Original Article

Association between intracranial aneurysm wall enhancement and intracranial atherosclerotic plaque: a cross-sectional study using high-resolution vessel wall imaging

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Background: Intracranial aneurysms and intracranial atherosclerosis are prevalent cerebrovascular diseases, and individuals with atherosclerosis have a higher incidence of aneurysms than those without atherosclerosis. However, few studies have conducted combined analyses to investigate the potential association between intracranial aneurysms and intracranial atherosclerosis. This retrospective cross-sectional study aimed to investigate the association between the characteristics of the aneurysm wall and intracranial large arterial plaque using high-resolution vessel wall imaging (HR-VWI).

Methods: Hospitalized patients diagnosed with anterior circulation unruptured intracranial aneurysms (UIAs), who were diagnosed at Huashan Hospital of Fudan University in Shanghai, China, between March 2016 to February 2018, were consecutively recruited for this study. The patients' pre-treatment HR-VWI images and 3D time-of-flight magnetic resonance angiography (3D-TOF-MRA) images were collected. The patients and UIAs were divided into two groups according to the presence or absence of plaque in the M1 segment of the middle cerebral artery (MCA). Clinical information and aneurysm characteristics were compared between the two groups. Aneurysm wall enhancement (AWE) and M1 plaque were graded on scales of 0 to 2 on HR-VWI. Based on the gradings, the correlation between AWE and the M1 plaques was analyzed.

Results: A total of 109 patients with 128 saccular UIAs in the anterior circulation were enrolled in the study. Of the patients, there were 56 patients (with 65 UIAs) in the group with M1 plaque and 53 patients (with 63 UIAs) in the group without plaque. There were significant differences between the two groups in terms of both their clinical information (age and hypertension) and aneurysm characteristics (AWE pattern and AWE degree). The grades of the AWE patterns and the AWE degrees of the UIAs were higher in the group with M1 plaque than in the group without plaque. In the M1 plaque group, the grade of M1 plaque was positively correlated with the grade of AWE pattern (correlation coefficient R=0.41, P=0.001) and the grade of AWE degree (correlation coefficient R=0.50, P<0.001).

Conclusions: MCA atherosclerosis plaque was associated with the AWE of saccular aneurysms. When evaluating UIAs, attention should also be paid to the large arterial wall, which may assist in assessing the stability of the aneurysm and enable better decision making.

Keywords: Intracranial aneurysm; intracranial atherosclerosis; magnetic resonance imaging (MRI)

Introduction

Saccular unruptured intracranial aneurysms (UIAs) are pathologic dilatations of the cerebral arteries (1). The overall prevalence of UIAs in adults worldwide was estimated to be 3.2% (2). However, the prevalence of UIAs in adult in Chinese communities detected by time-of-flight magnetic resonance angiography (TOF-MRA) has been reported to be as high as 7.0% (3). Most studies have shown that the formation of UIAs is a result of a mixture of hemodynamic stress, genetic susceptibility, and vascular risk factors (1,4,5). Notably, people with atherosclerosis have a 1.7 times higher prevalence of UIAs than those without atherosclerosis (2). Thus, it is necessary to investigate the association between these two diseases.

A previous histological analysis revealed that atherosclerosis may play an important role in the formation of aneurysms (6), which suggests that atherosclerotic plaques need to be monitored in patients with aneurysms. Age, hypertension, and smoking are considered common vascular risk factors for aneurysms and atherosclerosis (1,7). Understanding the relationship between these risk factors, aneurysms and atherosclerosis could provide insights into the mechanisms contributing to the development and progression of intracranial aneurysms, and could also help clinicians to better identify and manage UIA patients.

High-resolution vessel wall imaging (HR-VWI) has emerged as a non-invasive tool for diagnosing intracranial vascular diseases. Compared with the tools that show the vessel lumen, such as digital subtraction angiography, computed tomography angiography, and MRA, HR-VWI provides direct visualization of the vessel wall. It also enables the direct assessment of atherosclerotic plaque, including its morphological characteristics, intraplaque hemorrhages, and enhancement degree, and vessel wall thickening and remodeling (8,9). In addition, HR-VWI also plays an important role in evaluating the stability of aneurysms. To date, the presence of aneurysm wall enhancement (AWE) has generally been thought to be positively associated with aneurysm instability, while the absence of AWE has been used as a surrogate marker for aneurysm stability (10-12). However, to date, most previous studies have focused on either the UIA wall characteristics or intracranial atherosclerosis separately, and few studies have conducted combined analyses to investigate their potential association using HR-VWI.

