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A pathological perspective on the natural history of cerebral atherosclerosis

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Abstract

Background and Aims—To test the hypothesis that atherosclerosis is only partially represented by stenosis and that advanced atherosclerosis is more common than severe stenosis in non-cardioembolic infarcts.

Methods—Cerebral large arteries from 196 autopsy cases were studied. The revised AHA classification for atherosclerosis was used to determine the phenotype in each available artery. Cross-sectional lumen stenosis was obtained as defined by the Glagov's method.

Results—As age of cases increased, there was a progressive increment in the frequency of atherosclerotic lesions, rising from 5% of all arteries at age 20-40 to more than 40% at age 60 or older. Stenosis also increased with age: less than 3% of the arteries in those < 50 years had > 40% stenosis while one out of five arteries in those > 80 years had > 40% stenosis. In most cases (80%), atherosclerosis and stenosis were directly related. However, one out of five cases with advanced atherosclerosis had < 30% stenosis. In arteries supplying brain areas with non-cardioembolic infarcts, the majority of segments exhibiting advanced atherosclerosis had lumen stenosis of < 40%.

Conclusion—Although intracranial atherosclerosis is typically associated with stenosis, a substantial minority of cases shows advanced atherosclerosis in the absence of stenosis > 40%.

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Definitions based solely on stenosis may underestimate the extent and role of intracranial large artery atherosclerosis.

Keywords

cerebral atherosclerosis; stenosis; non-cardioembolic stroke

Introduction

Intracranial large artery atherosclerosis (ILAA) is among the most important causes of stroke. However, most of what we know about ILAA comes mostly from studies using lumen-based definitions of atherosclerosis. The assumption that the severity of stenosis captures in its entirety the risk of subsequent vascular events may be incorrect. Although the risk of recurrent stroke in the territory supplied by the index stenotic artery was greater with stenosis > 70% in the WASID trial, the majority of WASID participants (60%) had stenosis <70% at baseline, suggesting that most of the qualifying strokes occurred with lesser degrees of stenosis.(1, 2) It has been shown in a sample of cases with stroke that stenosis and atherosclerosis in cerebral arteries are associated with brain infarct in separate models, but it is yet undefined whether used together, atherosclerosis or stenosis are independent predictors of brain infarcts or if the association would be true including cases without infarcts.(3) Furthermore, in coronary atherosclerosis, the majority of events occur in arteries with <50% stenosis.(4, 5) A second assumption in lumen-based studies is that the referent segment of the artery studied is normal. However, studies of atherosclerosis in coronary and femoral arteries suggest that neighboring areas of intima close to a focal stenosis are rarely normal.(6, 7) The referent arterial segment used to determine the severity of stenosis is very likely to include intimal thickening and thus luminal narrowing. As a consequence, what is believed to be a normal referent or true lumen is in fact already modified by ongoing atherosclerosis, leading to underestimation of the magnitude of the intimal thickening and lumen reduction.

Given the scarcity of studies contrasting detailed histopathological phenotypes with stenosis in cerebral large arteries, we tested the hypothesis that atherosclerosis is only partially represented by stenosis and that advanced atherosclerosis is more common than severe stenosis in arteries supplying brain areas with non-cardioembolic infarcts.

Methods

Subjects for this study were drawn from the Brain Arterial Remodeling Study (BARS), a collection of large and penetrating intracranial arteries from cases with and without HIV assembled with the overall goal of studying brain arterial remodeling and cerebrovascular disease. For this analysis, we excluded cases with HIV. The sources of the autopsy cases in the BARS are four different brain collections from which demographic and clinical information were obtained as previously described.(8, 9) Ischemic brain infarct was ascertained in the autopsy in each case. Individuals who had ischemic infarcts and history of atrial fibrillation, endocarditis at death, mechanical valves, cardiac clots, or cortical infarcts in multiple arterial territories were considered to have cardioembolic infarcts. Infarcts in a

subcortical location or a single arterial territory without cardioembolic sources were considered to have non-cardioembolic infarcts. With the data available, we could not systematically discern between extracranial and intracranial atherosclerosis as stroke mechanisms.

