Original Article

The relationship between intracranial atherosclerosis and white matter hyperintensity in ischemic stroke patients: a retrospective cross-sectional study using high-resolution magnetic resonance vessel wall imaging

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Background: Both intracranial atherosclerosis and white matter hyperintensity (WMH) are prevalent among the stroke population. However, the relationship between intracranial atherosclerosis and WMH has not been fully elucidated. Therefore, the aim of this study was to investigate the relationship between the characteristics of intracranial atherosclerotic plaques and the severity of WMH in patients with ischemic stroke using high-resolution magnetic resonance vessel wall imaging.

Methods: Patients hospitalized with ischemic stroke and concurrent intracranial atherosclerosis at Beijing Tsinghua Changgung Hospital, a tertiary comprehensive stroke center, who underwent high-resolution magnetic resonance vessel wall imaging and conventional brain magnetic resonance imaging were continuously recruited from January 2018 to December 2018. Both intracranial plaque characteristics (plaque number, maximum wall thickness, luminal stenosis, T1 hyperintensity, and plaque length) and WMH severity (Fazekas score and volume) were evaluated. Spearman correlation or point-biserial correlation analysis was used to determine the association between clinical characteristics and WMH volume. The independent association between intracranial plaque characteristics and the severity as well as WMH score was analyzed using logistic regression. The associations of intracranial plaque characteristics with total white matter hyperintensity (TWMH) volume, periventricular white matter hyperintensity (PWMH) volume and deep white matter hyperintensity (DWMH) volume were determined using multilevel mixed-effects linear regression.

Results: A total of 159 subjects (mean age: 64.0±12.5 years; 103 males) were included into analysis. Spearman correlation analysis indicated that age was associated with TWMH volume (r=0.529, P<0.001), PWMH volume (r=0.523, P<0.001) and DWMH volume (r=0.515, P<0.001). Point-biserial correlation analysis indicated that

smoking (r=–0.183, P=0.021) and hypertension (r=0.159, P=0.045) were associated with DWMH volume. After adjusting for confounding factors, logistic regression analysis showed plaque number was significantly associated with the presence of severe WMH [odds ratio (OR), 1.590; 95% CI, 1.241–2.035, P<0.001], PWMH score of 3 (OR, 1.726; 95% CI, 1.074–2.775, P=0.024), and DWMH score of 2 (OR, 1.561; 95% CI, 1.150–2.118, P=0.004). Intracranial artery luminal stenosis was associated with presence of severe WMH (OR, 1.032; 95% CI, 1.002–1.064, P=0.039) and PWMH score of 2 (OR, 1.057; 95% CI, 1.008–1.109, P=0.023). Multilevel mixed-effects linear regression analysis showed that plaque number was associated with DWMH volume (β=0.128; 95% CI, 0.016–0.240; P=0.026) after adjusted for age and sex.

Conclusions: In ischemic stroke patients, intracranial atherosclerotic plaque characteristics as measured by plaque number and luminal stenosis were associated with WMH burden.

Keywords: Intracranial artery; atherosclerosis; white matter hyperintensity (WMH); high-resolution magnetic resonance vessel wall imaging

Submitted Jan 13, 2023. Accepted for publication Jun 06, 2024. Published online Jul 11, 2024.
doi: 10.21037/qims-23-64
View this article at: https://dx.doi.org/10.21037/qims-23-64

Introduction

Previous studies have demonstrated that white matter lesions characterized by white matter hyperintensity (WMH) on magnetic resonance fluid attenuated inversion recovery (FLAIR) imaging are frequently observed in patients with cerebrovascular symptoms or in aged population (1-3). WMH as a typical features of cerebral small vessel disease has been shown to be a marker of cognitive impairment (4) and stroke risk (5). Increasing evidence has indicated that individuals with severe WMH burden have higher risk of microvascular impairment, neuro-axonal damage and cognitive decline (6,7). Many factors contribute to WMH, such as age, hypertension (8), smoking (9), diabetes mellitus (10), immune-mediated vasculitis (11), certain infections (12), and several genetic diseases (13). Therefore, it is important to determine the modifiable risk factors for prevention of WMH.

Besides traditional cerebrovascular risk factors, atherosclerotic disease in intracranial large artery has also been found to be associated with WMH (14). A study including Korean population indicated that the presence of intracranial atherosclerosis was independently associated with WMH (15). Another study with asymptomatic adults also demonstrated that intracranial atherosclerosis was associated with larger WMH volume (14). However, there is a lack of evidence on the relationship between vulnerable characteristics of intracranial plaques and the severity of WMH.

The objective of this study was to investigate the association between intracranial atherosclerotic plaque characteristics determined by high-resolution magnetic resonance vessel wall imaging (HR-VWI) and WMH in ischemic stroke with symptomatic intracranial atherosclerosis. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-64/rc).

Methods

Study design

The data of this retrospective study were obtained from an intracranial atherosclerotic stroke cohort, in which ischemic stroke patients with intracranial atherosclerosis underwent HR-VWI (16). The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013), and the protocol of this study was approved by the ethics committee of Beijing Tsinghua Changgung Hospital (No. 22028-0-02). Written informed consent was exempted due to the retrospective nature of this study.