In this study, we aimed to investigate the association between UIA and intracranial atherosclerosis using HR-VWI. Given that posterior circulation aneurysms account for only 10–15% of intracranial aneurysms, and a higher incidence of dissecting and fusiform aneurysms in posterior circulation than in anterior circulation (13,14), we only focused on aneurysms arising from the anterior circulation. We compared the differences between two groups of UIA patients with and without middle cerebral artery (MCA) atherosclerotic plaque and analyzed the correlation between MCA plaque enhancement and the AWE characteristics to demonstrate the importance of not only evaluating aneurysms, but also comprehensively assessing cerebrovascular diseases. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1025/rc).

Methods

Patients

In this retrospective cross-sectional study, patients with clinically confirmed intracranial aneurysms, who underwent 3D-TOF-MRA and HR-VWI from March 2016 to February 2018 at the Huashan Hospital of Fudan University, were consecutively recruited. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a ruptured aneurysm or a subarachnoid hemorrhage (SAH); (II) had a fusiform or dissecting aneurysm; (III) had a previously treated aneurysm; (IV) had an aneurysm located in the posterior circulation; (V) had an aneurysm adjacent to the cavernous sinus or inferior sagittal sinus; and/or (VI) had motion artifacts (*Figure 1*). Data on patients' disease risk factors (hypertension, hyperlipidemia, diabetes mellitus, smoking, and alcohol consumption), SAH history, family history of SAH or aneurysm, and aneurysm-related clinical manifestations were collected.

This study was approved by the Ethics Committee of Huashan Hospital of Fudan University (IRB No. KY2019-009) and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was
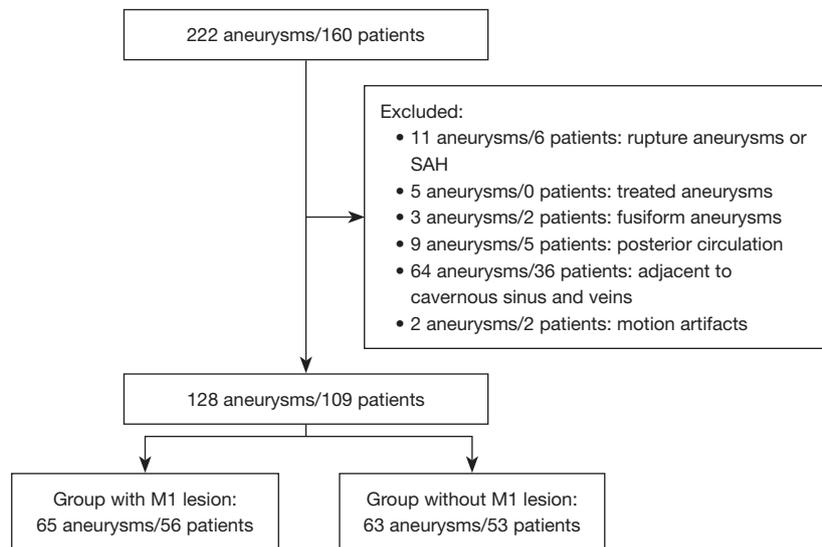
Figure 1 A flowchart of the patient recruitment process. SAH: subarachnoid hemorrhage.

obtained from each patient or their legal guardian (if the patient was aged under 18 years old).

Imaging protocol

All patients underwent 3T magnetic resonance (MR) (Discovery MR750; GE Healthcare, Milwaukee, WI, USA) with a 32-channel head coil. The imaging protocols included the 3D-TOF-MRA sequence (repetition time/echo time: 25/5.7 ms; pixel bandwidth: 20.83 kHz; slice thickness: 1.2 mm; field of view: 22×19.4 cm^2; matrix: 320×256 interpolated to 1,024×1,024), T1-weighted 3D CUBE fast-spin-echo sequence (repetition time/echo time: 600/13.7 ms; pixel bandwidth: 62.5 kHz; slice thickness: 1.0 mm; field of view: 20×20 cm^2; matrix: 288×288 interpolated to 512×512; echo chain length: 24) before and after injection of gadobutrol (Gd-BT-DO3A) (Gadovist, Bayer Schering Pharma, Berlin, Germany) at 0.1 mmol/kg.

