Original Article

High-resolution magnetic resonance imaging features of time-of-flight magnetic resonance angiography signal loss and its relevance to ischemic stroke

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Background: Focal signal loss of intracranial artery stenosis is commonly observed on three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA). We aimed to investigate the underlying pathophysiology of vessel signal loss observed on 3D-TOF-MRA and its relevance to recent ischemic stroke.

Methods: High-resolution magnetic resonance imaging (HR-MRI) was performed in 401 patients with unilateral or bilateral moderate-to-severe stenosis (50–99%) of the middle cerebral artery (MCA) on TOF-MRA. The patients were classified according to the presence or absence of focal signal loss in the M1 segment of the MCA. The wall features between the vessels with and without signal loss were compared, and their relationship with recent ischemic stroke was analyzed.

Results: A total of 414 stenotic lesions caused by atherosclerotic plaque were detected, including 231 with signal loss on TOF-MRA and 183 without. The signal loss group, compared to the group without signal loss, showed a higher degree of stenosis (P<0.001), grade 2 enhanced plaques (82.3% *vs.* 28.4%; P<0.001), and concentric pattern (63.2% *vs.* 34.4%; P<0.001). Multivariate analysis suggested grade 2 enhanced plaques and concentric pattern were independently associated with signal loss. Patients in the signal loss group were more likely to have had a recent ischemic stroke (62.4% *vs.* 40.4%; P<0.001).

Conclusions: In addition to the degree of stenosis, the vulnerability and morphology of plaques on HR-MRI may influence signals on 3D-TOF-MRA. The presence of signal loss on 3D-TOF-MRA is associated with recent ischemic stroke.

Keywords: Magnetic resonance angiography (MRA); signal loss; plaque morphology; plaque stability; ischemic stroke

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Introduction

Intracranial atherosclerotic stenosis (ICAS) is one of the leading causes of ischemic stroke worldwide, especially in Asian populations (1). The middle cerebral artery (MCA) is most frequently involved and accounts for approximately 40–70% of ICAS cases (2). Time-of-flight magnetic resonance angiography (TOF-MRA) is a widely used noninvasive imaging technique for evaluating ICAS. Focal

signal loss usually occurs in the intracranial arteries on three-dimensional (3D) TOF-MRA, with its distal vessels being relatively well visualized. This type of signal loss on MRA usually occurs in vessels with stenosis >50% (3). Previous studies on carotid artery and MCA stenosis, using digital subtraction angiography (DSA) as the standard, concluded that signal loss on MRA represents moderate-or-severe stenosis of vessels (4,5) and thus is often referred to as a "false positive" in clinical practice. However, focal signal loss does not occur in all arteries with moderate or severe stenosis, and There are no studies have examined what differentiates moderate-to-severe stenosis with signal loss from that without signal loss. Dual screening of TOF-MRA and high-resolution magnetic resonance imaging (HR-MRI) can ensure that the focal signal loss is at the point of arterial plaque formation and at the narrowest part of the lumen. HR-MRI, or more precisely, high-resolution intracranial vessel wall MRI (VW-MRI) (6), is a noninvasive magnetic resonance (MR) intracranial vascular wall imaging technique that can assess arterial stenosis and plaque characteristics (7-10). It is regarded as a reliable technique due to its high consistency with DSA for the diagnosis of intracranial arterial stenosis (11).

In this study, we focused on the M1 segment of MCA and used HR-MRI to investigate the vessel wall characteristics and clinical value of focal signal loss on 3D-TOF-MRA maximal intensity projection (MIP) images. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-24-329/rc).

