range in size from large cystic infarcts to lacunar infarcts to microinfarcts. Microinfarcts are strongly associated with cognitive impairment, especially in non-demented subjects,[1,2] but their associations with type of CVD are unclear. CVD may also be associated with AD pathology. CAA and parenchymal AD pathology (namely neurofibrillary tangles and amyloid-neuritic plaques) are frequently seen together; both are associated with apolipoprotein E ε4 (apoE ε4) and reduced clearance of beta-amyloid from the brain.[3] Associations between cerebral atherosclerosis and AD pathology have also been reported.[4,5]

We examined the relationship between CVD pathology including atherosclerosis, arteriolosclerosis and CAA, with measures of AD pathology and cerebral infarcts. The autopsy sample was derived from a longitudinal study focused on the effects of subcortical ischemic vascular disease (SIVD) and AD on brain structure and cognitive function.[6,7] In the present study, atherosclerosis refers to intimal thickening affecting basal large arteries; arteriolosclerosis refers to vessel wall thickening and sclerosis affecting arteries smaller than 300 μm in external diameter. We hypothesized that 1) atherosclerosis and arteriosclerosis would be associated with ischemic but not AD pathology; 2) CAA would be associated with apoE ε4, AD pathology, and microinfarcts.

METHODS

Sample

The sample comprises 163 autopsy cases from a multicenter longitudinal study of cognitively normal, SIVD, and AD participants (IVD Program Project, February 2011 neuropathology database). Among the first consecutive 175 autopsy subjects, 1 with fronto-temporal lobar degeneration and 11 with dementia with Lewy bodies (DLB score ≥ 3) were excluded from this analysis. The 175 autopsy cases were drawn from a sample of 736 subjects (291 deceased; autopsy rate 60%). Written informed consent was obtained from all subjects or surrogate decision maker following the protocols approved by the institutional review boards at each participating institution.

Recruitment

Subjects with cognitive impairment and dementia were recruited mainly from university-affiliated memory clinics; cognitively normal subjects were recruited from the community. The sample was enriched for subjects with SIVD, defined by the presence in proton density MRI of discrete gray matter and white matter hyperintensities > 2 mm in diameter, operationally defined as lacunes. Evidence of frank cerebral hemorrhage or cortical infarction excluded a subject from initial study enrollment, but not for continued clinical follow-up and autopsy.

Clinical evaluation

Initial clinical diagnosis was based on a comprehensive evaluation[8], including medical history, activities of daily living, physical and neurologic examination, Mini-Mental State Exam (MMSE),[9] laboratory testing, serial neuropsychological testing[10] and quantitative MRI measures.[11] ApoE4 genotype was obtained on 141 of 163 autopsy cases by polymerase chain reaction, followed by standard restriction isotyping. Presence or absence of hypertension, hyperlipidemia, diabetes, heart disease, transient ischemic attack and stroke were assessed initially and annually. For this analysis, a vascular factor was considered to be "present" if noted on any annual assessments.

Neuropathology tissue protocol

After death, the brain was removed, weighed and fixed in 10% neutral buffered formalin for at least two weeks. After removal of the brainstem, each cerebral hemisphere was sectioned coronally at 5 mm thickness. Macroscopic infarcts were measured, photographed, and blocked for microscopic examination. Tissue was obtained from 12 standardized regions in one cerebral hemisphere using a standardized protocol.[8] Tissue blocks were dehydrated through graded alcohols, embedded in paraffin, sectioned at 10 micron thickness, and stained with hematoxylin-eosin, cresyl violet, Congo red, and Bielschowsky silver. At the pathologist's discretion, cases were immuno-labeled using antibodies against alpha-synuclein, ubiquitin, glial fibrillary acidic protein, phosphorylated tau, and beta-amyloid. The range of neuropathologic lesions has been described.[12]

Neuropathologic evaluation

Each case was reviewed at Consensus Neuropathology Conferences, including two Board-certified neuropathologists (HVV, WGE) blinded to clinical diagnosis and apoE4 genotype. Severity of atherosclerosis and arteriolosclerosis were rated on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). Large arterial vessels were defined as vessels with diameter ≥ 1.5 mm (anterior, middle, and posterior cerebral arteries of the circle of Willis); small arterial vessels were those with diameter 0.2–1.5 mm. CAA was assessed using the modified 0–4 Vonsattel scale, in which "4" reflects the presence of one or more CAA-associated microangiopathies (e.g. microaneurysm formation).[13,14] Large cystic infarcts had infarct size > 1 cm in greatest dimension. Lacunar infarcts were visible grossly and had infarct size < 1 cm in greatest dimension. Microinfarcts were only visible upon microscropic examination. While microinfarcts were almost always visualized on routine hematoxylin and eosin-stained sections, they were sometimes highlighted using immunohistochemistry especially using a macrophage microglial marker (CD68).

For each autopsy case, Braak and Braak Stage (B&B),[15] CERAD-neuritic plaque,[16] and Lewy body score[17–18] were recorded. The severity of cerebrovascular ischemic brain injury was rated using a vascular brain injury pathology scoring (CVDPS) developed within this project, and previously described.[8] Subscores for cystic infarcts, lacunar infarcts, and microinfarcts summed the individual scores across all brain regions and normalized to a scale of 0–100. The three subscores were summed to a total CVDPS score (0–300). Acute infarcts or hemorrhages near the time of death were noted, but not included in the CVDPS score.