Patients

Patients with ischemic stroke and intracranial atherosclerosis admitted to a comprehensive stroke center between January 2018 and December 2018 were recruited. The inclusion criteria were as follows: (I) age ≥18 years old; (II) ischemic stroke with more than one cardiovascular risk factor; (III) ischemic stroke was caused by intracranial atherosclerosis which was detected by computed tomography angiography

or HR-VWI; and (IV) magnetic resonance (MR) imaging was performed within 4 weeks of symptoms onset. Patients with the following conditions were excluded: (I) stroke was caused by moderate-to-severe extracranial artery stenosis (stenosis ≥50%) or non-atherosclerotic intracranial artery diseases, such as dissection, vasculitis, or moyamoya disease; (II) MR imaging with poor image quality; (III) patients who underwent intracranial endovascular procedures before MR imaging; (IV) patients with known stroke history or dementia according to International Classification of Diseases, 10th edition.

Clinical variables collection

The demographic characteristics (age and sex) and cardiovascular risk factors were obtained from the medical records. In this study, according to the Chinese guidelines for the prevention and treatment of hypertension (2017 Revision), hypertension was counted if patients presented with systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, or patients who were on antihypertensive medication. According to the Chinese guidelines for the prevention and treatment of type 2 diabetes (2017), diabetes was considered if patients had fasting glucose ≥7 mmol/L or nonfasting glucose ≥11.1 mmol/L or were on anti-diabetic medication. Patients were defined as hyperlipidemia if they met one of the following standards, according to the Chinese guidelines on the prevention and treatment of dyslipidemia in adults (2016): (I) total cholesterol (TC) ≥5.2 mmol/L or Triglyceride (TG) ≥1.70 mmol/L; (II) self-reported physician diagnosed hyperlipidemia and were on statins. In addition, current smoking and history of coronary artery heart disease (CAD) were also collected.

MR imaging protocol

Brain and intracranial artery vessel MR imaging was performed on a 3.0 Tesla MR scanner (Discovery 750, GE Healthcare, Milwaukee, USA) with an eight-channel head coil. The MR imaging protocol includes: three-dimensional (3D) time-of-flight (TOF)-magnetic resonance angiography (MRA) and 3D CUBE T1-weighed imaging (3D CUBE T1W) for vessel wall imaging; T1 weighted (T1W) imaging, T2 weighted (T2W) imaging, T2-FLAIR imaging and DWI imaging for brain MRI. We used 3D TOF MRA and 3D CUBE T1W sequence to evaluate intracranial atherosclerotic plaque characteristics, T2-FLAIR sequences to assess WMH lesion. The imaging parameters are as follows: 3D TOF-MRA (axial plane): Spoiled Gradient Recalled (SPGR) sequence, repetition time (TR)/echo time (TE) 22/2.5ms, flip angle 20°, field of view (FOV) 22 [the head and foot direction (FH)] × 18 [the left and right direction (RL)] × 8.64 [the forward and backward direction (AP)] cm^3, and spatial resolution 0.6×1.0×1.2 mm^3, total scan time 3 minute 20 seconds; 3D CUBE-T1W (coronal plane): fast spin echo (FSE), slice thickness: 0.6 mm, TR/TE 800/16 ms, flip angle 90°, echo train length: 42, FOV 23 (FH) × 18.4 (RL) × 5.28 (AP) cm^3, and spatial resolution 0.7×0.6×0.6 mm^3, total scan time 6 minute 40 seconds. The imaging parameters for the brain routine MR imaging were: T1W imaging: FSE, TR/TE 2,000/10 ms, FOV 24×24 cm^2, spatial resolution 0.9×0.9 mm^2, slice thickness 5 mm, total scan time 1 minute 29 seconds; T2W imaging: FSE, TR/TE 5,700/97 ms, FOV 24×24 cm^2, spatial resolution 0.9×0.9 mm^2, slice thickness 5 mm, total scan time 1 minute 12 seconds; T2-FLAIR: inversion recovery (IR), TR/TE 9,000/150 ms, FOV 24×24 cm^2, spatial resolution 0.9×0.9 mm^2, slice thickness 5 mm, total scan time 1 minute 49 seconds; DWI: echo-planar imaging, TR/TE 3,000/65 ms, FOV 24×24 cm^2, spatial resolution 1.6×1.6 mm^2, slice thickness 5 mm, total scan time 42 seconds.