Methods

Patients

In this cross-sectional study, data from patients with MCA M1 segment focal signal loss or stenosis (50–99%) detected with TOF-MRA between January 2018 and December 2022 at the China-Japan Union Hospital of Jilin University Neurology Department were retrospectively reviewed. All patients fulfilled the following criteria: (I) completion of routine brain MRI [T1-, T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted imaging (DWI)], with HR-MRI being performed within 2 weeks; (II) lack of coexistent >70% ipsilateral extracranial or intracranial internal carotid artery stenosis; (III) no clinical evidence of cardioembolism (recent myocardial infarction within less than 3 weeks, atrial fibrillation, mitral stenosis or prosthetic valve, dilated cardiomyopathy, sick sinus syndrome, acute bacterial endocarditis, patent foramen ovale, etc.); (IV) good image quality for vessel wall and lumen identification; and (V) complete medical registration and treatment records. The following general clinical information was collected from all patients: age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, hyperhomocysteinemia, smoking, and alcohol consumption.

In total, 401 patients with moderate-to-severe stenosis (50–99%) of the MCA M1 segment on 3D-TOF-MRA MIP images were included in this study, comprising 417 stenosis lesions. Finally, 414 cases of atherosclerotic stenosis were included in the analysis, including 231 stenotic lesions with hyperhomocysteinemia and 183 stenotic lesions without focal signal loss in the MCA.

As shown on HR-MRI, 275 out of these 401 patients had severe stenosis in the M1 segment of the MCA, and they were divided into a symptomatic (n=151) and an asymptomatic (n=124) group based on whether they had recent ischemic stroke (a diagnosis of ischemic stroke within the preceding 2 weeks confirmed by DWI showing high signal and low or equal signal lesions based on the apparent diffusion coefficient at the corresponding locations in the brain parenchyma of the MCA blood supply area) (12,13). All the recent stroke survivors enrolled received systematic drug treatment after diagnosis, but none received endovascular stent treatment.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of China-Japan Union Hospital, Jilin University (No. 220506014). Written informed consent was obtained from all patients.

Imaging protocol

Imaging was performed using a 3-T system (MAGNETOM Skyra; Siemens Healthineers, Erlangen, Germany) equipped with a standard 8-channel head coil. The protocol consisted of 3D-TOF-MRA and pre- and postcontrast 3-dimensional T1-weighted HR-MRI. The 3D-TOF-MRA locator selected the MIP image and the source image of the 3D TOF-MRA as the topographic map to ensure that the cross-sectional image was perpendicular to the M1 segment of the MCA. The imaging parameters for high-resolution vessel wall imaging were as follows: repetition time/echo time, 900/15 ms; field of view, 127×164 mm^2; 192 slices; layer thickness, 0.63 mm; and matrix size, 256×256. The imaging parameters for TOF-MRA were as follows: repetition time/echo time, 20/3.69 ms; field of view, 200×200 mm^2,

158 slices; field of view, 200×200 mm^2; and matrix size, 352×256. Postcontrast HR-MRI was performed 5 minutes after the injection of a single dose (0.1 mmol/kg of body weight) of gadolinium-based contrast agent.

Image analysis

All image analysis and parameter measurements were performed using a research picture archiving communications system workstation (Philips, Amsterdam, the Netherlands). Stenosis was categorized as mild (0–49% stenosis), moderate (50–69% stenosis), severe (70–99% stenosis), and occluded. The following equation was used to determine the percent stenosis of an MCA: percent stenosis = $(1 - D_{stenosis}/D_{normal}) \times 100\%$, where $D_{stenosis}$ is the diameter of the artery at the site with the most severe degree of stenosis, and D_{normal} is the diameter of the proximal normal artery. Severe stenosis was defined as focalized signal reduction or loss in the MRA where $D_{stenosis}$ could not be measured with calipers (14).

Whole-brain HR-MRI was reviewed for a detailed analysis of the MCA M1 segment with moderate-to-severe stenosis in each patient. HR-MRI images were evaluated by two experienced neuroradiologists who were blinded to the identity and clinical information of the patients. Any disagreements were resolved through discussion. T1-weighted pre- and postcontrast images in three planes (axial, coronal, and sagittal) were analyzed to determine the presence of atherosclerotic plaques or other vascular lesions. Plaque was defined as a thickening of the vessel wall with reference to an adjacent proximal, distal, or contralateral vessel segment. Meanwhile, the culprit plaque was defined as the only lesion present within the vascular territory of the stroke or the most stenotic lesion when multiple plaques were present within the same vascular territory of the stroke (15).