Image analysis

The general aneurysm characteristics, including the location, side (left, right, or midline), number of aneurysms (single or multiple), maximum diameter (the maximum distance between any two points in the aneurysm sac, including the neck plane) (15), and morphology, were observed on the 3D-TOF-MRA images. According to a protocol proposed by Forbes *et al.* (16) for the International Study of Unruptured Intracranial Aneurysms (ISUIA),

there are four morphologic types of UIAs—type I: a single sac with even margins; type II: a single sac with a corrugate surface; type III: one or more secondary sacs protuberating from the main sac that is less than 25% of the total volume of the sac; and type IV: a protuberance arising directly from the primary neck of the aneurysm or the main sac and presenting 25% or more of the volume of the main sac.

The features of the aneurysm wall and the wall of the M1 segment of the MCA were then evaluated on the HR-VW images. First, the AWE patterns were classified into the following three grades—grade 0: no enhancement; grade 1: partial wall enhancement; and grade 2: circumferential wall enhancement (17). Second, the AWE degrees were defined as follows—grade 0: no enhancement; grade 1: mild enhancement, less than the choroid plexus or venous plexus enhancement; and grade 2: significant enhancement, similar to the enhancement of choroid plexus or venous plexus (18). Third, in accordance with Lindenholz *et al.*'s criteria (11), vascular lesions were defined as the presence in the M1 segment of the MCA of one or both of the following features: a focal or diffuse thickening of the artery wall greater than 50% of the wall of the adjacent vessel; and/or focal or diffuse significant contrast enhancement of the artery wall. Finally, based on a visual assessment of the enhanced degree, the M1 vascular lesions were classified into the following three grades—grade 0: no enhancement compared with the pre-contrast scan; grade 1: mild enhancement, less than the enhancement of the pituitary stalk; and grade 2: strong enhancement, similar to or greater
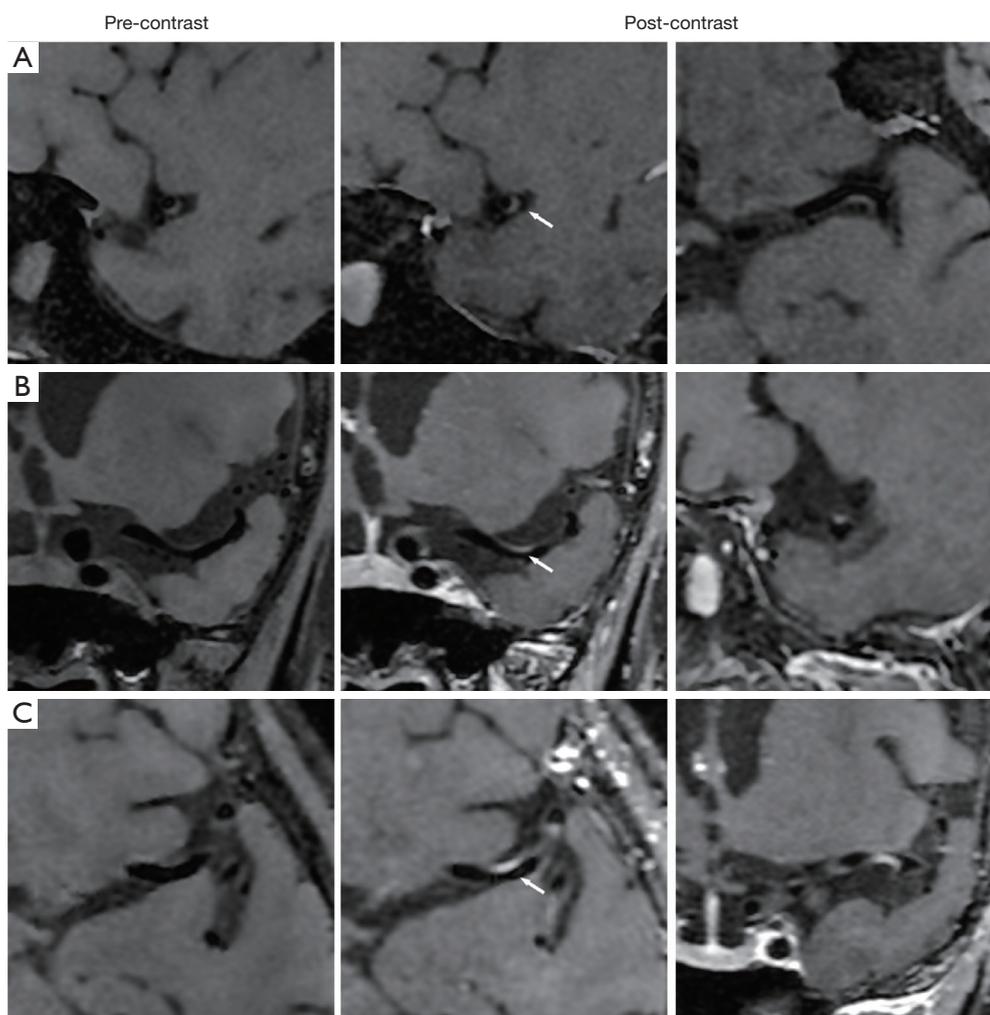
Pre-contrast   Post-contrast