MR image interpretation

All MR images were interpreted by two neuroradiologists independently after post-processing using the GE-Extend Workstation (AW workstation 4.6, GE Healthcare, Milwaukee, WI, USA). Two observers who had 5 years' experience in neurovascular imaging and were blinded to clinical information assessed the imaging independently. A third senior neuroradiologist who had 10 years' experience in neurovascular imaging would perform peer review when there was disagreement between two observers. Multiplanar reconstruction was conducted perpendicular to the arterial center line with slice thickness of 0.3 mm. The image quality for intracranial MR images was rated utilizing 4-scale score: 1 = poor, 2 = adequate, 3 = good, and 4 = excellent. MR images with poor image quality (score <2 points) were excluded (17). In this study, excellent-rated MR images showed clear vessel wall delineation throughout entire boundary. Good-rated MR images demonstrated effective visualization of the vessel wall, with only a small portion displaying obscure or invisible boundaries. Adequate-rated MR images indicated a reasonable image quality for visualizing the vessel wall, involving some parts but less

than a quadrant of obscure/invisible boundary. However, poor-rated MR images fail to visualize a significant portion of the vascular wall boundary. We analyzed plaque characteristics in the following arteries using Bouthillier's 1996 classification of the internal carotid artery into seven segments (18) and in conjunction with the anatomical structure of the intracranial arteries (19): A1 segment of anterior cerebral artery (ACA); M1–2 segments of middle cerebral artery (MCA); C2–7 segments of internal carotid artery; P1 segment of posterior cerebral artery (PCA); V4 segment of vertebral artery (VA); and basilar artery (BA) (20). Atherosclerotic plaque was considered when there is eccentric wall thickening (21). The maximum wall thickness (Max WT) of the atherosclerotic plaque was measured and T1 hyperintensity was identified when signal intensity within the plaque was 1.5 times higher than that in the normal vessel wall (22). When there were multiple atherosclerotic plaques in one patient, the Max WT was counted at the culprit artery and the most severe stenosis segment. The culprit artery was defined as arteries which were responsible for the most recent cerebrovascular symptoms. Luminal stenosis was measured on the TOF-MRA after maximum intensity projection using the WASID criteria (23). We randomly selected 20 patients to test the inter-rater reliability among evaluators in terms of measurements. The two observers had excellent agreement in identifying T1 hyperintensity and Max WT of intracranial plaques (24).

The WMH and acute infarction were evaluated on T2W FLAIR and DWI images respectively by two neurologists blinded to clinical information using the software of MIPAV (National Institutes of Health, USA). The acute infarction, which is defined as hyperintensity lesion on DWI images but isointensities on T1W images. White matter hyperintensities are lesion with hyperintensity on T2W FLAIR images which show isointensity or hypointensity on T1W images. We separated WMH from old infarction by their anatomical location, lesion size and imaging manifestations (25). WMH was assessed by quantitative volume and Fazekas scale. WMH volume was used for quantitative analysis, and Fazekas scale was used for categorical analysis. WMH was evaluated using Fazekas score system with the following criteria (26): periventricular white matter hyperintensity (PWMH): 0 = absence, 1 = caps or pencil-thin lining, 2 = smooth halo, and 3 = irregular PWMH extending into the deep white matter; deep white matter hyperintensity (DWMH) were rated as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, and 3 = large confluent areas. The TWMH with the Fazekas score ≤3 was considered as non-to-mild WMH group, and Fazekas score >3 was considered as severe WMH group (27). The areas on T2 FLAIR images corresponding to the acute infarction on DWI images were excluded when calculating the WMH volumes. PWMH was defined as lesion that is continuous with a lesion voxel within 4 mm of a ventricle, otherwise DWMH will be determined (28). The measurement areas for PWMH and DWMH volumes were illustrated in *Figure 1*.

Statistical analysis

Category variables were described as count and percentage and continuous variables with normal distribution were presented as mean ± standard deviation (SD). The consistency among evaluators for T1 hyperintensity and Max WT measurements was assessed using Cohen's kappa and the intraclass correlation (ICC) tests, respectively. Clinical characteristics were compared between patients with non-to-mild WMH and those with severe WMH group using independent *t*-test, Mann-Whitney U test, Chi-square, or Fisher test when appropriate. The relationship between clinical characteristics and WMH volume was analyzed using Spearman correlation or point-biserial correlation analysis. Binary logistic regression analysis was used to explore the relationship between intracranial atherosclerotic plaque characteristics and WMH severity, and multinomial logistic regression analysis was used to determine the association between intracranial atherosclerotic plaque characteristics and WMH score. The WMH volume was log transformed because it showed abnormal distribution, then. Associations of intracranial artery plaque characteristics with TWMH volume, PWMH volume and DWMH volume were determined using multilevel mixed-effects linear regression. In regression analyses, confounders with P values <0.2 in the single factor analysis were adjusted. Two-sided test was used, and all P value <0.05 was considered as statistically significant. All statistical analyses were performed by IBM SPSS 25.0 (IBM, New York, USA).