The plaque characteristics were also evaluated. First, the degree of stenosis of the MCA on HR-MRI was calculated using the following formula: $(1 - LA_{narrow}/LA_{reference}) \times 100\%$ (13). The sagittal precontrast T1-weighted images (T1WIs) were magnified to 300%, and the lumen area (LA) of the stenotic MCA was measured at the most narrow LA (LA_{narrow}) and the LA at the reference site ($LA_{reference}$). The reference site was defined as the nearest proximal segment of the MCA stenosis that was free of plaque or contained the least amount of lesion. When a proximal reference site was not available, the adjacent distal reference site was used. Second, plaque distribution was characterized as eccentric if wall involvement was <50% and concentric if it was >50% (16). Third, intraplaque hemorrhage was defined as a high signal on T1-weighted fat-suppressed images that was 150% higher than the signal of the adjacent brain tissue (17,18). Fourth, the plaque enhancement grade was classified as follows: grade 0 if the enhancement was not greater than that of the intracranial arterial walls without plaque in the same individual, grade 1 if the enhancement was greater than grade 0 but less than that of the pituitary infundibulum, and grade 2 if the enhancement was not less than that of the pituitary infundibulum. The degree of contrast enhancement (CE) was quantified using the following equation: $CE = (SI_{postcontrast} - SI_{precontrast})/SI_{precontrast} \times 100$, where $SI_{postcontrast}$ and $SI_{precontrast}$ are the plaque signal intensity (SI) after and before the standardized enhancement scan, respectively. Plaque SI was normalized by manual measurement the SI of the adjacent brain parenchyma (area of 15 mm^2) (19). Finally, in the HR-MRI evaluation of intracranial artery dissection, the pathognomonic radiological findings of intracranial artery dissection included mural hematoma, intimal flap, and double lumen (20).

Statistical analysis

SPSS 25 (IBM Corp., Armonk, NY, USA) for Windows was used for statistical analyses. Statistical significance was set at $P<0.05$. Nonnormally distributed continuous variables were compared using the median and interquartile ranges, and categorical variables were expressed as values and percentages. The differences between the groups were analyzed using the Chi-squared test or Fisher exact test for categorical variables and the Mann-Whitney test for nonnormally distributed continuous variables. Independent predictors of focal signal loss in the M1 segment of the MCA and independent risk factors for recent ischemic stroke were analyzed using binary logistic regression analysis. Factors with $P<0.1$ in the univariate analysis or that were considered as being closely related clinically to the dependent variable were included as covariates in the multivariate analysis.

Results

Patient characteristics

In total, 401 patients with moderate-to-severe stenosis (50–99%) of the MCA M1 segment on 3D-TOF-MRA MIP images were included in this study, comprising 417

Table 1 Characteristics of patients with and without signal loss

Characteristic	Signal loss (n=231)	Without signal loss (n=183)	P value
Male, n (%)	157 (68.0)	111 (32.0)	0.122
Age (years), median [IQR]	56 [45–66]	59 [52–66]	0.014
Hypertension, n (%)	120 (51.9)	113 (61.7)	0.046
Hyperlipidemia, n (%)	219 (94.8)	169 (92.3)	0.306
Hyperhomocysteinemia, n (%)	98 (42.4)	87 (48.5)	0.298
Diabetes mellitus, n (%)	93 (40.3)	78 (42.6)	0.628
Smoker, n (%)	104 (45.0)	71 (38.8)	0.203
Drinker, n (%)	60 (26.0)	48 (26.2)	0.953
Symptomatic[†], n (%)	134 (58.0)	54 (29.5)	<0.001