Pathologic diagnoses

Cut-off scores were selected for B & B and CVDPS scores to operationally define five pathologic diagnosis groups. We used B & B ≥ IV[19] to indicate the AD group (n = 81) and CVDPS score ≥ 20, as described previously[7,8, 20,21] to define the CVD group (n = 21). Cases with B & B ≥ IV and CVDPS score ≥ 20 were defined as the MIXED group (n = 15). Cases with B & B < IV and CVDPS < 20 were classified as having no significant pathologic abnormality. We further subdivided this group into normal controls (NC: cognitively normal and no significant pathology, n = 23) and OTHER (cognitively impaired without significant pathology, n = 23). These pathologic categories are used to describe the study sample (Table 1), but were not used for the data analyses.

Statistical analyses

Sample characteristics were compared among the five pathologic groups using analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables. Our major hypotheses, tested in the entire autopsy sample, examined the associations of pathologic measures of blood vessel disease and presence of an apoE ε4 allele to lesions within the brain parenchyma. Clinical history of vascular factors and pathologic measures of blood vessel disease (CAA, atherosclerosis, arteriolosclerosis) served as the main independent variables. Measures of pathologic changes in the brain parenchyma served as the dependent variables including B & B, CERAD neuritic plaque score, CVDPS score, and the subscores for cystic, lacunar, and microinfarcts.

Ordinal logistic regression was employed for the primary analysis. Dependent variables modeled as ordinal categorical variables included B & B (0–III, IV–V, VI), CERAD score (none-sparse, moderate, frequent), and CVDPS (CVDPS = 0, 0 < CVDPS < 20, CVDPS ≥ 20). Cystic infarct (CYSTIC = 0, CYSTIC > 0), lacunar infarct (LACUNAR = 0, LACUNAR > 0), and microinfarct (MICRO = 0, MICRO > 0) scores were modeled separately as binary dependent variables using logistic regression. Atherosclerosis (0–3), arteriolosclerosis (0–3), and CAA (0–4) were jointly modeled in the multivariable ordinal logistic regression models with adjustment for age at death, gender, race/ethnicity, and years of education. In a separate model, apoE4 genotype was added as a covariate. Evaluation of the proportional odds assumption held for all models. Results are presented as proportional odds ratios with 95% confidence interval (CI). The proportional odds ratios are interpreted as the odds of being at medium or higher categories of the dependent variable, relative to the low category (or at the high category, relative to medium or lower categories), per unit increase of the independent variable. Multicollinearity statistics showed a variance inflation factor of 2.51 for atherosclerosis, and 2.49 for arteriolosclerosis; values exceeding 10 are often regarded as indicating multicollinearity.[22] Therefore we retained atherosclerosis and arteriolosclerosis jointly in the multivariable logistic regression models. All statistical testing was performed at a 5% level of significance using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Sample characteristics

The sample included 81 AD, 21 CVD, 15 MIXED AD/CVD, 23 OTHER, and 23 NC cases (Table 1). These pathologic groups did not differ in age at death, years of education, or duration of illness. Higher proportions of females were seen in the NC and OTHER groups. Ethnic minorities and a history of stroke were more frequently represented in the CVD and MIXED groups. Cognitive impairment (MMSE) was more severe and presence of apoE ε4 was more frequent in the AD and MIXED groups. These pathologic groups are presented for descriptive purposes only and were not used in the primary analyses.

The distribution of atherosclerosis, arteriolosclerosis, and CAA are shown by pathology group (Figure 1). Atherosclerosis and arteriolosclerosis were more severe in the CVD group ($p < 0.0001$), while CAA was more severe in the AD and MIXED groups ($p < 0.0001$). Atherosclerosis and arteriolosclerosis were highly correlated (Spearman $r = 0.70$), but not with CAA (Spearman $r = 0.01$ for atherosclerosis; 0.09 for arteriolosclerosis). The distribution of AD pathology and infarcts for the total sample are shown in Figure 2. B & B and CERAD scores were highly correlated (Spearman $r = 0.80$) but not with CVDPS (Spearman $r = -0.13$ for B & B, -0.09 for CERAD).

Correlations of vascular factors with parenchymal pathology

Diabetes was inversely associated with B & B ($p = 0.002$) and CERAD score ($p = 0.04$). History of TIA, stroke, and severity of arteriolosclerosis and atherosclerosis showed significant positive associations with the CVDPS score (Table 2).

Associations between CVD- and parenchymal pathology

Atherosclerosis was significantly positively associated with CVDPS (OR = 2.1, 95%CI = 1.2–3.7, $p = 0.01$) (Table 3). Neither atherosclerosis nor arteriolosclerosis were associated with AD pathology. CAA was not associated with CVDPS, but was associated with Braak & Braak Stage (OR = 1.5, 95%CI = 1.1–2.1, $p = 0.03$) and CERAD neuritic plaque score (OR = 1.5, 95%CI = 1.1–2.2, $p = 0.02$). ApoE ε4 was independently associated with AD pathology (Braak & Braak Stage: OR = 2.98, 95%CI = 1.43–6.2, $p = 0.004$; CERAD score: OR = 2.82, 95%CI = 1.34–5.93, $p = 0.006$).

