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Magnetic Resonance Imaging of Plaque Morphology, Burden, and Distribution in Patients With Symptomatic Middle Cerebral Artery Stenosis

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Background and Purpose—Intracranial atherosclerosis is a major cause of ischemic stroke worldwide. Intracranial vessel wall imaging is an upcoming field of interest to assess intracranial atherosclerosis. In this study, we investigated total intracranial plaque burden in patients with symptomatic middle cerebral artery stenosis, assessed plaque morphological features, and compared features of symptomatic and asymptomatic lesions using a 3T vessel wall sequence.

Methods—Nineteen consecutive Chinese patients with ischemic stroke and transient ischemic attack (mean age: 67 years; 7 females) with a middle cerebral artery stenosis were scanned at 3T magnetic resonance imaging; the protocol included a time-of-flight magnetic resonance angiography and the T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition sequence before and after (83%) contrast administration. Chi-square tests were used to assess associations between different plaque features. Statistical significance was set at $P<0.05$.

Results—Vessel wall lesions were identified in 18 patients (95%), totaling 57 lesions in 494 segments (12% of segments). Lesions were located primarily in the anterior circulation (82%). Eccentric lesions were associated with a focal thickening pattern and concentric lesions with a diffuse thickening pattern ($P<0.001$). When differentiating between asymptomatic and symptomatic lesions, an association ($P<0.05$) was found between eccentricity and asymptomatic lesions, but not for enhancement or a specific thickening pattern. Symptomatic lesions did not have any specific morphological features.

Conclusions—Our results lead to a 2-fold conclusion: (1) The classification system of both thickening pattern and distribution of the lesion can be simplified by using distribution pattern only and (2) differentiation between symptomatic and asymptomatic atherosclerotic lesions was possible using intracranial vessel wall imaging. **(*Stroke*. 2016;47: 1797-1802. DOI: 10.1161/STROKEAHA.116.013007.)**

Key Words: atherosclerosis ■ brain ■ magnetic resonance imaging ■ stroke

Intracranial atherosclerotic disease is a major cause of ischemic stroke worldwide and the most common cause in the Asian population.[1] Patients suffering from intracranial atherosclerosis have a high subsequent stroke risk.[1] In subjects with asymptomatic middle cerebral artery (MCA) stenosis, the overall annual stroke risk is 2.8%, whereas in patients with symptomatic middle artery stenosis the risk is even 4 times high.[2] For many years, lumenography-based methods were used to assess intracranial atherosclerotic disease by means of luminal narrowing, and it was thought that stenosis grade was an accurate reflection of disease burden.[3] In recent years, however, a shift has taken place toward imaging the intracranial vessel wall rather than the lumen as a result of advancing knowledge on the development of atherosclerotic plaques. Nowadays, it is common knowledge that outward arterial remodeling occurs, enabling plaques to develop without luminal narrowing.[4,5]

From histopathologic studies, examining the carotid and coronary arteries, it is known that plaques containing a large necrotic core or intraplaque hemorrhage and of a soft composition are typically at risk for plaque rupture.[6–8] Furthermore, several magnetic resonance imaging (MRI) studies have

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shown the additional value of atherosclerotic plaque characteristics, such as thin or ruptured fibrous caps, albeit in the extracranial vascular territories.[9] In 2014, Corban et al[10] showed that the combination of plaque burden, wall shear stress, and plaque phenotype (including several plaque characteristics) can predict atherosclerotic plaque progression and vulnerability in the coronary arteries. The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) trial demonstrated that large plaque burden is associated with more advanced plaques in the coronaries.[11] Knowledge of atherosclerotic burden and plaque characteristics/morphology of the intracranial vasculature is important because it may provide insight into vulnerability status similar to the extracranial arteries. Similar as it was for the extracranial arteries, intracranial vessel wall imaging is now an upcoming field of interest.[12–18] However, because the intracranial arteries are much harder to assess, less is known about the total intracranial plaque burden and their morphological features. The remodeling pattern and plaque distribution within the plaque, eg, superior, inferior, dorsal, or ventral are among the few characteristics that have been assessed in MCA stenosis only.[19] Several other, smaller studies have proposed specific intracranial plaque characteristics such as eccentricity and enhancement.[17,20,21] Especially, enhancement is thought to be of importance for assessment of plaque vulnerability.[22] Besides morphological features of the intracranial plaques itself, understanding of the morphological plaque differences between asymptomatic and symptomatic atherosclerotic lesions may be useful for risk stratification and treatment options. Therefore, in this study, we investigated total intracranial plaque burden in patients with symptomatic middle cerebral artery stenosis, assessed morphological features of the plaque itself, and compared these features of symptomatic lesions to those of asymptomatic lesions using a 3T vessel wall sequence.