[†], a recent ischemic stroke. The P values were calculated using the Mann-Whitney test for continuous data and the Chi-square test for categorical data. IQR, interquartile range.

stenosis lesions, including 233 stenotic lesions with and 184 stenotic lesions without focal signal loss in the MCA. On HR-MRI, there were 231 atherosclerotic plaques and 2 intercalations in the group with signal loss, and there were 183 atherosclerotic plaques and 1 intercalation in the group without signal loss. Finally, 414 cases of atherosclerotic stenosis were included in the analysis. *Table 1* presents the patient demographics and the main risk factors of atherosclerosis. The differences in age and hypertension between the two groups were statistically significant (P<0.05), as determined through univariate analysis.

Plaque features in the two types of stenosis

The two groups were significantly different in terms of degree of stenosis (P<0.001), plaque enhancement grade (P<0.001), and plaque morphology (P<0.001). The focal signal loss group, as compared to the no-signal loss group, were more likely to have grade 2 enhanced plaques (82.3% *vs.* 28.4%, P<0.001) and concentric plaques (63.2% *vs.* 34.4%, P<0.001) (*Table 2*). Similar results were observed in patients with severe stenosis as shown on HR-MRI, with the the signal loss group showing a higher prevalence of grade 2 enhanced plaques (P<0.001) and concentric plaques (P=0.002) than the no-signal loss group (*Table 2*). A representative case is shown in *Figure 1*.

Association of plaque features with signal loss

Age, hypertension, and plaque characteristics were used as input variables for the logistic regression analysis. The degree of stenosis, grade 2 enhanced plaques, and concentric plaques remained significant in the multivariate analysis (P=0.025, P<0.001, and P=0.004, respectively), with odds ratios (ORs) of 1.600 [95% confidence interval (CI): 1.062–2.411], 8.552 (95% CI: 5.230–13.984), and 2.039 (95% CI: 1.257–3.307), respectively (*Table 3*).

Associations of signal loss with recent ischemic stroke

The incidence of recent ischemic stroke among patients with severe stenosis on HR-MRI was higher in the group with signal loss than in that without signal loss (62.4% *vs.* 40.4%; P<0.001) (Table S1). A representative case is shown in *Figure 1*. The details of patient demographics, main atherosclerosis risk factors, and stenosis types on MRA are summarized in *Table 4*. Multifactorial logistic regression analysis showed that focal signal loss in the MCA M1 segment on MRA was an independent risk factor for recent ischemic stroke (OR =2.547; P<0.001) (Table S2).

Discussion

In this study, we compared the wall characteristics of vessels with signal loss and those without signal loss using HR-MRI. In addition to the degree of stenosis, we found the vulnerability and morphology of plaques to be independently associated with vessel signal loss. The stroke occurrence in the group with vessel signal loss was significantly higher than that in the group without signal loss.

Table 2 Comparison of HR-MRI features between the groups

HR-MRI feature	Signal loss (n=231)	Without signal loss (n=183)	P value	Signal loss^{severe} (n=181)	Without signal loss^{severe} (n=94)	P^{severe} value
Stenosis degree, n (%)			<0.001	NA	NA	NA
Mild	9 (3.9)	25 (13.7)				
Moderate	39 (16.9)	64 (35.0)				
Severe	181 (78.4)	94 (51.4)				
Occluded	2 (0.9)	0 (0.0)				
Plaque enhancement grade, n (%)			<0.001			<0.001
Grade 0	8 (3.4)	97 (53.0)		2.8%	39.4%	
Grade 1	33 (14.3)	34 (18.6)		13.8%	20.2%	
Grade 2	190 (82.3)	52 (28.4)		83.4%	40.4%	
Grade 2 *vs.* non-grade 2[†]	190/41	52/131	<0.001	151/30	38/56	<0.001
IPH, n (%)	3 (1.3)	0 (0)	0.258	NA	NA	NA
Plaque distribution, n (%)			<0.001			0.002
Concentric	146 (63.2)	63 (34.4)		66.3%	46.8%	
Eccentric	85 (36.8)	120 (65.6)		33.7%	53.2%	
Mean stenosis ratio (%)	NA	NA		89.2%	84.5%	

[†], item is expressed in numerical values only. The P values for categorical data were calculated using the Chi-square test and Fisher exact test. HR-MRI, high-resolution magnetic resonance imaging; NA, not available; MCA, middle cerebral artery; IPH, intraplaque hemorrhage.