We ran separate multivariable ordinal logistic regression models without apoE ε4 (data not shown) and compared these results with Table 3. Addition of apoE ε4 genotype to the multivariable analyses did not significantly alter the associations between CVD-type and parenchymal pathology.

Associations between CVD pathology and type of cerebral infarcts

Atherosclerosis was positively associated with microinfarcts (OR = 2.3; 95%CI = 1.2–4.4) and cystic infarcts (OR = 2.0; 95%CI = 1.0–4.2) (Table 4). Arteriolosclerosis showed borderline positive correlation with lacunar infarcts (OR = 2.0; 95%CI = 1.0–4.2). CAA was inversely associated with lacunar infarcts (OR = 0.5; 95%CI = 0.3–0.8). ApoE ε4 was not associated with any type of cerebral infarction.

DISCUSSION

In this autopsy sample enriched for cases with Alzheimer and SIVD, we found differential associations between types of CVD and parenchymal brain pathology. We report a strong and novel association between cerebral atherosclerosis and microinfarcts. Atherosclerosis was also associated with cystic infarcts, but not AD pathology. Arteriolosclerosis showed a positive correlation of borderline statistical significance with lacunar infarcts, but not AD pathology. CAA, on the other hand, was positively associated with AD pathology, but negatively associated with lacunar infarcts. Addition of apoE genotype to the multivariate analyses did not alter these findings. The independent contributions of CAA to B & B and CERAD score were slightly attenuated as expected, since the apoE ε4 genotype is associated with both CAA and AD pathology.

Associations between microinfarcts and cognitive impairment have been highlighted in several large autopsy studies. In the Honolulu Asia Aging Study (HAAS) of Japanese-American men, microinfarcts were found in 64% of 436 autopsy cases.[2] Microinfarcts contributed significantly and independently of neurofibrillary tangles to brain atrophy and cognitive impairment, especially in cases without overt dementia. In the Religious Orders Study (ROS), microinfarcts were observed in 30% of 425 autopsied cases.[1] Persons with multiple cortical microinfarcts had higher odds of dementia 1.89 (95%CI = 1.03–3.47). Microinfarcts contributed in an additive fashion to neurofibrillary tangles to lower cognition, including perceptual speed and semantic and episodic memory. Correlations between microinfarcts and type of CVD, however, were not reported in either the HAAS or ROS.

In the present study, microinfarcts were found in 40% of cases and were most strongly correlated with cerebral atherosclerosis. In several cases with abundant microinfarcts, we noted evidence of thrombi in neighboring meningeal arteries, suggesting the possibility of artery to artery thrombo-emboli. These observations suggest paradoxically, but perhaps not surprisingly, that microinfarcts may result from large artery disease. They also raise the possibility that statins or anti-platelet medications might reduce the incidence of microinfarcts.

Microinfarcts have been observed in cases of severe CAA.[23] We also observed microinfarcts in several of our cases with Grade 4 CAA, although the sample size (n = 5) was small and the association was not statistically significant. We further observed qualitative differences in the morphological appearance of microinfarcts. In CAA, the microinfarcts tended align along radial penetrating cortical arteries, whereas in cases with atherosclerosis the microinfarcts tended to appear as individual star-shaped lesions.

We were unable to confirm previous controversial associations between atherosclerosis and AD-associated neuritic plaques and neurofibrillary tangles.[24] In the National Alzheimer Coordinating Center (NACC) database, Honig et al[5] found an association between severe atherosclerosis in the Circle of Willis and frequent vs. none to moderate neuritic plaque scores (OR = 3.9; 95%CI = 2.0–7.5). However, the Baltimore Longitudinal Study on Aging (BLSA) found no relationship between the degree of atherosclerosis in the intracranial vessels, aorta, or heart and the degree of AD-type brain pathology.[25] We also found no

associations between severity of atherosclerosis and B & B Stage of neurofibrillary tangles or CERAD ratings of neuritic plaques (Tables 2–4). These inconsistencies in findings may reflect sample selection. If comparisons are made between cases with dementia (with both AD and atherosclerosis) and normal controls with neither AD nor atherosclerosis, a spurious association may be found between AD and atherosclerosis. A broad representation of atherosclerosis and cognition reflective of that represented in the general population is more likely to be achieved in community-based autopsy series or in a study focusing on vascular dementia than in Alzheimer center brain banks. In our sample, the pathologic groups did not differ in the prevalence of hypertension, hyperlipidemia, and CAD. The distribution of atherosclerosis and arteriolosclerosis in Figure 1 also suggests a good range of atherosclerosis in normal controls.