Figure 2 Grading of an M1 lesion (arrows). (A) Grade 0: no enhancement. (B) Grade 1: mild enhancement, less than the enhancement of the pituitary stalk. (C) Grade 2: strong enhancement, similar to the enhancement of the pituitary stalk.

than the enhancement of the pituitary stalk (*Figure 2*) (8).

For patients with bilateral M1 lesions, the side with the higher grade was selected as the M1 lesion grade; for patients with multiple aneurysms, the largest aneurysm was selected to analyze the characteristics of AWE. The image evaluations were performed independently by two neuroradiologists, with more than 10 years of experience each, who were blinded to the patients' clinical data. Disagreements between the observers were resolved by discussion.

Statistical analysis

The Shapiro-Wilk test was used to assess normality. The clinical characteristics of the patients and imaging features of the aneurysms in the two groups were compared using the independent *t*-test for normally distributed variables, the Mann-Whitney *U* test for non-normally distributed variables and ordinal categorical variables, and Pearson's χ^2 test or Fisher's exact test for unordered categorical variables. The data are expressed as the mean ± standard deviation or the median [interquartile range] for the continuous variables, and the frequency or percentage for the categorical variables. Kendall's and Spearman's correlation analyses were conducted to assess the relationship between the aneurysm wall characteristics and M1 lesion grade. A two-sided P value <0.05 was considered statistically significant. All the statistical analyses were performed using SPSS (version 25.0, IBM Corp., Armonk, NY, USA).

Table 1 Comparison of the clinical characteristics of the patients between the groups

Clinical characteristics	Group with M1 lesion (n=56)	Group without M1 lesion (n=53)	P value
Female	36 (64.3)	33 (62.3)	0.83
Age (year)	62.8±9.1	56.3±10.9	<0.001*
Multiple aneurysms	22 (39.3)	15 (28.3)	0.23
Clinical symptoms	21 (37.5)	21 (39.6)	0.50
Hypertension	38 (67.9)	24 (45.3)	0.02*
Hyperlipidemia	19 (33.9)	11 (20.8)	0.12
Diabetes mellitus	10 (17.9)	7 (13.2)	0.50
Smoking	14 (25.0)	15 (28.3)	0.70
Alcohol	7 (12.5)	7 (13.2)	0.91
SAH history	1 (1.8)	3 (5.7)	0.35
Family history	3 (5.4)	3 (5.7)	>0.99

Values are presented as the number (%) or mean ± standard deviation. *, statistical significance. SAH, subarachnoid hemorrhage.

Results

Overall clinical and aneurysmal characteristics

In this study, we recruited a total of 160 patients with 222 aneurysms. Based on the exclusion criteria, 51 patients with 94 aneurysms were excluded from the study (*Figure 1*). Thus, the data of 109 patients with 128 saccular UIAs located in anterior circulation were analyzed. Among the patients, 40 were men and 69 were women. The patients had a median age of 61 years (range, 17 to 80 years). Thirty-seven patients had multiple UIAs (56 UIAs).