Methods

Subjects

This prospective study was approved by the Institutional Review Board of the Chinese University of Hong Kong. All subjects gave written informed consent. Between February and September 2014, consecutive Chinese patients with a symptomatic MCA stenosis, as confirmed by digital subtraction angiography (DSA), clinical workup, and conventional MRI, were included in this study. Patients were thus selected based on the presence of stenotic atherosclerotic disease. All patients had to be able to endure the MRI examination and have no contraindications for MRI. Patient characteristics including age, sex, and general vascular risk factors were collected during patient's visit to the hospital. Some study subjects have been used in a recent technical study comparing the current sequence with 3 other vessel wall sequences for evaluating the best usable sequence (submitted data), in which summarizing baseline data (eg, average age and sex) and visualization of the vessel wall was reported.

Imaging

MRI was performed using a 3T Achieva MR system (Philips Healthcare, Cleveland, OH) with an 8-channel Sense head coil. The protocol included a transverse 3D T_1-weighted (T_1w) volumetric isotropically reconstructed turbo spin echo Acquisition (VIRTA) sequence,[13] before and after (83% of patients) contrast administration, and a time-of-flight magnetic resonance angiography (TOF-MRA) sequence. Before acquisition of the contrast-enhanced T1w VIRTA sequence, 0.1 mL/kg of a gadolinium-containing contrast agent (Dotarem, Gadoteric acid 0.5 mmol/mL; Guerbet, Roissy CdG Cedex, France) was administered to the patient. The following scan parameters were used for the T_1w VIRTA: field of view: 200×167×45 mm^3, acquired resolution: 0.6×0.6×1.0 mm^3, reconstructed resolution: 0.5×0.5×0.5 mm^3 using zero filling, repetition time 1500 ms, echo time 36 ms, Sense factor 1.5 (phase-encode direction), echo spacing 4.0 ms, turbo spin echo+startup echoes 56+6, and scan duration 6:51 minutes. Anti-DRIVen Equilibrium (DRIVE) module was used for increased cerebrospinal fluid suppression. Additionally, we used a minimum flip angle of 25° in the variable flip angle refocusing pulse train for increased flow suppression (in cerebrospinal fluid and blood).[23] Scan parameters for the TOF-MRA sequence were as follows: field of view 200×200×56 mm^3, acquired resolution 0.4×0.6×0.7 mm^3, repetition time/echo time 23/3.5 ms, and scan duration 3:07 minutes.

Image Analysis

Images were analyzed on an offline workstation (Philips) by 1 observer (N.D., 3 years of experience); a second observer (A.K., 7 years of experience) analyzed a subset of images (n=10). The observers were blinded for clinical data. On the T_1w VIRTA images, all major arteries of the Circle of Willis and its branches were scored for presence of vessel wall lesions (both symptomatic and asymptomatic); the contralateral side or the vessel wall more proximal or distal to the lesion was used as reference. The MCA stenosis that was identified as the culprit lesion by DSA was used as the symptomatic lesion and the other lesions as asymptomatic. Next, we assessed morphological features, by scoring thickening pattern, distribution pattern, and enhancement pattern of the lesion. The thickening pattern was scored as focal or diffuse, where focal was defined as a short region or focal point lesion and diffuse as a lesion over a longer trajectory (eg, >0.5 cm). Next, the distribution of the lesion was characterized as either eccentric (<50% wall involvement) or concentric (>50% wall involvement).[17] Furthermore, pre- and post-contrast scans were compared to assess contrast enhancement of the vessel wall, where the signal intensity of the vessel wall was compared with the signal intensity of brain parenchyma next to the wall. The infundibulum was used to assure normal cerebral distribution of contrast agent. Finally, the TOF-MRA was used for confirmation of the observed vessels and to assess whether scored vessel wall lesions could be appreciated on the TOF-MRA as well. TOF-MRA lesions were defined as normal, irregular, stenotic, occluded, or irregular and occluded.