We examined the relationship between vascular factors and parenchymal pathology (Table 2). Epidemiologic studies report an association between vascular factor and clinically-diagnosed AD;[26,27] however autopsy studies derived from epidemiologic cohorts have not shown a relationship between vascular factors and AD pathology,[24] for review see Chui.[25] The epidemiologic literature reports associations between diabetes mellitus and increased incidence of clinically-diagnosed AD.[28] In the current study, we noted a positive trend between diabetes mellitus and infarct scores, but a negative association with AD pathology. Our ascertainment of diabetes mellitus was relatively crude (based on self-reported or informant-reported history of diabetes mellitus). No associations between diabetes mellitus and AD pathology were reported in the HAAS;[29] ROS[30] or in the Vaantaa Study.[31] Taken together, these findings suggest that associations between diabetes and risk of dementia may be mediated through the additive burden of infarcts, rather than acceleration of AD pathology.

The major strengths of this study are the inclusion of a broad spectrum of subjects with both SIVD and AD, unimpaired elderly, together with a standardized neuropathologic assessment of the brain parenchyma. A limitation of our study was the use of semiquantitative measures to rate severity of vascular pathology. The weighted kappa of 0.54 from 15 autopsy subjects indicated moderate test-retest reliability for the arteriolosclerosis score.

In sum, microinfarcts were most strongly associated with atherosclerosis. Possible pathogenetic mechanisms include artery-to-artery emboli, especially micro-emboli that may include atheroemboli or platelet-fibrin emboli. Arteriolosclerosis was positively, while CAA was negatively correlated with lacunar infarcts, which might prove helpful in clinical differentiation of arteriolosclerotic from CAA-related vascular brain injury.

Acknowledgments

None

SOURCES OF FUNDING

This research was supported in part by National Institute on Aging Grants P01 AG12435, P50 AG05142, and P50 AG16570.

REFERENCES

1. Arvanitakis Z, Leurgans SE, Barnes LL, Bennett DA, Schneider JA. Microinfarct pathology, dementia, and cognitive systems. Stroke; a journal of cerebral circulation. 2011; 42:722–727.
2. Launer LJ, Hughes TM, White LR. Microinfarcts, brain atrophy, and cognitive function: The honolulu asia aging study autopsy study. Annals of neurology. 2011; 70:774–780. [PubMed: 22162060]
3. Holtzman DM. Role of apoe/abeta interactions in the pathogenesis of alzheimer's disease and cerebral amyloid angiopathy. J Mol Neurosci. 2001; 17:147–155. [PubMed: 11816788]
4. Beach TG, Wilson JR, Sue LI, Newell A, Poston M, Cisneros R, et al. Circle of willis atherosclerosis: Association with alzheimer's disease, neuritic plaques and neurofibrillary tangles. Acta neuropathologica. 2007; 113:13–21. [PubMed: 17021755]
5. 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. [PubMed: 15699381]
6. Chui HC. Subcortical ischemic vascular dementia. Neurol Clin. 2007; 25:717–740. vi. [PubMed: 17659187]
7. Jagust WJ, Zheng L, Harvey DJ, Mack WJ, Vinters HV, Weiner MW, et al. Neuropathological basis of magnetic resonance images in aging and dementia. Ann Neurol. 2008; 63:72–80. [PubMed: 18157909]
8. Chui HC, Zarow C, Mack WJ, Ellis WG, Zheng L, Jagust WJ, et al. Cognitive impact of subcortical vascular and alzheimer's disease pathology. Ann Neurol. 2006; 60:677–687. [PubMed: 17192928]
9. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975; 12:189–198. [PubMed: 1202204]
10. Mungas D, Reed BR, Jagust WJ, DeCarli C, Mack WJ, Kramer JH, et al. Volumetric mri predicts rate of cognitive decline related to ad and cerebrovascular disease. Neurology. 2002; 59:867–873. [PubMed: 12297568]
11. Fein G, Di Sclafani V, Tanabe J, Cardenas V, Weiner MW, Jagust WJ, et al. Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. Neurology. 2000; 55:1626–1635. [PubMed: 11113215]
12. Vinters HV, Ellis WG, Zarow C, Zaias BW, Jagust WJ, Mack WJ, et al. Neuropathologic substrates of ischemic vascular dementia. J Neuropathol Exp Neurol. 2000; 59:931–945. [PubMed: 11089571]
13. Vonsattel JP, Myers RH, Hedley-Whyte ET, Ropper AH, Bird ED, Richardson EP Jr. Cerebral amyloid angiopathy without and with cerebral hemorrhages: A comparative histological study. Ann Neurol. 1991; 30:637–649. [PubMed: 1763890]
14. Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. Stroke. 1997; 28:1418–1422. [PubMed: 9227694]
15. Braak H, Braak E, Bohl J. Staging of alzheimer-related cortical destruction. Eur Neurol. 1993; 33:403–408. [PubMed: 8307060]
16. Mirra SS, Heyman A, McKeel D, Sumi SM, Crain BJ, Brownlee LM, 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. [PubMed: 2011243]
17. McKeith IG. Consensus guidelines for the clinical and pathologic diagnosis of dementia with lewy bodies (dlb): Report of the consortium on dlb international workshop. J Alzheimers Dis. 2006; 9:417–423. [PubMed: 16914880]
18. McKeith IG, Galasko D, Kosaka K, Perry EK, Dickson DW, Hansen LA, et al. Consensus guidelines for the clinical and pathologic diagnosis of dementia with lewy bodies (dlb): Report of the consortium on DLB international workshop. Neurology. 1996; 47:1113–1124. [PubMed: 8909416]
19. Consensus recommendations for the postmortem diagnosis of alzheimer's disease. The national institute on aging, and reagan institute working group on diagnostic criteria for the neuropathological assessment of alzheimer's disease. Neurobiol Aging. 1997; 18:S1–S2. [PubMed: 9330978]