We summarized the location, side, maximum diameter, morphology, and AWE characteristics of the UIAs. There were 65 aneurysms (51%) in the internal carotid artery (ICA), including 14 aneurysms located at the bifurcation of the ICA into the posterior communicating artery, 10 aneurysms (8%) in the anterior cerebral artery, 21 aneurysms (16%) in the anterior communicating artery (ACoA), and 32 aneurysms (25%) in the MCA. The side distribution ratio was similar, with 52 aneurysms (41%) on the left side, 55 (43%) on the right side, and 21 ACoA aneurysms (16%) in the midline. The median maximum diameter of the 128 aneurysms was 6.21 mm (range, 2.25 to 29.08 mm). In terms of the morphologic types, type III was the most common, followed by type II, type IV, and type I (48%, 28%, 13%, and 11%, respectively). Of the aneurysms, 72 (56%) showed wall enhancement of varying extents and degrees on the HR-VW images.

Differences between groups with and without MCA atherosclerosis

In total, 56 patients with M1 lesions had 65 UIAs, and 53 patients without M1 lesions had 63 UIAs. In the M1 lesion cases, the vascular thickening was eccentric and focal, and there were no cases of diffuse thickening or enhancement as observed in vasculitis. Age, hypertension, and AWE characteristics differed significantly between the two groups. Patients with M1 lesions were older than those without M1 lesions (62.8±9.1 versus 56.3±10.9 years, P<0.001). The proportion of patients with hypertension was higher in patients with M1 lesions than in patients without M1 lesions (67.9% versus 45.3%, P=0.02). The aneurysms were more likely to show circumferential enhancement and mild enhancement in the group with M1 lesions, while no enhancement was observed in more than half of the aneurysms in the group without M1 lesions. The other clinical features and aneurysm characteristics did not differ significantly between the two groups (*Tables 1,2*).

Correlations between the M1 lesions and aneurysm characteristics

Among the 56 patients with M1 lesions, 21 (38%) had plaques on the left side, 7 (12%) had plaques on the right side, and 28 (50%) had bilateral plaques. No obvious correspondence was found between the sides of UIAs and

Table 2 Comparison of the aneurysm characteristics between the groups

Aneurysmal characteristics	Group with M1 lesion (n=65)	Group without M1 lesion (n=63)	P value
Location			0.64
ICA	31 (47.7)	34 (54.0)	
ACA	4 (6.2)	6 (9.5)	
ACoA	11 (16.9)	10 (15.9)	
MCA	19 (29.2)	13 (20.6)	
Side			0.88
Left	25 (38.5)	27 (42.9)	
Right	29 (44.6)	26 (41.3)	
Middle line	11 (16.9)	10 (15.9)	
Maximum diameter (mm)	6.07 [4.39–7.92]	6.28 [4.09–9.26]	0.88
Morphology			0.59
Type I	9 (13.8)	5 (7.9)	
Type II	17 (26.2)	19 (30.2)	
Type III	29 (44.6)	32 (50.8)	
Type IV	10 (15.4)	7 (11.1)	
AWE pattern			0.009*
Grade 0	21 (32.3)	35 (55.6)	
Grade 1	20 (30.8)	18 (28.6)	
Grade 2	24 (36.9)	10 (15.9)	
AWE degree			0.01*
Grade 0	21 (32.3)	35 (55.6)	
Grade 1	26 (40.0)	12 (19.0)	
Grade 2	18 (27.7)	16 (25.4)	
Management			0.55
Conservative management	21 (32.3)	19 (30.2)	
Endovascular management	19 (29.2)	24 (38.1)	
Microsurgical clipping	25 (38.5)	20 (31.7)	

Values are presented as the number (%) or median [interquartile range]. *, statistical significance. ICA, internal carotid artery; ACA, anterior cerebral artery; ACoA, anterior communicating artery; MCA, middle cerebral artery; AWE, aneurysm wall enhancement.