Statistical Analysis

IBM SPSS version 20.0 for Windows was used for statistical analysis. Chi-square tests were used to assess associations between different plaque morphological features, between asymptomatic and symptomatic lesions, and between symptomatic lesions and MRA findings. The Dice similarity coefficient and the intraclass correlation coefficient with 95% confidence intervals were calculated to evaluate inter-rater reproducibility.[24] Statistical significance was set at $P<0.05$.

Results

Subjects

Between February and September 2014, 19 patients (7 females; mean age: 67 years; range: 47–81 years) with a symptomatic MCA stenosis underwent 3T imaging at a median time of 592 days after symptom onset (acute/subacute patients [n=4] range: 6–72 days; chronic patients [n=15] range: 145–2740). Of these 19 patients, 2 had had a transient ischemic attack and 17 had had an ischemic stroke. No major (motion) artifacts that hampered image analysis were observed. Patient demographics and cerebrovascular risk factors are summarized in Table 1.[25]

Table 1. Demographics of 19 Patients With Ischemic Stroke or TIA

	Total (%)
Age, mean (range), y	67 (47–81)
Sex (male)	12 (63)
Diagnosis	
TIA	2 (11)
Ischemic stroke	17 (89)
TIA/stroke mechanism*	
Large-artery atherosclerosis	18 (95)
Cardioembolism	1 (5)
Cardiovascular risk factors	
Any cardiovascular risk factor	18 (95)
Systolic blood pressure (mm Hg±SD)	155±30†
Hypertension	15 (79)
Hyperlipidemia	9 (47)
Diabetes mellitus	4 (21)
Current smoker	6 (31)
Atrial fibrillation	1 (5)

TIA indicates transient ischemic attack.

*According to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification system.[25]

†Measurements available for 15 patients.

Table 2. Plaque Burden in 18 Patients With MCA Stenosis

Location	Right*	Left*	Total (n=57)*
ICA	10	8	18
Distal carotid segment	6	3	9
Bifurcation A1-M1-ICA	4	5	9
MCA	10	17	27
M1 segment	9	13	22
Bifurcation M1-M2	0	2	2
M2 segment	1	2	3
Anterior cerebral artery	0	2	2
A1 segment	0	1	1
A2 segment	0	1	1
Basilar artery	…	…	3
Posterior cerebral artery	2	5	7
Bifurcation BA-P1	2	2	4
P1 segment	0	0	0
P2 segment	0	3	3
Total number of lesions	22	32	57

BA-P1 indicates bifurcation of the basilar artery-P1 segment; ICA, internal carotid artery; and MCA, middle cerebral artery.

*Number of lesions at location.

Distribution, Burden, and Characteristics

Intracranial vessel wall lesions were identified in 18 patients (95%), and multiple lesions were found in 15 patients. A strong inter-rater reliability was found: intraclass correlation coefficient, 0.71 and 95% confidence interval, 0.196 to 0.920. Inter-rater agreement on the evaluation of locations was moderate–good: Dice similarity coefficient, 0.57. A total of 57 lesions in 494 segments (12% of segments) were identified. Of these lesions, 47 (82%) were found in the anterior circulation (internal carotid artery [ICA], n=18; MCA, n=27; and anterior cerebral artery, n=2) and 10 (18%) in the posterior circulation (basilar artery, n=3 and posterior cerebral artery, n=7; Table 2 and Figure 1). Among the 57 lesions, 25 (44%) enhanced after contrast administration (Figure 2), 43 (75%) were eccentric, 14 (25%) were concentric, 42 (74%) were focal, and 15 (26%) were diffuse (Table 3). Eccentric lesions were significantly associated with a focal thickening pattern (Figure 2; Figure I in the online-only Data Supplement) and concentric lesions with a diffuse thickening pattern in plaques of the anterior circulation ($P<0.001$). Nineteen lesions (33%) were symptomatic (MCA lesions; 1 patient with bilateral lesions) and 38 lesions (67%) were asymptomatic. When differentiating between asymptomatic and symptomatic lesions, a significant association ($P<0.05$) was found between eccentricity and asymptomatic lesions (asymptomatic lesions: 32 eccentric, 84% versus symptomatic lesions: 11 eccentric, 58%) but not for enhancement or a specific thickening pattern. Symptomatic lesions did not have any specific morphological features. Furthermore, vessel wall lesions that appeared normal or irregular on MRA were more often asymptomatic, whereas lesions that appeared stenotic or occluded were symptomatic ($P<0.001$; Figure 2). Thirty MRA lesions were found: 26 in the anterior circulation and 4 in the posterior circulation. Besides the observed vessel wall lesions, we found, of these 30 MRA lesions, 8 additional lesions on MRA that were not visible on the vessel wall scan. Of these lesions, 6 were irregular, 1 was stenotic (Figure 3), and 1 was irregular/stenotic. Both lesions that were stenotic were also symptomatic lesions.