20. Jung S, Zarow C, Mack WJ, Zheng L, Vinters HV, Ellis WG, et al. Preservation of neurons of the nucleus basalis in subcortical ischemic vascular disease. Arch Neurol. 2012; 69:879–886. [PubMed: 22393167]
21. Reed BR, Mungas DM, Kramer JH, Ellis W, Vinters HV, Zarow C, et al. Profiles of neuropsychological impairment in autopsy-defined alzheimer's disease and cerebrovascular disease. Brain. 2007; 130:731–739. [PubMed: 17267522]
22. Allison, PD. Logistic regression using the sas system: Theory and application. Cary, North Carolina: SAS Institute Inc.; 1999.
23. Soontornniyomkij V, Lynch MD, Mermash S, Pomakian J, Badkoobehi H, Clare R, et al. Cerebral microinfarcts associated with severe cerebral beta-amyloid angiopathy. Brain Pathol. 2010; 20:459–467. [PubMed: 19725828]
24. Chui HC, Zheng L, Reed BR, Vinters HV, Mack WJ. Vascular risk factors and alzheimer's disease: Are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. Alzheimers Res Ther. 2012; 3:36.
25. Dolan H, Crain B, Troncoso J, Resnick SM, Zonderman AB, Obrien RJ. Atherosclerosis, dementia, and alzheimer disease in the baltimore longitudinal study of aging cohort. Ann Neurol. 2010; 68:231–240. [PubMed: 20695015]
26. Breteler MMB. Vascular risk factors for Alzheimer's disease: An epidemiologic perspective. Neurobiology. 2000; 21:153–160.
27. Luchsinger J, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer's disease. Neurology. 2005; 23:545–551.
28. Chui HC, Zheng L, Reed BR, Vinters HV, Mack WJ. Vascular risk factors and alzheimer's disease: Are these risk factors for plaques and tangles or for concomitant vascular pathology that increases the likelihood of dementia? An evidence-based review. Alzheimers Res Ther. 2012; 4:1. [PubMed: 22182734]
29. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, apoe gene, and the risk for dementia and related pathologies: The honolulu-asia aging study. Diabetes. 2002; 51:1256–1262. [PubMed: 11916953]
30. Arvanitakis Z, Schneider JA, Wilson RS, Li Y, Arnold SE, Wang Z, et al. Diabetes is related to cerebral infarction but not to ad pathology in older persons. Neurology. 2006; 67:1960–1965. [PubMed: 17159101]
31. Ahtiluoto S, Polvikoski T, Peltonen M, Solomon A, Tuomilehto J, Winblad B, et al. Diabetes, alzheimer disease, and vascular dementia. A population-based neuropathologic study. Neurology. 2010; 75:1195–1202. [PubMed: 20739645]