Table 3 Side distribution of the M1 lesions and UIAs

Sides of UIAs	Sides of M1 lesions		
	Left M1	Right M1	Bilateral M1
Left	10	4	11
Right	10	1	18
Middle line	3	2	6

UIAs, unruptured intracranial aneurysms.

the sides of plaques (*Table 3*). At the patient level, within the M1 lesion group, the grades of the M1 lesions were positively correlated with the grades of the AWE pattern (correlation coefficient R=0.41, P=0.001) and the grades of the AWE degree (correlation coefficient R=0.50, P<0.001) of the UIAs. In addition, we found that the aneurysm walls always showed at least grade 1 enhancement when the M1 lesion was evaluated as grade 2 and vice versa. The

Table 4 Grades of the M1 lesions and the corresponding grades of the AWE pattern and the AWE degree of the UIAs at the patient level

	Grade	M1 lesions			Correlation coefficient	P value
		Grade 0	Grade 1	Grade 2		
AWE pattern	Grade 0	7	11	0	0.41	0.001
	Grade 1	4	10	3		
	Grade 2	0	16	5		
AWE degree	Grade 0	7	11	0	0.50	<0.001
	Grade 1	4	17	1		
	Grade 2	0	9	7		

AWE, aneurysm wall enhancement; UIAs, unruptured intracranial aneurysms.

grade evaluations of the M1 lesions and aneurysm AWE characteristics are set out in *Table 4*, and some typical cases are shown in *Figure 3*. Other aneurysm characteristics, such as the maximum diameter and morphological type, were not correlated with the grades of the M1 lesions.

Discussion

In this study, we found an association between intracranial AWE and intracranial atherosclerosis using HR-VWI. The patients with and without atherosclerosis in the M1 segment of the MCA differed significantly in terms of age, hypertension, and the AWE pattern and the AWE degree of the UIAs. The grades of the AWE pattern and the AWE degree were moderately correlated with the grade of the M1 lesions.

Intracranial atherosclerosis and intracranial aneurysms are two common intracranial arterial diseases and had a co-existence rate of 51% in our study. In the study of Bae *et al.* (19), the presence of atherosclerosis in UIAs and parent arteries confirmed by clipping was observed in 81 cases (53% of the overall cases). Similar pathways are involved in the onset and development of intracranial atherosclerosis and intracranial aneurysms, including endothelial cell dysfunction, vessel wall remodeling, and abnormal blood flow at specific arterial sites (1,20). A previous study showed that the incidence of MCA aneurysms was significantly higher in patients with cerebrovascular diseases than in patients without cerebrovascular diseases (21), and indicated that plaque in the arterial muscular layer leads to collagen fiber deposition, focal vessel dilatation, and aneurysm formation. In addition, vascular inflammation, which contributes to endothelial dysfunction, the disruption of the internal elastic lamina and collagen matrix, and vasa

vasorum activation and proliferation, occurs during the formation and development of aneurysms (22). Both AWE and atherosclerotic plaque enhancement have been shown to correspond with damaged endothelial cell junctions, neovascularization, and inflammatory infiltration (23,24). These common mechanisms may explain the positive correlation between AWE grade and M1 lesion grade. A previous study used semi-automatic methods to identify AWE and parent vessel enhancement at 7T MR, promoting objectivity in assessment (25). The high field strength and quantitative analysis have promoted objectivity in assessment but delineating the aneurysm wall is labor intensive. Given the feasibility of clinical practice, we used a visual evaluation of AWE grades, similar to numerous previous studies (17,18,26).