Discussion

In this study, we evaluated total intracranial plaque burden and plaque morphology and compared morphological features of symptomatic lesions to those of asymptomatic lesions in patients with a symptomatic MCA stenosis. We demonstrate that (1) most lesions were found in the distal ICA, intracranial bifurcation of the ICA, and in the M1 segment of the MCA, (2) besides the confirmed culprit MCA lesion, most patients had additional asymptomatic lesions, and (3) eccentric lesions were associated with focal thickening and asymptomatic lesions, whereas symptomatic lesions did not have any specific morphological features.

Similar to what has been found by other studies using lumenography-based methods, and one other vessel wall study, we observed the distal ICA, intracranial ICA bifurcation, and the M1 segment of the MCA as predilection locations for the development of atherosclerotic plaques.[26–30] In a study on coronary arteries performed by Corban et al,[10] it was hypothesized that low shear stress may play a role in the predilection of plaques to develop in bifurcations. These plaques might also be at increased risk for rupture, hence higher risk for causing future ischemic events. Another explanation for the majority of lesions found in the distal ICA may be the

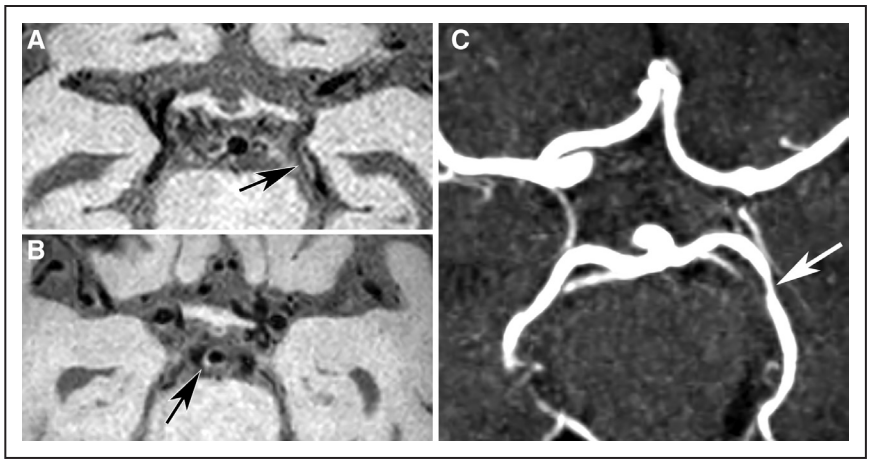

Figure 1. A 72-year-old female patient with a left partial anterior circulation infarct. **A**, On transverse T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition images, an eccentric, focal lesion was found in the P2 segment of the left posterior cerebral artery (arrow). Also, an eccentric, focal lesion (arrow in **B**) was observed in the basilar artery without causing luminal stenosis (arrow in **C**). **C**, Transverse time-of-flight magnetic resonance angiography shows an asymptomatic stenosis of the P2 segment at the same location as the vessel wall lesion (arrow).

fact that all of our patients had a symptomatic MCA stenosis, so our population is biased toward the anterior circulation. Nevertheless, we have also demonstrated that 18% of the lesions were not found in the anterior circulation and even more, 67% of our lesions were found to be asymptomatic and were found in areas other than the region of the culprit lesion.