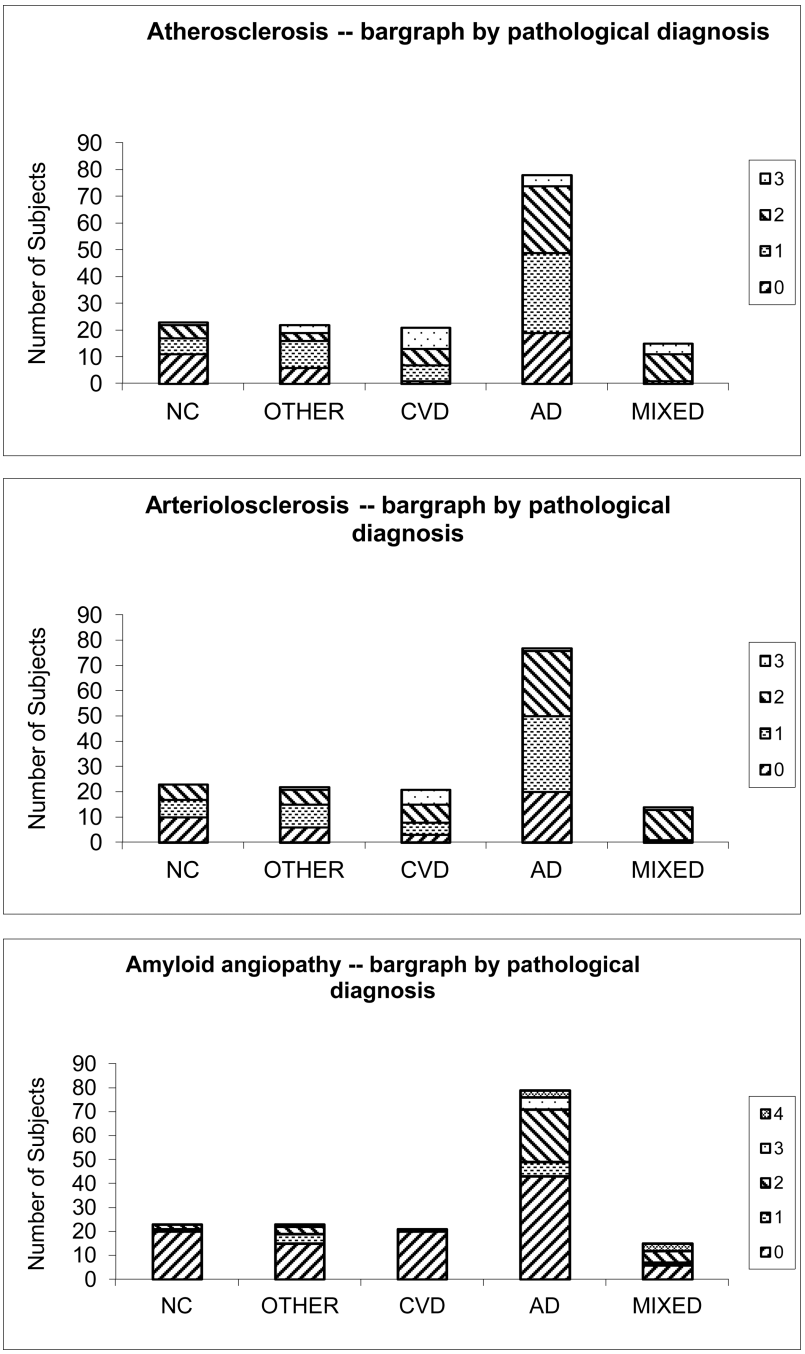

Figure 1.

Severity of three subtypes of cerebrovascular disease (atherosclerosis, arteriolosclerosis, and amyloid angiopathy) by pathologic diagnosis

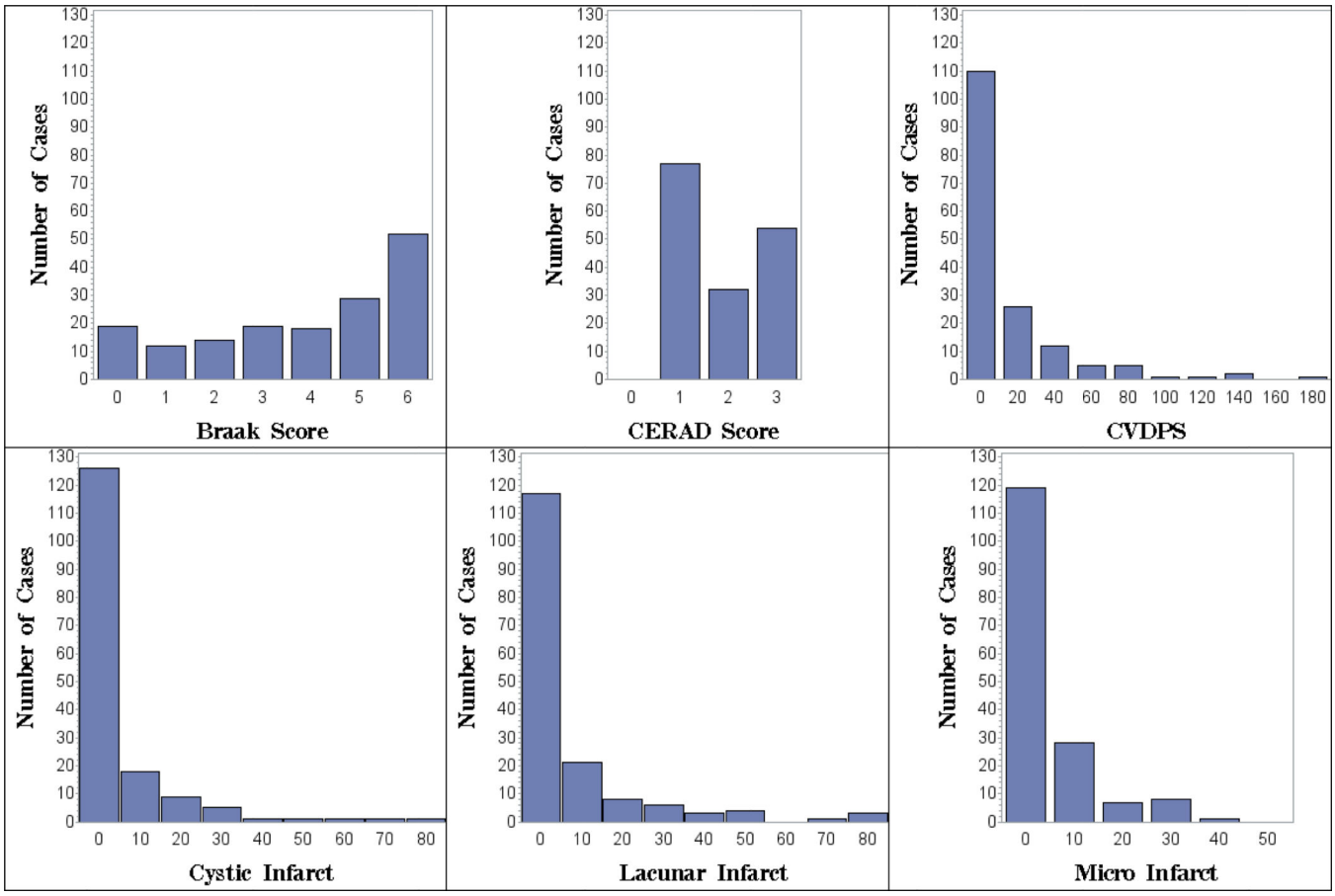

Figure 2.