The focal signal loss phenomenon was thought to be a "false positive" or "flow void" owing to the velocity and direction of blood flow during the imaging process, reflecting moderate or severe stenosis (5,21). As the lumen diameter of the artery decreases, blood flow velocity increases as blood passes through the stenotic segment. Moreover, a jet with subsequent turbulent flow can be observed near the vessel wall in the poststenotic segment. In the TOF sequence, the loss of phase coherence of moving spins occurs with fast and turbulent flow, eventually leading to reduced flow SI (5,21). In this study, the degree of stenosis was independently associated with focal signal loss, which is consistent with previous findings (4,5).

MRA signal loss has been reported to be correlated with stenosis shape. Sharp-edged stenosis is more likely to lead to signal loss than is smoothly shaped stenosis when the severity of stenosis and flowrate are equivalent (22). Plaque enhancement is usually considered to be a sign of unstable plaque (23,24), which is often characterized by surface ulceration (25,26). The surface irregularities of enhanced plaques or the unsmooth edges of the stenosis wall caused by ulceration may be the reasons for signal loss (22). We found that compared to the group without signal loss, the group with signal loss had a higher proportion of grade 2-enhanced plaque, which was independently correlated with focal signal loss. Nevertheless, to further clarify the impact of factors other than the degree of stenosis on signal loss, we compared the data from patients with severe stenosis as confirmed by HR-MRI. Although the ratio of stenosis of the two groups was highly similar (*Table 2*), the results obtained were similar to those mentioned. Therefore, grade 2 contrast-enhanced plaque may be a more influential factor in signal loss than the degree of stenosis. Furthermore, a similar analysis was performed on mild stenosis as confirmed with HR-MRI in both the signal loss and the stenosis group (9 and 25 cases, respectively). Consequently, a higher proportion of plaque enhancement was observed in the signal loss group (P=0.002; Table S3). This finding is of note despite the small sample size it is derived from, but we did not investigate it further in our study.

An orifice shape in stenosis has been reported to contribute to signal loss when stenosis severity and flowrate are equivalent (22). In comparison with eccentric plaques, concentric plaques may easily cause orifice-type stenosis in