Most eccentric lesions had a more focal thickening pattern. This is in line with earlier research from Swartz et al,[17] in which the authors showed that patients suffering from atherosclerotic disease had focal, eccentric lesions compared with patients with other pathologies who had diffuse and concentric lesions. We did not observe any association between symptomatic nor with asymptomatic plaques and enhancement. Intracranial plaque enhancement has been reported inconsistently, and the exact mechanisms are not known because histopathologic validation is lacking.[22,26,31] It could be that we have missed some lesion enhancement, because in some patients no postcontrast scan was obtained or because most patients were chronic stroke patients. On the contrary, it may be that lesion enhancement is less important for the intracranial arteries as it is for the extracranial arteries, where enhancement is a well-established feature of plaque vulnerability.[32,33] For the intracranial arteries, one of the differences that may partly explain why we do not observe associations with enhancement is the abundance of vasa vasorum. In early life vasa vasorum are rare in the intracranial arteries and predominantly found in the proximal parts of the brain vessels.[34,35] During aging, the vasa vasora get more abundant, and they may also develop in patients with pathologies like vasculitis, aneurysms, and atherosclerosis. When vasa vasora are the only causative factor for the enhancement in the intracranial vessel wall, this would imply that the entire vessel tree will enhance in older patients and patients with atherosclerosis. We do, however, not observe abundant enhancement of the intracranial vessels. This may suggest that different mechanisms are involved in the intracranial vessel wall enhancement.

Asymptomatic and symptomatic lesions were found to have a different morphological feature. The asymptomatic lesions

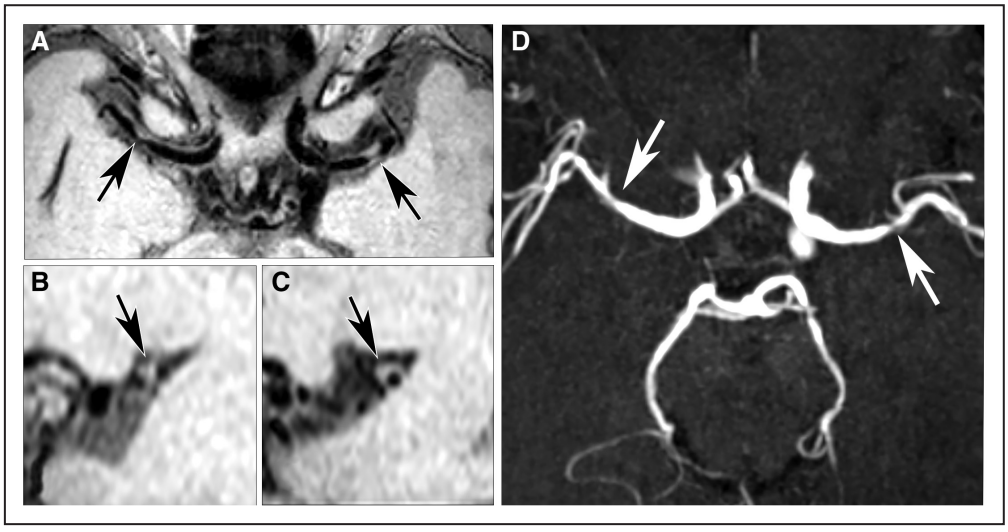

Figure 2. A 78-year-old female patient presented with an acute left transient ischemic attack. **A**, Bilateral focal vessel wall lesions were observed in the middle cerebral arteries on the transverse T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition image (arrows in **A**). Sagittal image reconstructions of the (**B**) right middle cerebral artery (MCA) lesion and (**C**) left MCA lesion showing that both lesions are eccentric. **D**, Transverse time-of-flight magnetic resonance angiography shows a corresponding symptomatic left MCA stenosis and an asymptomatic irregular right MCA (arrows in **D**).

Table 3. Plaque Characteristics of 57 Plaques in Patients With MCA Stenosis

Plaque Characteristic	Anterior Circulation*	Posterior Circulation*	Total (n=57)*
Enhancement			
Yes	24	1	25
No	16	5	21
NA	7	4	11
Configuration			
Concentric	12	2	14
Eccentric	35	8	43
Thickening			
Focal	33	9	42
Diffuse	14	1	15
MRA			
Normal	21	6	27
Irregular	10	2	12
Stenosis	12	2	14
Occluded	1	0	1
Irregular and occluded	3	0	3

MCA indicates middle cerebral artery; MRA, magnetic resonance angiography; and NA, no postcontrast scan available.