Distribution of Braak & Braak neurofibrillary tangle stage, CERAD neuritic plaque score, CVDPS score, cystic infarct, lacunar infarct, and microinfarct scores.

Table 1

Demographic Data by Pathologic Diagnosis (N = 163)

	NC (N = 23)	OTHER (N = 23)	CVD (N = 21)	AD (N = 81)	MIXED (N = 15)	P-value*
Age at death (years)	84.6 (5.9)†	85.1 (6.7)	82.1 (8.6)	84.9 (7.1)	83.2 (6.7)	0.5
Education (years)	14.9 (3.1)	13.8 (3.1)	14.8 (3.4)	14.3 (3.6)	14.7 (2.7)	0.79
Duration of illness (years)	-	8.5 (3)	7.7 (4.2)	9.9 (3.8)	10.5 (5.7)	0.2
Gender						
Male	7 (30)	11 (48)	15 (71)	50 (62)	8 (53)	0.04
Female	16 (70)	12 (52)	6 (29)	31 (38)	7 (47)	
Race						
White	19 (83)	22 (96)	16 (76)	74 (91)	11 (73)	0.04‡
Hispanic	0 (0)	0 (0)	1 (5)	2 (2)	1 (7)	
African American	0 (0)	0 (0)	2 (10)	0 (0)	2 (13)	
Asian	4 (17)	1 (4)	2 (10)	5 (6)	1 (7)	
Mini-Mental State Exam	28.1 (2.9)	20.9 (8.9)	23.3 (7.7)	15.3 (8.6)	10.9 (7.7)	<0.0001
Time from last clinic visit to death (yrs)	2 (2.6)	1.2 (1.4)	1 (0.8)	1.3 (1)	1 (1.2)	0.11
Total lacunar volume (% ICV)	0.014 (0.023)	0.032 (0.054)	0.072 (0.07)	0.009 (0.022)	0.082 (0.163)	<0.0001§
White matter hyperintensity (% ICV)	1 (0.9)	2.8 (2.1)	3 (2.5)	1.2 (1.3)	3.2 (3.1)	0.002§
Time from last MRI to death (yrs)	3.6 (3)	2.6 (1.9)	2.3 (2)	3.9 (2.5)	3.7 (2.5)	0.06
ApoE ε4 allele (n = 141)						
No	17 (81)	14 (64)	17 (81)	31 (48)	5 (38)	0.008
Yes	4 (19)	8 (36)	4 (19)	33 (52)	8 (62)	

*P-value from ANOVA for continuous variables, from chi-square test for categorical variables

†Mean (SD) or N (%)

‡P-value from Fisher exact test

§P-value from Kruskal-Wallis test

NC = cognitively normal and no significant pathology, OTHER = cognitively impaired without significant pathology, CVD = cerebrovascular disease, AD = Alzheimer disease, MIXED = cases with CVD and AD

Table 2

Association between vascular risk factors, Alzheimer pathology, and vascular brain injury in the total sample (n = 163):

		Braak & Braak Stage			
		0–III (n = 64)	**IV–V (n = 47)**	**VI (n = 52)**	**P- value***
Hypertension, no (%)		52 (82.5)	40 (85.1)	46 (88.5)	0.67
Hyperlipidemia		28 (45.2)	22 (47.8)	20 (40)	0.73
Diabetes		17 (27)	2 (4.3)	5 (9.6)	0.002
Coronary Artery Disease		18 (29)	11 (24.4)	11 (23.9)	0.80
TIA		14 (21.9)	9 (19.1)	9 (17.3)	0.82
Stroke		20 (31.3)	14 (29.8)	13 (25.0)	0.75
Arteriolosclerosis†		44 (69.8)	37 (82.2)	37 (75.5)	0.34
Atherosclerosis‡		45 (71.4)	36 (78.3)	41 (82)	0.4
Amyloid angiopathy§	Severe	0 (0)	7 (15.2)	5 (9.8)	0.0002
	Moderate	10 (15.6)	14 (30.4)	21 (41.2)	
ApoE ε4 allele (n = 141)		14 (23)	19 (46.3)	24 (61.5)	0.0004
		CERAD Score			
		None-Sparse (n = 77)	**Moderate (n = 32)**	**Frequent (n = 54)**	**P- value***
Hypertension, no (%)		63 (82.9)	28 (87.5)	47 (87)	0.74
Hyperlipidemia		33 (44)	10 (32.3)	27 (51.9)	0.22
Diabetes		17 (22.4)	2 (6.3)	5 (9.3)	0.04
Coronary Artery Disease		22 (30.1)	7 (23.3)	11 (22)	0.56
TIA		12 (15.6)	12 (37.5)	8 (14.8)	0.02
Stroke		23 (29.9)	11 (34.4)	13 (24.1)	0.57
Arteriolosclerosis†		50 (67.6)	26 (81.3)	42 (82.4)	0.11
Atherosclerosis‡		54 (72)	25 (78.1)	43 (82.7)	0.37
Amyloid angiopathy§	Severe	3 (3.9)	5 (16.1)	4 (7.5)	<0.0001
	Moderate	10 (13)	11 (35.5)	24 (45.3)	
ApoE ε4 allele (n = 141)		16 (23.5)	13 (48.1)	28 (60.9)	0.0002
		CVDPS			
		None (n = 71)	**< 20 (n = 56)**	**> = 20 (n = 36)**	**P- value***
Hypertension, no (%)		56 (78.9)	50 (89.3)	32 (91.4)	0.13
Hyperlipidemia		29 (42)	24 (42.9)	17 (51.5)	0.64
Diabetes		10 (14.1)	5 (8.9)	9 (25.7)	0.09
Coronary Artery Disease		20 (29.9)	12 (22.2)	8 (25)	0.63
TIA		6 (8.5)	17 (30.4)	9 (25)	0.006
Stroke		11 (15.5)	15 (26.8)	21 (58.3)	<0.0001
Arteriolosclerosis†		43 (61.4)	43 (82.7)	32 (91.4)	0.001