Results

Clinical characteristics of study population and their associations with WMH severity

From January 2018 to December 2018, a total of

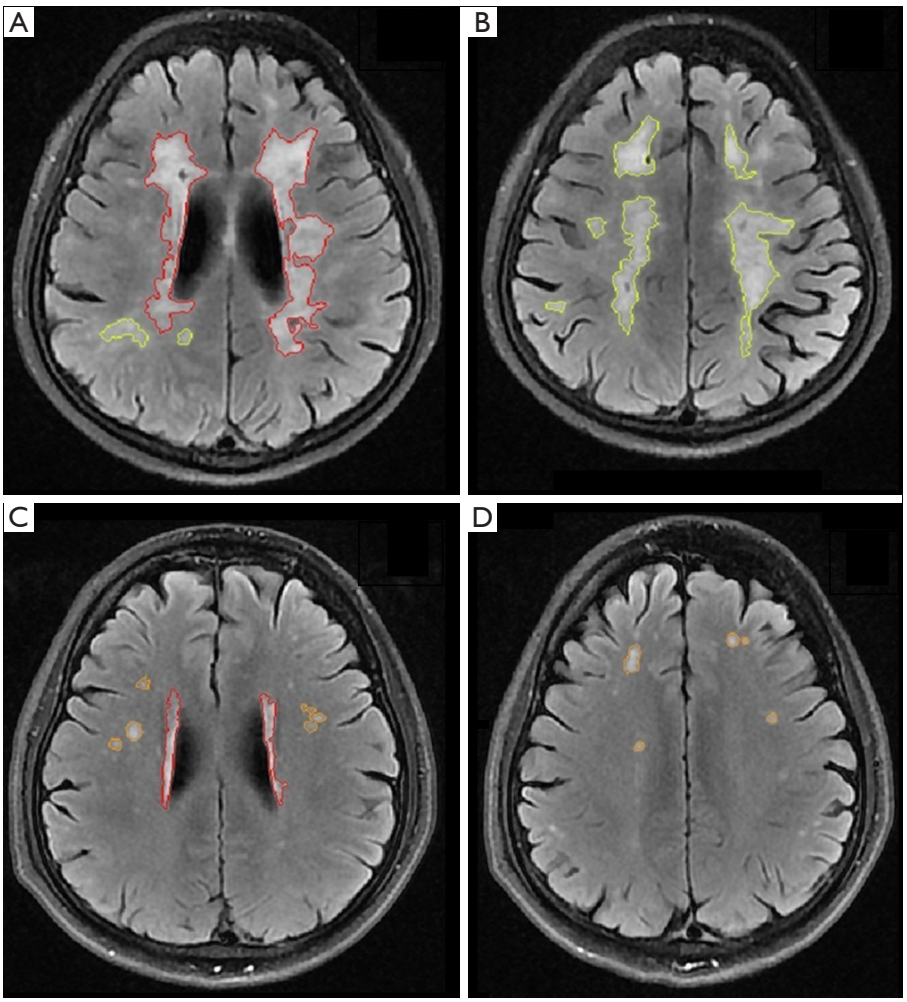

Figure 1 Example of white matter hyperintensity in patients with five intracranial atherosclerosis plaques and one intracranial atherosclerosis plaque. Upper row (A,B): patient with five plaques. The red area shows periventricular white matter hyperintense; the yellow area shows deep white matter hyperintense. Bottom row (C,D): patient with one plaque. The red area shows periventricular white matter hyperintense; the orange area shows deep white matter hyperintense.

174 patients were included. Of 174 recruited patients, 15 (mean age: 73.0±10.0 years; 9 males) were excluded due to the following reasons: poor image quality (n=2) and stroke caused by other causes (n=13; 8 patients with atrial fibrillation; 2 patients with oral anticoagulants; 3 patients with atrial fibrillation and oral anticoagulants). Finally, 159 patients were included in the study (*Figure 2*). The clinical characteristics of this study population are detailed in *Table 1*. Of the remaining 159 patients (mean age: 64.0±12.5 years; 103 males), 117 (73.6%) had hypertension, 60 (37.7%) had diabetes, 45 (28.3%) had hyperlipidemia, 55 (34.6%) were smoking and 20 (12.6%) had CAD. Significant difference was found in age (71.68±9.8 *vs.* 60.6±12.1 years, P<0.001) but not in other clinical characteristics (all P>0.05) between patients with severe WMH and those with non-to-mild WMH (*Table 1*).

Intracranial atherosclerotic plaque characteristics and WMH

The two readers demonstrated substantial consistency in vessel wall plaque evaluation, with κ=1.0 for T1 hyperintensity, ICC =0.94, 95% confidence interval (CI) (0.85–0.97) for Max WT measurement. Of 159 patients, 17 (10.7%) had one atherosclerotic plaque in intracranial artery and 142 (89.3%) had multiple atherosclerotic plaques