*Number of lesions at location.

were associated with more eccentric distribution of the plaque, but symptomatic lesions were both eccentric and concentric. It may be that concentric lesions are more advanced plaques as compared with eccentric lesions, because >50% of the vessel wall (in the sagittal view) is affected in case of a concentric lesion.[17] We also found that all DSA-proven MCA stenoses yielded a positive/outward-remodeling pattern. It might be interesting to examine whether differences exists in remodeling pattern between symptomatic and asymptomatic MCA stenoses in a group not selected based on DSA. Besides the difference between these lesions, an interesting point to mention is the differences in appearance of lesions in the Chinese population as compared with the western population.[21,26] Lesions in the Chinese population appear to be thicker, more often eccentric, and less diffuse. In future research, it would be interesting to test this hypothesis directly, because risk stratification criteria may be different between different ethnicities.

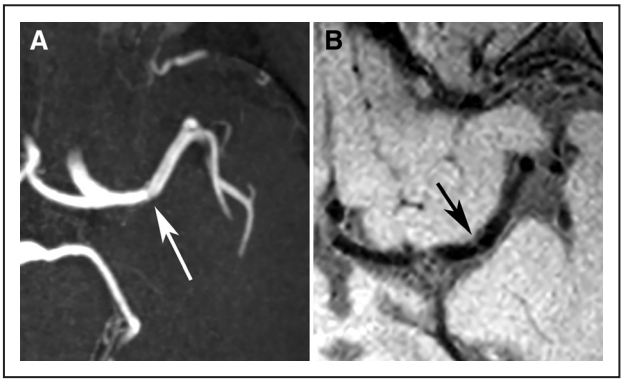

Figure 3. A 64-year-old male patient presented with a left partial anterior circulation infarct caused by a left middle cerebral artery (MCA) stenosis. **A**, Transverse time-of-flight magnetic resonance angiography shows a small stenosis in the left MCA (white arrow). **B**, On the transverse T1-weighted volumetric isotropically reconstructed turbo spin echo acquisition image, no corresponding vessel wall lesion was found (black arrow).

There are several limitations to our study. First, our sequence has a limited field of view; some lesions may have been missed, especially in the posterior circulation and in the more distally located vessels. The number of lesions found is therefore probably an underestimation of the true plaque burden. Second, patients were selected based on the presence of an MCA stenosis, as confirmed by DSA; therefore, we only included patients with stenotic atherosclerotic disease. As a result, this may have accounted for the plaque distributions found in this study. The selection based on a symptomatic MCA stenosis also accounts for the associations found between MRA and symptomatic/asymptomatic vessel wall lesions. In future, we should also include patients without DSA-proven stenosis or with strokes of the posterior circulation to investigate whether similar distribution patterns exist and whether correlations between MRA and vessel wall persist. Third, both acute and chronic patients were included in this study, because the patients were recruited via different ways. Therefore, the range between onset of stroke/TIA and scanning is broad. This may possibly explain the lack of association between enhancement and the MCA stenosis. However, the exact mechanisms of contrast enhancement still need to be established. Furthermore, the used sequence was added as a pilot sequence; therefore, the number of patients scanned with this sequence is relatively small. Finally, because of a lack of histology, we are not sure whether all the lesions observed are lesions that are at risk, whether they are of atherosclerotic origin, or whether they are vessel wall lesions at all. This lack of confirmation by histology is because it is rather difficult to obtain the intracranial arteries, because no intravascular interventions similar to those in the extracranial arteries are performed, such as carotid endarterectomy for the external carotid arteries. However, new research using Circle of Willis specimen shows promise in this field.[36,37]

Conclusions

We have demonstrated that most vessel wall lesions in patients with a symptomatic MCA stenosis are found in the distal ICA, intracranial bifurcation of the ICA, and in the M1 segment of the MCA, corresponding to similar distributions found for ischemic strokes.[38] Moreover, intracranial atherosclerotic plaques were mainly associated with an eccentric configuration and a focal thickening pattern and concentric lesions with a diffuse thickening pattern. This may imply that the classification system of both thickening pattern and distribution of the lesion can be simplified by using distribution pattern within the lesion only. Finally, asymptomatic lesions were found to be more often eccentric, whereas symptomatic lesions did not have any specific morphological features. This may enable differentiation between symptomatic and asymptomatic atherosclerotic lesions in the future.

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Disclosures

None.

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