		Braak & Braak Stage			
		0–III (n = 64)	IV–V (n = 47)	VI (n = 52)	P- value*
Atherosclerosis‡		43 (61.4)	44 (83)	35 (97.2)	<0.0001
Amyloid angiopathy§	Severe	4 (5.6)	5 (9.3)	3 (8.3)	0.65
	Moderate	23 (32.4)	15 (27.8)	7 (19.4)	
ApoE ε4 allele (n = 141)		23 (39.7)	22 (44.9)	12 (35.3)	0.67

*P-value from chi-square test

†Arteriolosclerosis present = 1–3 (mild, moderate, severe)

‡Atherosclerosis present = 1–3 (mild, moderate, severe)

§Amyloid Angiopathy present: moderate = 1–2, severe = 3–4

Table 3

Multivariable Ordinal Logistic Regression Evaluating Associations between Pathologic Measures of Cerebrovascular Disease and AD-, Vascular Brain Injury-Pathology (N = 163)*

Neuropathology Variables	Braak & Braak Stage†		CERAD‡		CVDPS §	
	OR (95%CI)	P-value	OR (95%CI)	P- value	OR (95%CI)	P-value
Atherosclerosis (0–3)	1.5 (0.9, 2.7)	0.14	1.1 (0.6, 1.9)	0.71	2.1 (1.2, 3.7)	0.01
Arteriolosclerosis (0–3)	0.9 (0.5, 1.6)	0.54	1. 2 (0.6, 2.1)	0.63	1.6 (0.9, 2.9)	0.13
CAA (0–4)	1.5 (1.1, 2.1)	0.03	1.5 (1.1, 2.2)	0.02	0.7 (0.5, 1.1)	0.12
ApoE ε4 (yes/no)	3.0 (1.4, 6.2)	0.004	2.8 (1.3, 5.9)	0.01	1.2 (0.5, 2.5)	0.72

*All models were adjusted for age at death, gender, ethnicity, and years of education

†Braak & Braak stage = 0–III, IV–V, and VI

‡CERAD = none-sparse, moderate, and frequent

§CVDPS = 0, 0 < CVDPS < 20, and CVDPS ≥ 20

CVDPS = cerebrovascular disease parenchymal pathology scores; CAA = cerebral amyloid angiopathy; MICRO = microinfarct

Table 4

Multivariable Logistic Regression Evaluating Associations between Pathologic Measures of Cerebrovascular Disease and Cerebral Infarcts (N = 163) *

Neuropathology Variables	MICROINFARCT†		LACUNAR‡		CYSTIC§	
	OR (95%CI)	P-value	OR (95%CI)	P- value	OR (95%CI)	P-value
Atherosclerosis (0–3)	2.3 (1.2, 4.4)	0.01	1.4 (0.7, 2.7)	0.32	2.0 (1.0, 4.2)	0.049
Arteriolosclerosis (0–3)	1.1 (0.6, 2.2)	0.79	2.0 (0.9, 4.2)	0.07	1.2 (0.5, 2.5)	0.69
CAA (0–4)	1.3 (0.9, 1.9)	0.24	0.5 (0.3, 0.8)	0.01	0.6 (0.4, 1.1)	0.08
ApoE ε4 (yes/no)	0.5 (0.2, 1.2)	0.12	0.9 (0.4, 2.3)	0.86	1.7 (0.6, 4.3)	0.3

*All models were adjusted for age at death, gender, ethnicity, and years of education

†MICRO = 0 (n = 97), and MICRO > 0(n = 66, range = 4.2–41.7)

‡LACUNAR = 0 (n = 117), and LACUNAR > 0 (n = 46, range = 3–75)

§CYSTIC = 0 (n = 126), and CYSTIC > 0 (n = 37, range = 5.6–83.3)

CVDPS = cerebrovascular disease parenchymal pathology scores; CAA = cerebral amyloid angiopathy; MICRO = microinfarct; LACUNAR = lacunar infarct; CYSTIC = cystic infarct.