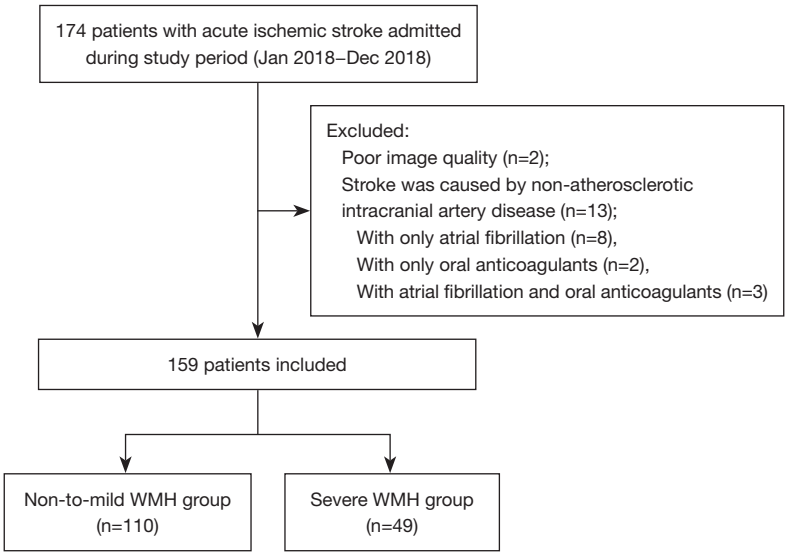

Figure 2 Flow chart of subjects screening. WMH, white matter hyperintensity.

Table 1 Baseline characteristics comparison of subjects included

Characteristics	All patients (n=159)	Non-to-mild WMH group (n=110)	Severe WMH group (n=49)	P value
Age, years	64.0±12.5	60.6±12.1	71.6±9.8	<0.001
Sex, male	103 (64.8)	73 (66.4)	30 (61.2)	0.531
Smoking	55 (34.6)	41 (37.3)	14 (28.6)	0.287
Hypertension	117 (73.6)	77 (70.0)	40 (81.6)	0.124
Hyperlipidemia	45 (28.3)	33 (30.0)	12 (24.5)	0.476
Diabetes	60 (37.7)	42 (38.2)	18 (36.7)	0.862
CAD	20 (12.6)	11 (10.0)	9 (18.4)	0.142
TC, mmol/L	4.5±1.1	4.5±1.2	4.4±0.9	0.914
TG, mmol/L	1.8±1.1	1.8±1.2	1.7±1.0	0.997
LDL-C, mmol/L	2.7±1.0	2.7±1.0	2.6±0.9	0.920
HDL-C, mmol/L	1.0±0.3	1.0±0.3	1.0±0.3	0.297
Antiplatelet agents	37 (23.3)	22 (20.0)	15 (30.6)	0.144
Antihypertensive agents	94 (59.1)	62 (56.4)	32 (65.3)	0.275
Lipid-lowering drugs	32 (20.1)	22 (20.0)	10 (20.4)	0.953

Continuous variables with a normal distribution were expressed as mean ± standard deviation; classified variables were summarized as counts (percentages). CAD, coronary artery disease; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; WMH, white matter hyperintensity.

in intracranial arteries. The plaque distribution in different intracranial artery segments is presented in *Figure 3*. As can be seen from *Figure 3*, intracranial arterial plaques were more common in C2–7 segments of internal carotid artery (83.0%) and M1–2 segments of MCA (53.5%). The mean ± SD of the plaque number, Max WT, degree of luminal stenosis, and plaque length was 3.48±1.84, 2.00±0.61 mm, 37.6%±14.6%, and 6.62±4.88 mm, respectively. Of 159 patients, 53 (33.3%) of them presented with T1 hyperintensity plaque. One hundred and forty-three

(89.9%) of them presented with WMH (Fazekas score ≥1). The mean Fazekas score was 2.64±1.66. Of 143 patients with WMH, the median (P25, P75) volume of TWMH, PWMH, and DWMH was 70.70 (18.00, 19.14) cm^3, 46.97 (13.09, 114.80) cm^3, and 20.45 (3.67, 70.67) cm^3, respectively.

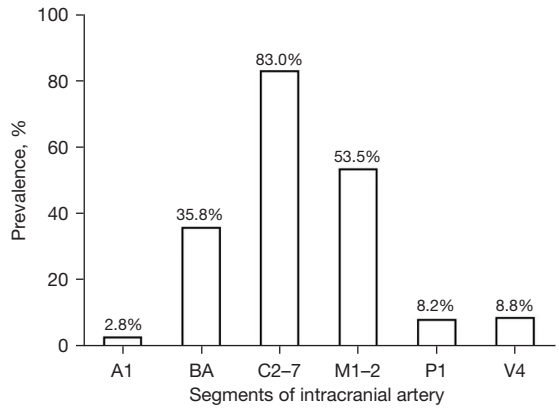

Figure 3 Atherosclerotic plaques distribution in intracranial vascular beds. A1, A1 segment of anterior cerebral artery; BA, basilar artery; C2–7, C2–7 segments of internal carotid artery; M1–2, M1–2 segments of middle cerebral artery; P1, P1 segment of posterior cerebral artery; V4, V4 segment of vertebral artery.

Clinical characteristics of study population and their associations with WMH volume

Table 2 summarizes the associations between clinical characteristics and WMH volume. Age was associated with TWMH volume, PWMH volume, and DWMH volume, all P values <0.05, with r=0.529, 0.523, 0.515, respectively. Smoking was associated with DWMH volume (r=–0.183, P=0.021). And hypertension was associated with DWMH volume (r=0.159, P=0.045).