We found that UIA patients with atherosclerosis were older and had a higher proportion of hypertension than those without atherosclerosis. Notably, both age and hypertension were identified as factors increasing the risk of aneurysm rupture according to the Population, Hypertension, Age, Size of aneurysm, Earlier SAH, Site of aneurysm (PHASES) score (27). In addition, the proportion of aneurysms presented with AWE was higher in the atherosclerotic group (68%) than in the non-atherosclerotic group (44%). Previous studies have shown that AWE is one of the most important biomarkers of aneurysm instability and is more common in symptomatic, growing, or ruptured intracranial aneurysms (26,28,29). Recently, another study of a large Finnish sample found that the abdominal aortic calcification index, which reflects the overall atherosclerotic burden, was higher in patients with intracranial aneurysms than patients without intracranial aneurysms, and increased the risk for ruptured intracranial aneurysms (30). In line with these studies, we confirmed the association between
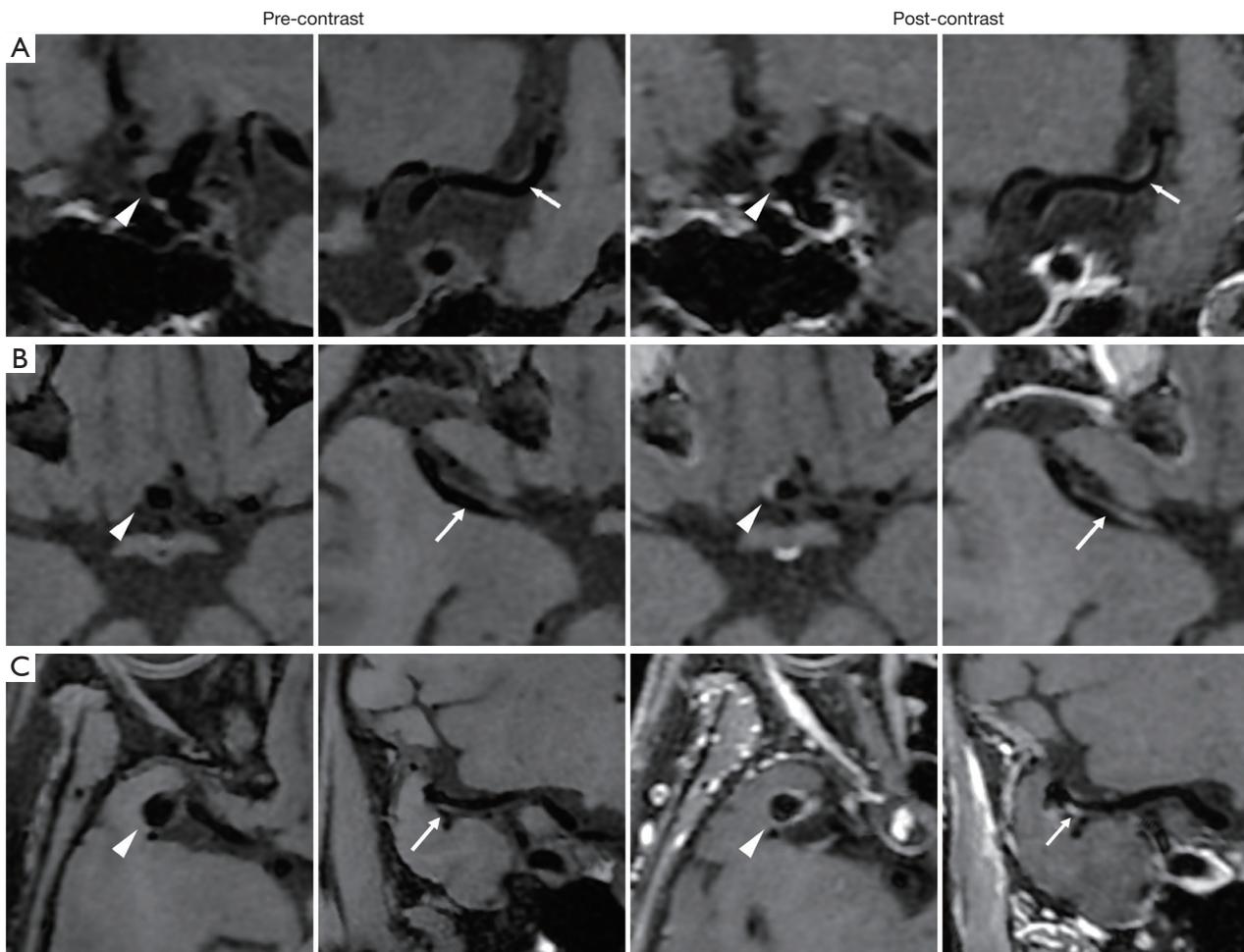
Figure 3 Cases of UIAs with different enhancement patterns (arrowheads) and their corresponding M1 lesion grades (arrows). (A) A case of a 73-year-old female patient: an aneurysm without enhancement (grade 0 of AWE pattern and AWE degree), located in the left internal carotid artery with focal thickening of its wall (grade 0). (B) A case of a 65-year-old female patient: an aneurysm with AWE (grade 1 of AWE pattern and degree), located in the anterior communicating artery, while the right MCA showed mild enhancement of the vessel wall (grade 1). (C) A case of a 71-year-old female patient: an aneurysm with AWE (grade 2 of AWE pattern and degree), located in right MCA, showing strong focal enhancement of the vessel wall (grade 2). UIA, unruptured intracranial aneurysm; AWE, aneurysm wall enhancement; MCA, middle cerebral artery.