All arteries of the circle of Willis were systematically extracted by the lead investigator (JosG). Six micron thick cross-sections were obtained from the proximal and distal segment of each paraffin-embedded artery, stained with H&E and elastin van Gieson, and digitized using Olympus Soft Imaging Solutions software and microscope, with 10× magnification and scale=0.643 $\mu\text{m}/\text{pixel}$. Using color segmentation thresholding, areas within the lumen, internal elastic lamina (IEL), media, and adventitia were obtained and corrected for shrinkage. (9, 10) Stenosis was calculated by dividing the actual lumen area by the area encircled by the IEL (or potential lumen) and multiplying by 100 as described by Glagov et al. (10) A graphic explanation of this method has been previously reported with good to excellent reliability.(9, 11)

We used the revised classification of atherosclerosis lesions as described in Virmani et al. (12) This classification includes non-atherosclerotic phenotypes like normal intima, xanthoma and adaptive intima thickening as well as lesions typically deemed pre- or atherosclerotic such as pathological intima thickening (PIT), fibrous cap atheroma (FA), thin fibrous cap atheroma (TFCA) and fibrocalcific plaques. However, the definition for TFCA was modified for this study because we lack immunologic data regarding plaques inflammation to assess for plaque vulnerability. (12) We used instead the median distance in microns from the more luminal border of the necrotic core and the lumen by artery type (e.g. ICA, ACA, MCA, VA, etc.) to attribute the phenotype TFCA (below the median) versus FA (above the median, figure 1). A 5 % sample of arteries from the BARS was used to calculate inter-rater reliability with a senior neuropathologist (JaG) being the second rater. Visual assessments for the rest of the arteries were made by JosG under the guidance of co-author senior neuropathologists (SM and JaG) and a vascular pathologist (RV). Using the ratings as a normalized distribution scale, the intraclass correlation coefficient was 0.85 (95% CI 0.76-90, excellent reliability). Categorizing lesions into advanced atherosclerosis (FA, TFCA, or fibrocalcific plaques) yielded $\kappa=0.72$.

Statistical analysis

Percentages of histopathological arterial phenotypes and mean stenosis were used as outcomes. Stenosis was further arbitrarily categorized as 0-20, 21-40, and > 41 %. We used a mixed model to assess the relationship between atherosclerosis as predictor of stenosis, and adjusted logistic for age, sex, race/ethnicity, and vascular risk factors. A P value of <0.05 was considered statistically significant. Statistical analysis was carried out with SAS software, version 9.3 (SAS Institute Inc., Cary, NC) and the graphs were produced with IBM SPSS Statistics 21 (Release 21.0.0, IBM 2013).

Results

a) Sample studied

This analysis included 196 cases with a mean age of 55 years (± 17 SD, median 51, range 21-102 years). There were 63% men, 74 % non-Hispanic whites, 14% Hispanics and 12 % non-Hispanic blacks. Hypertension was present in 39%, diabetes in 15%, dyslipidemia in 20% and smoking in 49%. The prevalence of ischemic infarcts was 16 % (N=32, 13 were cardioembolic, 15 non-cardioembolic and 4 were unclassifiable). The mean number of arteries per case was 7.

b) Atherosclerosis prevalence by age and location

With increasing age, the prevalence of intima lesions typically considered atherosclerotic rose from < 5 % in donors in the 20-40 year age group to 40% in donors 60 or older (Figure 2a). There was a spectrum of pathologies within individuals, however. For example, 54 % of subjects had either normal intima or xanthomas with minor degrees of adaptive intima thickening, 21 % had coexistence of PIT with either normal arteries or xanthomas, and 17% had FA or TFCA coexisting with normal or minimally altered arteries. Only 8 % of the sample had all arteries with some degree of intima thickening and > 50 % of the arteries in these cases had evidence of advanced atherosclerosis.