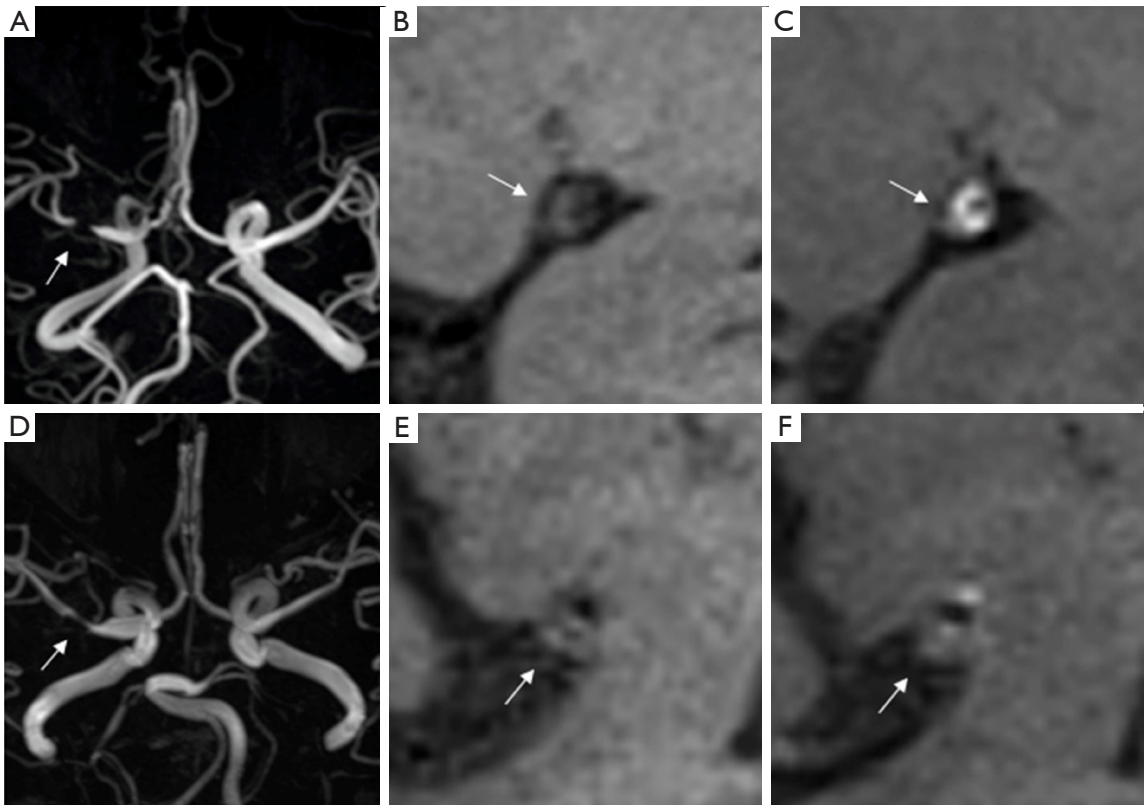

Figure 1 Magnetic resonance images of a case with and without signal loss. HR-MRI images of an MCA with focal signal loss (A-C) and an MCA without signal loss (D-F). (A) MRA showing focal signal loss in the M1 segment of the right MCA (arrow). (B) HR-MRI T1WI sagittal section of the narrowest vessel showing severe luminal stenosis and concentric plaque (arrow), with the ratio of stenosis being 90%. (C) T1WI+C* showing grade 2 enhanced plaque (arrow). (D) MRA showing a narrow M1 segment of the right MCA without signal loss (arrow), with the ratio of stenosis being 59.7%. (E) HR-MRI T1WI sagittal section of the narrowest vessel showing severe luminal stenosis and eccentric plaque (arrow), with the ratio of stenosis being 88%. (F) T1WI+C* showing grade 0 enhancement of the plaque (arrow). HR-MRI, high-resolution magnetic resonance imaging; MCA, middle cerebral artery; MRA, magnetic resonance angiography; T1WI, T1-weighted image; T1WI+C*, T1-wighted image of contrast-enhanced magnetic resonance imaging.

Table 3 Multivariate logistic regression analysis of signal loss

Characteristic	OR (95% CI)	P value
Age	0.991 (0.971–1.011)	0.390
Hypertension	0.687 (0.419–1.126)	0.137
Grade 2 enhanced plaque, n (%)	8.552 (5.230–13.984)	<0.001
Concentric plaque, n (%)	2.039 (1.257–3.307)	0.004
Stenosis degree	1.600 (1.062–2.411)	0.025

OR, odds ratio; CI, confidence interval.

the vessel lumen. In this study, an independent association with focal signal loss was observed for concentric plaque. Similar results were also found in the HR-MRI severe stenosis data, with the proportion of concentric plaque being higher in the signal loss group. Therefore, concentric plaque may be another factor that is more influential than the degree of stenosis in signal loss.