AWE and intracranial atherosclerosis and suggested that intracranial atherosclerosis might be a potential predictor of increased risk of intracranial aneurysm rupture.

There was no significant difference between the patients with and without atherosclerosis in the distribution of the location, side, size, and morphology of the UIAs. Some studies have shown that hemodynamics have an effect on the growth and morphological changes of aneurysms (31,32). We speculate that the morphological characteristics of aneurysms are more susceptible to hemodynamic influences than the effects of vessel wall inflammation.

More attention is being paid to the atherosclerotic changes associated with UIA. Bae *et al.* (19) identified Framingham risk scores, diabetes mellitus, and aneurysm size as independent risk factors for atherosclerotic change in aneurysms. In a histopathologic analysis of 54 UIAs, Quan *et al.* (33) suggested that atherosclerotic plaques in UIAs were more likely to be present as focal wall enhancement rather than uniform wall enhancement. However, in our study, the aneurysms in the group with MCA atherosclerosis showed circumferential enhancement slightly more frequently than focal enhancement. Thus,

the AWE resulting from atherosclerotic changes within aneurysmal walls may not be exactly the same as the AWE associated with atherosclerosis in large vessel walls. Another study found that apolipoprotein B was a risk factor for AWE of intracranial fusiform aneurysms (34). Compared to the above studies, our study had a different aim; it sought to investigate the characteristics of AWE between the subgroups with and without atherosclerotic plaques to clarify the association between AWE and intracranial macrovascular atherosclerotic plaques (not limited to the plaques within the UIAs). A thorough assessment of the cerebrovascular in the entire brain using HR-VWI may help clinicians to promptly identify atherosclerosis-related aneurysms and make better clinical decisions.

Recently, individualized care, which considers a patient's overall medical condition, the specifics of each aneurysm, and the risks of treatment, was proposed (35). A prospective cohort study launched by ISUIA showed that previous ischemic cerebrovascular disease was a predictive factor of poor open-surgical outcomes for UIAs (risk ratio =1.90, 95% confidence interval: 1.1–3.0) (36). Since our treatment strategy was based on guidelines for the management of UIA patients (35,37), no difference in the treatments between the two groups was found in our study. A recent randomized controlled trial found that statin was effective in decreasing the AWE of UIAs after a six-month conservative treatment (38). For preoperative decision making, we suggest that intracranial atherosclerosis should be considered along with the assessment of AWE.

Our study had several limitations. First, it was performed at a single center and had a limited sample size. Second, we defined MCA atherosclerosis as abnormal vessel wall thickening and enhancement on HR-VWI. A pathological analysis was not performed. Third, the study had a retrospective cross-sectional design that ignored the effects of pseudo-enhancement, and no data on patients' individual medications were obtained. A future longitudinal study, including HR-VWI and four-dimensional flow MR, will help to comprehensively clarify the contribution of intracranial arteriosclerosis to the formation, development, and rupture of intracranial aneurysms and could assist clinicians in making precise decisions.

Conclusions

The UIAs showed a higher grade of AWE in patients with MCA atherosclerosis, and the grade of vascular inflammation was positively correlated with the grade of the AWE pattern

and the AWE degree. In the evaluation of the UIAs with HR-VWI, more attention should also be paid to the large arterial wall, which may assist in assessing the stability of the aneurysm and enable better clinical decision making.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1025/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1025/coif). L.H. is an employee of Parkway Shanghai Hospital. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that any questions related to the accuracy or integrity of any part of the work have been appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Huashan Hospital of Fudan University (IRB No. KY2019-009). Informed consent was obtained from each patient or their legal guardian (if the patient was aged under 18 years old).

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