Among cases with arteries from both hemispheres, 48 % had no atherosclerosis on either side, 19% had PIT in one side and no atherosclerosis on the other side, 15% had at least one TFCA or FA in one side and no atherosclerosis on the contralateral hemisphere and 18% had TFCA, FA or PIT in both hemispheres. Comparing the anterior versus the posterior circulations disclosed that 51% of the cases had no atherosclerosis in either system, 18% had PIT in one circulation and no atherosclerosis in the other, 11 % had FA or TFCA in the posterior circulation and no atherosclerosis in the anterior circulation while only 6 % had atherosclerosis in the anterior circulation and no atherosclerosis in the posterior circulation. Fourteen percent of the sample had FA or TFCA in both the anterior and the posterior circulation.

c) Stenosis prevalence by age and location

Stenosis also rose with age: stenosis $> 40\%$ was rare in cases < 40 years while the oldest groups had greater degrees of stenosis (Figure 2b). Analyzing the spread of stenosis within each case disclosed arteries with minimal degrees of stenosis coexisting with arteries with a maximum stenosis that varied from 10 % to a maximum of 70%. However, the average difference between the lowest and highest degrees of stenosis among the arteries within each case was within 12 % suggesting a high degree of concordance in stenosis within individuals. For example, comparing the average stenosis from arteries in the anterior circulation to that of the posterior circulation demonstrated that their mean stenosis differed by < 5 % in 64% of the subjects, by 6 to 10% in 26 % and by 11 to 21 % in only 10 %. The average arterial stenosis of one hemisphere vs. the contralateral showed that both means were within 5% of each other in 75% of the cases, between 6-10 % in 19 %, and between 11 and 15% in only 6 % of the cases.

The average difference in stenosis between proximal and distal segments of the same artery was between 4-5% for all arteries. In only a minority of occasions (9%) the difference in stenosis between the proximal and distal portion of the same artery exceeded 10% and the maximum difference was never greater than 22 %. However, the concordance in stenosis within the same arterial segment decreased as the average arterial stenosis increased.

d) Correlation between stenosis and histopathological phenotypes

As atherosclerosis progressed in severity, the degree of stenosis rose (Fig 3a). However, less than 50% of arteries with FA or TFCA had stenosis that exceeded 40% (Fig 3b). Plotting the extent of atherosclerosis against the extent of stenosis in arteries from the same case showed that as the extent of atherosclerosis progressed, the extent of stenosis generally progressed with it. However, there were a large proportion of cases that had at least one FA or TFCA while the degree of stenosis did not exceed 40% in any of these arteries. Despite the discrepancy noted in stenosis versus atherosclerosis, the relationship between advanced atherosclerosis as a predictor of stenosis remained significant after adjusting for sex, age and vascular risk factors (Beta coefficient 16.04 ± 0.84 , $P < 0.001$).

e) Stenosis versus atherosclerosis in non-cardioembolic infarcts

We matched the supplying artery to the infarcted territory in 12/15 non-cardioembolic infarcts (Table 4). Five out of twelve cases had predominantly small artery disease, while in 7/12 there was coexistence of advanced ILAA with small artery disease. Among cases with ILAA, 11 arterial segments exhibited FA or TFCA, and among these advanced atherosclerotic lesions, six had luminal stenosis of $< 40\%$. In an adjusted model with age, sex, and vascular risk factors, advanced atherosclerosis (OR 7.61, 95% CI 1.8-32.8) was associated with non-cardioembolic independent of stenosis $> 40\%$ (OR 0.21, 0.1-1.4).

Discussion

We report here that the degree of stenosis and atherosclerosis in the cerebral arteries rose with age. The degree of stenosis was more concordant among arteries within each case while the distribution of advanced atherosclerosis appeared more heterogeneous. Furthermore, advanced atherosclerosis was found in brain arteries with relatively minor degrees of stenosis. In arteries with advanced atherosclerosis supplying brain areas containing infarcts, the majority of TFCA or FA had arterial stenosis of $< 40\%$. These findings suggest that the degree of stenosis does not fully account for cerebral atherosclerosis burden.