Association between intracranial plaque characteristics and WMH score

After adjusting for age, sex, hypertension, CAD and antiplatelet agents, logistic regression analysis showed that plaque number was significantly associated with the presence of severe WMH [odds ratio (OR), 1.590; 95%

Table 2 Association between clinical characteristics and WMH volume

Characteristics	TWMH volume		PWMH volume		DWMH volume	
	r	P value	r	P value	r	P value
Age	0.529	<0.001	0.523	<0.001	0.515	<0.001
Sex	–0.026	0.746	–0.045	0.574	0.046	0.563
Smoking	–0.133	0.096	–0.120	0.132	–0.183	0.021
Hypertension	0.132	0.097	0.133	0.095	0.159	0.045
Hyperlipidemia	–0.048	0.551	–0.021	0.794	0.013	0.871
Diabetes	0.045	0.573	0.035	0.666	0.017	0.835
CAD	0.123	0.123	0.130	0.102	0.087	0.276
TC	–0.022	0.782	–0.007	0.926	–0.030	0.707
TG	–0.020	0.800	–0.026	0.747	–0.039	0.632
LDL-C	–0.047	0.562	–0.034	0.674	–0.051	0.527
HDL-C	0.003	0.975	0.009	0.911	0.056	0.491
Antiplatelet agents	0.119	0.134	0.138	0.083	0.050	0.533
Antihypertensive agents	0.042	0.607	0.040	0.623	0.106	0.186
Lipid-lowering drugs	0.008	0.917	0.004	0.963	–0.019	0.815

WMH, white matter hyperintensity; TWMH, total white matter hyperintensity; PWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; CAD, coronary artery disease; TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

Table 3 Association between intracranial plaque characteristics and the WMH score

WMH severity	Plaque number		Max WT		Stenosis		T1 hyperintensity		Plaque length	
	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Presence of severe WMH	1.590 (1.241–2.035)	<0.001	1.217 (0.643–2.304)	0.546	1.032 (1.002–1.064)	0.039	1.429 (0.641–3.188)	0.383	1.007 (0.904–1.123)	0.895
PWMH score										
Fazekas score 0	REF		REF		REF		REF		REF	
Fazekas score 1	0.956 (0.632–1.445)	0.830	1.973 (0.720–5.410)	0.187	1.036 (0.992–1.082)	0.110	1.586 (0.451–5.583)	0.472	1.127 (0.929–1.368)	0.226
Fazekas score 2	1.369 (0.889–2.109)	0.154	2.302 (0.772–6.864)	0.135	1.057 (1.008–1.109)	0.023	1.393 (0.365–5.320)	0.628	1.137 (0.927–1.395)	0.216
Fazekas score 3	1.726 (1.074–2.775)	0.024	1.887 (0.553–6.435)	0.311	1.047 (0.992–1.106)	0.096	1.075 (0.236–4.899)	0.925	1.198 (0.956–1.501)	0.116
DWMH score										
Fazekas score 0	REF		REF		REF		REF		REF	
Fazekas score 1	0.911 (0.691–1.202)	0.511	1.391 (0.701–2.762)	0.345	1.003 (0.974–1.032)	0.855	1.501 (0.610–3.693)	0.377	1.085 (0.968–1.217)	0.162
Fazekas score 2	1.561 (1.150–2.118)	0.004	1.337 (0.597–2.992)	0.480	1.031 (0.995–1.068)	0.095	0.683 (0.255–1.831)	0.448	1.072 (0.939–1.223)	0.307
Fazekas score 3	1.341 (0.908–1.980)	0.140	1.287 (0.443–3.737)	0.643	1.019 (0.970–1.071)	0.451	1.871 (0.436–8.033)	0.399	1.013 (0.829–1.238)	0.901

Adjusted for age, sex, smoke, hypertension, CAD and antiplatelet agent. WMH, white matter hyperintensity; Max WT, maximum wall thickness; OR, odds ratio; CI, confidence interval; PWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; CAD, coronary artery disease.

CI, 1.241–2.035, P<0.001], PWMH score of 3 (OR, 1.726; 95% CI, 1.074–2.775, P=0.024), and DWMH score of 2 (OR, 1.561; 95% CI, 1.150–2.118, P=0.004). In addition, our results showed that intracranial artery luminal stenosis was associated with presence of severe WMH (OR, 1.032; 95% CI, 1.002–1.064, P=0.039), and PWMH score of 2 (OR, 1.057; 95% CI, 1.008–1.109, P=0.023) after adjusted for confounding factors. However, luminal stenosis had no significant association with DWMH score (P>0.05, *Table 3*). We didn't find the association between other plaque characteristic (Max WT, T1 hyperintensity and plaque length) and WMH burden (all P>0.05, *Table 3*).

Association between intracranial plaque characteristics and WMH volume

Multivariate linear regression analysis showed that plaque number was significantly associated with DWMH volume (β=0.128; 95% CI, 0.016–0.240; P=0.026) after adjusted for age, sex. But there was no significant correlation between the two variables after further correction of smoking, hypertension, CAD and antiplatelet agent confounding factors (*Table 4*). However, no significant association was found between plaque number and TWMH volume or PWMH volume after adjusting for confounding factors (all P>0.05, *Table 4*). Multivariate linear regression analysis revealed that intracranial artery Max WT, luminal stenosis, T1 hyperintensity and plaque length were not significantly associated with TWMH, PWMH and DWMH volume after adjustment of confounding factors (all P>0.05, *Table 4*).