Our findings have certain clinical implications. Luminal stenosis with intracranial atherosclerotic plaque >50% is currently considered to be an independent predictor of ischemic stroke (27). However, studies have reported no significant differences in the degree of stenosis between symptomatic and asymptomatic groups of patients with moderate-to-severe MCA stenosis (13,28). The influence of collateral circulation status, plaque stability, hemodynamic effects, and other potential factors in predicting the risk of subsequent recurrent events may outweigh that of the

Table 4 Comparison of patient characteristics and 3D-TOF-MRA signal loss between the symptomatic and asymptomatic groups

Characteristic	Symptomatic (n=151)	Asymptomatic (n=124)	P value
Male, n (%)	98 (64.9)	85 (68.5)	0.524
Age (years), median [IQR]	56 [48–66]	57 [49–65]	0.725
Hypertension, n (%)	82 (54.3)	70 (56.5)	0.722
Hyperlipidemia, n (%)	146 (96.7)	120 (96.8)	0.968
Hyperhomocysteinemia, n (%)	74 (49.0)	44 (35.5)	0.024
Diabetes mellitus, n (%)	67 (44.4)	51 (41.1)	0.589
Smoker, n (%)	69 (45.7)	46 (37.1)	0.150
Drinker, n (%)	42 (27.8)	29 (23.4)	0.404
3D-TOF-MRA signal loss, n (%)	113 (74.8)	68 (54.8)	<0.001

The P values were calculated using the Mann-Whitney test for categorical data with the Chi-square test for continuous data. 3D-TOF-MRA, three-dimensional time-flight method magnetic resonance angiography; IQR, interquartile range.

degree of stenosis. A series of studies have confirmed that plaque CE and concentric plaques are closely related to the occurrence and recurrence of acute ischemic stroke; furthermore, it has been demonstrated that concentric plaques involve a wider area of the vessel wall and are more likely to develop into unstable plaques (19,29-34). This was confirmed in our study, as grade 2 enhanced plaques were more common in concentric than in eccentric plaques and concentric plaque was more prevalent in the focal signal loss group, which may explain the higher frequency of recent ischemic stroke in this group.

Although HR-MRI is superior in analyzing atherosclerotic plaque features and particularly important for the risk stratification of ischemic stroke due to intracranial arterial stenosis (35,36), it has obvious limitations in clinical application, such as the need for specialized imaging equipment and sequences and long scanning times. In this study, we showed that 3D-TOF-MRA, which is a relatively simple technique, can predict some of the wall features while obtaining information on the lumen of intracranial arteries. These results support the value of 3D-TOF-MRA MIP in the risk stratification of ischemic stroke in patients with intracranial vascular stenosis. Furthermore, DSA remains the gold standard for assessment of arterial stenosis. This study used the highly consistent characteristics of HR-MRI and DSA to evaluate stenosis (11), but DSA was not used for in-depth validation, which could be implemented in future research.

This study involved certain limitations which should be acknowledged. First, as we employed a retrospective design, future cohort studies can be devised to produce higher-quality evidence. Second, HR-MRI imaging scans were performed to be as perpendicular to the M1 segment of the stenotic MCA as possible; however, the tortuous shape of the MCA vessel alignment might have slightly affected the observations and measurements in this study. Third, unfortunately, the evaluation of the degree of vascular stenosis in this study was not been confirmed by DSA. Fourth, studies involving intraindividual comparisons with contrast-enhanced computed tomography angiography are needed in the future. Finally, further pathological confirmation regarding the vessel wall condition at the site of signal loss was not obtained.

Conclusions

Our findings suggest that focal signal loss on MRA can indicate the stability of atherosclerotic plaques and plaque morphology and be used to effectively assess ischemic stroke. In addition, patients with MRA focal signal loss in the MCA M1 segment had a higher incidence of recent ischemic stroke than those with moderate-to-severe—and even severe—stenosis. This may provide valuable insight into the risk stratification of patients with severe stenosis in the MCA.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-24-329/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-329/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. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of China-Japan Union Hospital, Jilin University (No. 220506014). Written informed consent was obtained from all patients.

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