Although we recognize the limitation of cross-sectional data, the results presented here enrich what is known about the natural history of cerebral atherosclerosis. We suggest that as individuals age, the stresses of blood flow lead to adaptive intimal thickening and xanthomas formation in cerebral large arteries. These compensatory responses are deemed normal and in the majority of cases regress.(12, 13) However, in a minority of individuals between 20 to 40 years old, arteries may undergo pathological intimal thickening.(14) As individuals age further, there is progression of the intimal disease evolving into FA, a lesion characterized by a necrotic lipid-filled core, recognized by the confluence of lipid material, typically localized in the intima near to the media, with visible cholesterol clefts and

evidence of macrophages apoptosis.(12, 15) This lesion is pathognomonic of atherosclerosis and it is separated from the lumen by a thick fibrous cap (Fig 1). As atherosclerosis progresses there is incremental tissue deposition in the intima that leads to stenosis. The IEL degenerates and is observed with gaps and duplications as the intimal disease progresses. (14) Due to factors not entirely clear, the intima expansion varies among individuals, however, giving rise to heterogeneity of lesions that range from atheromas with lumen preservation to atheromas with near occlusive stenosis.

We found a wide discrepancy in the extent of atherosclerosis between hemispheres and among the anterior and the posterior circulation. In contrast, the degree of stenosis across different arterial bed was more uniform, especially within the same arterial segment. These findings fit well with prior results demonstrating the presence of atherosclerotic plaques contralateral to a symptomatic MCA, although the degree of stenosis, neoangiogenesis and lipid core were higher ipsilateral to an ischemic stroke.(16, 17) It is not clear why there exist this differential progression of atherosclerosis within the same individual. A possible explanation might be related to differential blood flow exposure in the brain as reflected by the heterogeneous caliber of brain arteries, presumably acquired in utero as an adaptive response to the differential growth of the brain parenchyma. (18-20) This congenital asymmetry might expose one hemisphere or an arterial bed to oscillatory wall shear stress that the other arteries are not exposed to, rendering these arteries susceptible to develop atherosclerosis.(21) In fact, in our sample the proximal segments of the cerebral arteries right after a bifurcation showed greater degrees of stenosis and atherosclerosis.(8) The progressive narrowing of the lumen in one arterial bed might lead to increase flow in collaterals arteries. This might be a reason why in the majority of cases atherosclerosis was limited to an arterial territory and was not widespread as we expected it would be. Our inferences, although plausible, remain to be verified.

The clinical impact of this study is important. It has long been a concern that lumen-based studies may underestimate the degree of atherosclerosis and that stenosis *per se* does not fully capture the risk of vascular events.(22) The results presented here add support to the notion that ILAA is more commonly confined to an arterial bed and their daughter arteries than generalized to all cerebral arteries. However, when clinicians diagnose ILAA using lumen-based studies such as CTA, MRA or less frequently conventional angiograms, they look for a dent in the lumen or luminal irregularities within the same artery as supportive evidence. With this logic, a greater differential in stenosis among neighboring segments within the same artery would facilitate visualizing a stenosis. Here we report that in the majority of cases with stenosis within the same artery, the differential rarely exceeds 10% and the differential range in stenosis increased as the disease increased in severity. It is the likely that by the time the sought evidence of ILAA in lumen-based studies is found, the degree of stenosis as defined by cross-sectional lumen reduction nears 40%. As a consequence, the specificity of lumen-based stenosis is greater than its sensitivity to detect advanced atherosclerotic lesions. Some encouraging results have been published regarding the diagnosis of cerebral atherosclerosis with intravascular ultrasound and 7T MRI in pathological specimens, but the clinical utility of these techniques remains limited and the precision to distinguished specific atherosclerotic phenotypes other than eccentric versus

concentric is not always convincing.(23, 24) We hope that the re-emergence in interest for pathological data to study the biology of the cerebral arteries may guide more precise definitions of atherosclerosis to be used in high resolution MRI.