Discussion

This study investigated the relationship between intracranial atherosclerotic plaque characteristics and WMH in symptomatic patients with intracranial atherosclerosis using HR-VWI. We found that the plaque number of intracranial arteries was independently associated with the severity of WMH, high PWMH score, high DWMH score and DWMH volume. Intracranial arterial luminal stenosis was associated with WMH severity and high PWMH score. Our findings suggest that the burden of intracranial atherosclerosis characterized by plaque number and luminal stenosis might be an effective indicator of white matter

Table 4 Association between intracranial plaque characteristics and WMH volume

WMH volume	Plaque number		Max WT		Stenosis		T1 hyperintensity		Plaque length	
	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value	β (95% CI)	P value
TWMH volume										
Model 1	0.045 (−0.037 to 0.126)	0.284	0.028 (−0.207 to 0.264)	0.813	0.008 (−0.002 to 0.018)	0.118	−0.077 (−0.381 to 0.227)	0.617	0.008 (−0.031 to 0.047)	0.680
Model 2	0.034 (−0.049 to 0.117)	0.422	0.024 (−0.211 to 0.260)	0.838	0.008 (−0.002 to 0.018)	0.132	−0.067 (−0.378 to 0.244)	0.672	0.010 (−0.029 to 0.049)	0.617
PWMH volume										
Model 1	0.047 (−0.039 to 0.133)	0.283	0.064 (−0.183 to 0.312)	0.608	0.010 (0.000 to 0.021)	0.058	−0.016 (−0.337 to 0.304)	0.921	0.011 (−0.030 to 0.052)	0.598
Model 2	0.036 (−0.052 to 0.123)	0.423	0.061 (−0.186 to 0.308)	0.627	0.010 (−0.001 to 0.021)	0.065	−0.003 (−0.330 to 0.324)	0.984	0.014 (−0.028 to 0.055)	0.519
DWMH volume										
Model 1	0.128 (0.016 to 0.240)	0.026	0.183 (−0.143 to 0.509)	0.269	0.008 (−0.006 to 0.022)	0.283	0.197 (−0.225 to 0.619)	0.358	0.023 (−0.031 to 0.078)	0.396
Model 2	0.110 (−0.005 to 0.225)	0.061	0.172 (−0.154 to 0.498)	0.299	0.007 (−0.007 to 0.021)	0.337	0.221 (−0.221 to 0.653)	0.313	0.022 (−0.032 to 0.077)	0.419

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, smoking, hypertension, CAD and antiplatelet agent. WMH, white matter hyperintensity; β, standard regression coefficient; CI, confidence interval; Max WT, maximum wall thickness; TWMH, total white matter hyperintensity; PWMH, periventricular white matter hyperintensity; DWMH, deep white matter hyperintensity; CAD, coronary artery disease.

lesion.

In the present study, most of patients had multiple atherosclerotic plaques in intracranial arteries, particularly in intracranial internal carotid artery. The prevalence of multiple intracranial atherosclerotic plaques had been reported in previous studies. A community-based cohort study showed that nearly 20% of individuals had multiple intracranial atherosclerotic plaques, particularly in black men (the prevalence of multiple plaques was 32%) (29). Recently, a study in Chinese population suggested that patients with recurrent stroke had more intracranial plaques than those with first-time stroke (30). Previous study demonstrated that multiple atherosclerotic plaques had higher risk of stroke recurrence (31). The number of plaques may represent the burden of atherosclerotic disease and co-existing multiple atherosclerotic plaques may indicate higher burden of atherosclerosis. Many risk factors contribute to multiple atherosclerotic plaques, such as age, smoking, diabetes, and systolic blood pressure (32-35). WMH and atherosclerotic plaques usually share similar risk factors (36,37). However, our results showed that smoking was negatively associated with DWMH volume, which is inconsistent with most studies (38,39), which may be related to our small sample size and the small number of smokers in the enrolled patients (34.6%).

Plaque number had positive correlations with severe WMH, high PWMH score, high DWMH score, and DWMH volume in our study, which suggested that the burden of atherosclerotic disease by the plaque number might be a predictor of WMH. Plaque number is one of the important indicators of atherosclerotic burden. The potential mechanism of the relationship between large artery atherosclerosis and small vessel disease of WMH might be based on the fact that these two types of diseases shared many common risk factors (40). In addition, arterial stiffness has been demonstrated to be associated with WMH (41). It can be seen that there is a significant correlation between plaque number and WMH.

Our data showed that intracranial artery luminal stenosis was a dependent risk factor of severe WMH in this population. And luminal stenosis was also associated with high PWMH score. The relationship between arterial luminal stenosis and WMH is controversial. Several previous studies indicated that there was a significant relationship between carotid artery stenosis and the presence of WMH. Chutinet *et al.*'s study demonstrated that extracranial carotid artery stenosis was associated with greater WMH volume after adjustment for intracranial stenosis (P=0.04). Romero *et al.* thought that internal carotid artery stenosis ≥50% was associated with larger volume of WMH (OR, 2.35; 95% CI,

1.08–5.13). Stenosis degree of carotid artery was associated with white matter score in Manolio *et al.*'s study (P<0.01). As for Saba *et al.*'s study, a correlation was observed between the presence of leukoaraiosis and degree of carotid stenosis (Pearson correlation, r=0.23; P<0.001) (42-45). Some investigators believe that cerebral arterial stenosis could lead to chronic hypoperfusion of the white matter, then results in degeneration of myelinated fibers, which is a consequence of repeated selective oligodendrocyte death. On the contrary, other studies suggest that there is a lack of cause-effect relationship between large artery stenosis and WMH (46). Rothwell *et al.* (47) hold the point of view that low blood flow is not sufficient to lead to ischemic event in the brain tissues in symptomatic carotid artery stenosis, and poststenotic narrowing may be protective factor, because blood flow distal to the stenosis is insufficient to carry emboli to the brain. Hence, the relationship between luminal stenosis and the presence of WMH needs further study.

Another interesting finding of our study is that intracranial atherosclerotic plaques characteristics may be related to the distribution of WMH. Our study suggested that plaque number of intracranial arteries was associated with DWMH volume rather than PWMH volume. Anatomically, deep white matter is fed by medullary artery arising from the cortical branches of middle cerebral artery, and this region is more sensitive to arteriosclerosis (48). In addition, our study results suggested that luminal stenosis may be associated with high PWMH score, but not DWMH score. Previous study indicated that hemodynamic compromise was associated with PWMH (49), this is because periventricular white matter is supplied by ventriculofugal vessels, which are noncollateralizing and close to large artery (50). Whether the risk factors and pathophysiological mechanisms of PWMH and DWMH are different needs further study.

Our study results indicate some clinical implications. In patients with acute ischemic stroke, patients who have a larger number of intracranial artery plaques are more likely to have coexisting severe WMH, which had been established to be correlated with cognitive impairment and stroke risk. And, patients with severe WMH may have more intracranial artery plaques and a greater risk of ischemic stroke. In addition, luminal stenosis and severe WMH may be of mutual relationship. Therefore, intracranial plaque characteristics and WMH can be used as clinical predictors to assist clinicians in predicting clinical prognosis and providing appropriate pre-symptomatic interventions.

There are some limitations in our study. First, the assessment of the volume of WMH was not normalized by the brain volume among different individuals. Second, this is a cross-sectional study and the cause-effect relationship between intracranial plaque characteristics and severity of WMH could not be deduced. In the future, larger prospective studies are needed to elucidate the causal relationship between intracranial plaque characteristics and WMH. Third, other imaging features of cerebral small vessel diseases except WMH had not been investigated in this study. Fourth, the HR-VWI in this study was not an isotropic acquisition, and multiplanar reconstruction of the intracranial vessel wall could potentially result in inaccuracies of plaque characteristics and measurement errors. Finally, motion artifacts may affect the image quality and subsequent plaque characterization. In the future, it is better to use motion-robust HR-VWI technique to further boost up the evaluation accuracy.

In future research, we may consider to include only patients with anterior circulation plaques to explore the relationship between intracranial atherosclerotic plaques and WMH from the perspective of perfusion mechanisms. Furthermore, since the left and right perfusion zones may have different effects on the characteristics of intracranial atherosclerotic plaques and WMH, it is necessary to differentiate the left and right hemispheres in future studies.

Conclusions

Plaque number of intracranial arterial was associated with the severity of white matter lesion. Intracranial arterial luminal stenosis may be associated with severe white matter lesion. And the correlation between intracranial atherosclerotic plaque characteristics and WMH is worthy of further study.

Acknowledgments

We are particularly grateful to all the people who have given us help on our study.
Funding: This study was funded by the Hebei Medical Science Research Project (No. 20240973), Beijing Municipal Science and Technology Commission (No. D171100003017003), the Ministry of Science and Technology of the People's Republic of China (No. 2017YFC1307904), and the National Natural Science Foundation of China (No. 81771825).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-64/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-64/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the principles of the Declaration of Helsinki (as revised in 2013), and the protocol of this study was approved by the ethics committee of Beijing Tsinghua Changgung Hospital (No. 22028-0-02). Written informed consent was exempted due to the retrospective nature of this study.

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Cite this article as: Li M, Song X, Wei Q, Wu J, Wang S, Liu X, Guo C, Gao Q, Zhou X, Niu Y, Guo X, Zhao X, Chen L. The relationship between intracranial atherosclerosis and white matter hyperintensity in ischemic stroke patients: a retrospective cross-sectional study using high-resolution magnetic resonance vessel wall imaging. Quant Imaging Med Surg 2024;14(8):6002-6014. doi: 10.21037/qims-23-64