The most important limitation to this report is inherent to autopsy reports: the progressive nature of the disease is inferred by changes observed in certain groups that are assumed to be a continuum across different ages. We were not able to obtain every single artery of the circle of Willis in all cases, and we were not able to evaluate for extracranial carotid disease, which limits the certainty about stroke etiology in non-cardioembolic infarcts. Also, a minority of the cases here are not from the US which might introduce bias inherent to different environments and although controlling for vascular risk factors might partially account for this, it is possible that other unmeasured variables might be responsible for some of the reported associations. Finally, our definition of fibrous cap atheroma might not identify arteries with atheromas at a higher risk of rupture given the lack of inflammation data.

Conclusions

The majority of the cerebral large arteries undergo pathological changes with aging. These changes consist of atherosclerosis with the progressive development of PIT, FA and eventually the thinning of the thick fibrous cap separating the atheromas from the lumen leading to TFCA. There is a parallel increment in stenosis with atherosclerosis although in some cases the intima expansion is dissociated from the development of pathological features of atherosclerosis typically associated with clinical events. Advanced atherosclerosis was common in arteries supplying brain areas with non-cardioembolic infarcts, and among these arteries, only a minority of lesions with advanced atherosclerosis exhibited stenosis > 40%. Quantifying better ILAA in living individuals should be a top priority for researchers in the field, and once achieved, new openings for novel risk stratification and perhaps treatments can be foreseen.

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References

1. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005; 352(13):1305–16. [PubMed: 15800226]
2. Kasner SE, Chimowitz MI, Lynn MJ, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation*. 2006; 113(4):555–63. [PubMed: 16432056]

3. Mazighi M, Labreuche J, Gongora-Rivera F, Duyckaerts C, Hauw JJ, Amarenco P. Autopsy prevalence of intracranial atherosclerosis in patients with fatal stroke. *Stroke*. 2008; 39(4):1142–7. [PubMed: 18309170]
4. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation*. 1988; 78(5 Pt 1):1157–66. [PubMed: 3180375]
5. Almeida MQ, Azevedo MF, Xekouki P, et al. Activation of cyclic AMP signaling leads to different pathway alterations in lesions of the adrenal cortex caused by germline PRKAR1A defects versus those due to somatic GNAS mutations. *J Clin Endocrinol Metab*. 2012; 97(4):E687–93. [PubMed: 22259056]
6. Pasterkamp G, Wensing PJ, Hillen B, Post MJ, Mali WP, Borst C. Impact of local atherosclerotic remodeling on the calculation of percent luminal narrowing. *Am J Cardiol*. 1997; 79(4):402–5. [PubMed: 9052339]
7. Pasterkamp G, Schoneveld AH, van Wolferen W, et al. The impact of atherosclerotic arterial remodeling on percentage of luminal stenosis varies widely within the arterial system. A postmortem study. *Arterioscler Thromb Vasc Biol*. 1997; 17(11):3057–63. [PubMed: 9409293]
8. Gutierrez J, Rosoklija G, Murray J, et al. A quantitative perspective to the study of brain arterial remodeling of donors with and without HIV in the Brain Arterial Remodeling Study (BARS). *Front Physiol*. 2014; 5:56. [PubMed: 24600402]
9. Gutierrez J, Goldman J, Honig LS, Elkind MSV, Morgello S, Marshall RS. Determinants of cerebrovascular remodeling: Do large brain arteries accommodate stenosis? *Atherosclerosis*. 2014; 235(2):371–9. [PubMed: 24929285]
10. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med*. 1987; 316(22):1371–5. [PubMed: 3574413]
11. Gutierrez J, Elkind MSV, Petito C, Chung DY, Dwork AJ, Marshall RS. The contribution of HIV infection to intracranial arterial remodeling: A pilot study. *Neuropathology*. 2013; 33(3):256–63. [PubMed: 23067346]
12. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000; 20(5):1262–75. [PubMed: 10807742]
13. Stary HC, Blankenhorn DH, Chandler AB, et al. A definition of the intima of human arteries and of its atherosclerosis-prone regions. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Circulation*. 1992; 85(1):391–405. [PubMed: 1728483]
14. Klassen AC, Sung JH, Stadlan EM. Histological changes in cerebral arteries with increasing age. *J Neuropathol Exp Neurol*. 1968; 27(4):607–23. [PubMed: 5687757]
15. Burke AP, Kolodgie FD, Farb A, Weber D, Virmani R. Morphological predictors of arterial remodeling in coronary atherosclerosis. *Circulation*. 2002; 105(3):297–303. [PubMed: 11804983]
16. Klein IF, Labreuche J, Lavalley PC, et al. Is moderate atherosclerotic stenosis in the middle cerebral artery a cause of or a coincidental finding in ischemic stroke? *Cerebrovasc Dis*. 2010; 29(2):140–5. [PubMed: 19955738]
17. Chen XY, Wong KS, Lam WW, Zhao HL, Ng HK. Middle cerebral artery atherosclerosis: histological comparison between plaques associated with and not associated with infarct in a postmortem study. *Cerebrovasc Dis*. 2008; 25(1-2):74–80. [PubMed: 18033961]
18. Gutierrez J, Sultan S, Bagci A, et al. Circle of Willis configuration as a determinant of intracranial dolichoectasia. *Cerebrovasc Dis*. 2013; 36(5-6):446–53. [PubMed: 24281350]
19. Lazorthes G, Gouaze A, Santini JJ, Lazorthes Y, Laffont J. The modelling of the circle of Willis. Role of compressions of the afferent arterial tracts in the movements of the cervical spine and the cephalic extremity. *Neurochirurgie*. 1971; 17(5):361–78. [PubMed: 5002933]
20. Padget, DH. The circle of Willis: its embryology and anatomy. In: Dandy, WE., editor. *Intracranial arterial aneurysm*. New York: Comstock; 1945. p. 74-85.

21. Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. *Arteriosclerosis*. 1985; 5(3):293–302. [PubMed: 3994585]
22. Stary HC, Chandler AB, Dinsmore RE, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis. A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis, American Heart Association. *Arterioscler Thromb Vasc Biol*. 1995; 15(9):1512–31. [PubMed: 7670967]
23. Majidi S, Sein J, Watanabe M, et al. Intracranial-derived atherosclerosis assessment: an in vitro comparison between virtual histology by intravascular ultrasonography, 7T MRI, and histopathologic findings. *AJNR Am J Neuroradiol*. 2013; 34(12):2259–64. [PubMed: 23811977]
24. Bodle JD, Feldmann E, Swartz RH, Rumboldt Z, Brown T, Turan TN. High-resolution magnetic resonance imaging: an emerging tool for evaluating intracranial arterial disease. *Stroke*. 2013; 44(1):287–92. [PubMed: 23204050]

Figure 1.

Intima xanthoma is defined as the presence of foam cell in the intima with minimal intima hyperplasia (arrow). Intima thickening occurs as result of intima hyperplasia and extracellular matrix deposition (arrow). Pathological intima thickening consist of deposition of lipid loosely arrange in the intima without clear confluence and without cholesterol clefts observed. Fibrous cap atheromas have a necrotic core, defined as a focal, well-defined accumulation of lipids, cholesterol clefts and devoid of cellular elements (encircled in black). The necrotic core is separated from the lumen by a thick fibrous cap (red bar). Thin fibrous cap atheromas are distinguished from the thick fibrous cap atheroma by a thinner cap separating it from the lumen (green bar). Fibrocalcific plaques demonstrate large, confluent areas of calcification in the intima (arrows) with or without atheromas. The degree of lumen reductions is variable with more advanced degrees of stenosis.

2a: Histopathological phenotype by age group

2b: Severity of stenosis by age group

Figure 2.

As age of cases increased, there was a progressive increment in the frequency of atherosclerotic lesions, rising from 5% of all arteries at age 20-40 to more than 40% at age 60 or older (2A). Stenosis also increased with age: less than 3% of the arteries in those 50 years had > 40% stenosis while one out of five arteries in those > 80 years had > 40% stenosis (2B).

3a: Mean stenosis by histological phenotype

3b: Proportion of stenosis categories by histological phenotype

Figure 3.

As the severity of atherosclerosis rose, the mean stenosis also increased (3A). However, a substantial minority of arteries harboring lesions typically considered of advanced atherosclerosis (i.e. fibrous cap atheroma, thin fibrous cap atheroma and fibrocalcific plaques) had no greater than 40% stenosis (3B).

Table 1
Description of non-cardioembolic brain infarcts and their supplying arteries

Case	Infarct location	Ipsilateral arteries supplying the infarcted area (s)	Atherosclerosis classification *	Lumen stenosis (%)
1	Putamen	Proximal ICA	PIT	12
		Distal ICA	PIT	11
		Proximal M1	IT	14
		Distal M1	PIT	14
		M1 penetrator 1	-	14
2	Caudate head	Distal ICA	Normal	< 5
		Proximal A1	PIT	14
		A1 penetrator 1	-	12
		A1 penetrator 2	-	10
3	Putamen	Distal ICA	IT	12
		Proximal M1	IT	17
		Distal M1	IT	12
		Distal ICA penetrator	-	9
4	Subcortical anterior parietal white matter	Distal ICA	PIT	49
		Distal ICA penetrator 1	-	19
		Distal ICA penetrator 2	-	19
		Proximal M1	TFCA	64
		Distal M1	PIT	40
		Distal M1 penetrator	-	11
5	Hippocampus	Proximal BA	IT	13
		Proximal BA penetrator	-	26
		Distal BA	IT	7
		Distal BA penetrator	-	14
		Proximal P1	IT	13
		Proximal P1 penetrator	-	11
		Distal P1	IT	9
		Distal P1 penetrator	-	10
6	Parietal cortex	Distal ICA	PIT	19
		Proximal M1	TFCA	51
		Distal M1	TFCA	58
7	Superior cerebellar cortex	Right proximal V4	IT	19
		Right distal V4	TFCA	53
		Right distal V4 penetrator	-	15
		Left proximal V4	IT	14
		Left distal V4	IT	13
		Proximal BA	PIT	15

Case	Infarct location	Ipsilateral arteries supplying the infarcted area (s)	Atherosclerosis classification *	Lumen stenosis (%)
		Distal BA	IT	19
8	Anterior fronto-temporal subcortical infarcts	Distal ICA	FA	22
		Distal ICA penetrator	-	6
		Proximal M1	PIT	19
9	Medial frontal white matter	Proximal A1	PIT	50
		Distal A1	IT	40
10	Rostral basal ganglia	Proximal ICA	TFCA	32
		Proximal ICA penetrator 1	-	17
		Proximal ICA penetrator 2	-	10
		Distal ICA	FA	26
		Proximal M1	FA	48
		Distal M1	TFCA	38
		Distal M1 penetrator	-	16
11	Pontine infarct	Proximal BA	IT	12
		Distal BA	IT	11
		Distal BA penetrator	-	9
12	Rostral basal ganglia	Proximal M1	IT	12
		Proximal M1 penetrator	-	25
		Distal M1	TFCA	29
		Proximal M2	TFCA	36
		Proximal M2 penetrator	-	13

* Based on the modified AHA atherosclerosis classification. Penetrating arteries do not typically exhibit the phenotypes noted in large arteries.

Abbreviations: ICA, supraclinoid internal carotid artery; M1, First segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; A1, first segment of the anterior cerebral artery; BA, basilar artery; V4, fourth segment (intracranial) of the vertebral artery; P1, first segment of the posterior cerebral artery; IT, intima thickening; PIT, pathological intima thickening; FA, fibrous-cap atheroma; TFCA, thin-fibrous cap atheroma.