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X.S. Liu, H.L. Zhao, Y. Cao, Q. Lu and J.R. Xu

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ORIGINAL RESEARCH

Comparison of Carotid Atherosclerotic Plaque Characteristics by High-Resolution Black-Blood MR Imaging between Patients with First-Time and Recurrent Acute Ischemic Stroke

X.S. Liu
H.L. Zhao
Y. Cao
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BACKGROUND AND PURPOSE: It has been shown that patients with a first ischemic stroke are at high risk of developing recurrent stroke due to carotid atherosclerotic plaque rupture. However, no one has defined the difference in plaques between initial and recurrent stroke. This study sought to investigate the characteristics of carotid plaque between patients with first-time and recurrent acute ischemic stroke by using MR imaging.

MATERIALS AND METHODS: Eighty-nine patients with recent acute ischemic stroke were recruited. All subjects underwent carotid high-resolution black-blood MR imaging. The index carotid arteries, defined as the arteries responsible for the ipsilateral stroke, were analyzed quantitatively and qualitatively. Carotid plaque burden and compositional features between patients with first-time and recurrent ischemic stroke were compared.

RESULTS: Of 89 recruited patients, 51 had first-time stroke and 38 had recurrent stroke. The mean WA, WT, and PWV were greater in patients with recurrent stroke than in patients with first-time stroke (all, $P < .05$). Compared with patients with first-time stroke, those with recurrent stroke showed significantly higher prevalence of calcification (44.7% versus 23.5%, $P = .035$) as well as a larger volume of LRNC (179.14 ± 254.81 mm^2 versus 71.65 ± 111.15 mm^2, $P = .027$). IPH or fibrous cap rupture or both were observed in 15.8% of patients with recurrent stroke and 3.9% of patients with first-time stroke.

CONCLUSIONS: Carotid plaques in patients with recurrent ischemic stroke are significantly aggravated compared with those in patients with first-time stroke, and monitoring carotid plaques in patients with initial stroke by MR imaging may be helpful for secondary stroke prevention.

ABBREVIATIONS: IPH = intraplaque hemorrhage; LA = lumen area; LRNC = lipid-rich necrotic core; MPRAGE = magnetization-prepared rapid acquisition of gradient echo; PWV = percentage wall volume; TOF = time-of-flight; TVA = total vessel area; WA = wall area; WT = wall thickness

Previous studies have demonstrated that patients with ischemic cerebrovascular events, such as TIA and stroke, are at high risk of developing recurrent stroke.[1-3] Carotid artery atherosclerosis is one of the major causes of acute large-vessel-disease stroke, which is a subtype of ischemic stroke according to the Trial of Org 10172 in Acute Stroke Treatment classification.[4] Clinically, measuring luminal stenosis via angiographic techniques has been considered the most effective strategy for evaluation of atherosclerotic disease severity.[5] Recent studies, however, have shown that vulnerable plaques may occur in arteries with low-grade stenosis (lumen reduction lower than 50%).[6-8] Therefore, it is important to directly visualize atherosclerotic plaques and characterize their vulnerability by using noninvasive imaging techniques.

Studies have demonstrated that high-resolution black-blood MR imaging is an ideal method to study carotid atherosclerosis.[6,9-11] MR imaging enables not only quantification of plaque burden but also characterization of the compositional features of carotid atherosclerotic disease, such as calcification, LRNC, IPH, and fibrous cap status.[6,10-12] Using this imaging technique, investigators have revealed significant differences in the tissue composition and morphology of symptomatic and asymptomatic plaques[13] and have demonstrated that vulnerable plaques defined by MR imaging accelerate recurrent cerebrovascular events.[14] However, these authors[13,14] did not study the plaque features in patients with recurrent stroke compared with those with initial stroke. Consequently, it is not certain whether the plaque is aggravated from the time of first ischemic attack to recurrent stroke.

We hypothesized that patients with recurrent stroke develop more advanced atherosclerotic lesions than those with first-time stroke, and the purpose of this study was to compare the characteristics of carotid atherosclerotic plaques between patients with first-time and recurrent acute ischemic stroke by using high-resolution black-blood MR imaging techniques.

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From the Department of Radiology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

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Drs Huilin Zhao and Xiaosheng Liu contributed equally to this work and are considered co-first authors.

Please address correspondence to Jianrong Xu, MD, Department of Radiology, Renji Hospital, Shanghai Jiao Tong University School of Medicine, 1630 Dongfang Rd, Shanghai 200127, China; e-mail: renjixjr@gmail.com

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Materials and Methods

Study Population

The study protocol was approved by the institutional review board, and informed consent was obtained from all patients before initiation of the study. Patients with acute ischemic stroke symptoms in the anterior circulation presenting to the emergency department were recruited in this study. The exclusion criteria were as follows: 1) probable cardiac source of embolism, 2) carotid aneurysm and arteritis, 3) intracranial artery stenosis shown by brain MR angiography, and 4) previous carotid endarterectomy on the index side or previous neck irradiation. All patients underwent neurologic examination, electrocardiography, laboratory analysis, and brain and carotid MR imaging examination. Patient data, including age, sex, stroke risk factors (such as hypertension, diabetes, hyperlipidemia, and history of ischemic heart disease), and stroke status (first-time or recurrent ischemic stroke) were collected from medical records. The presence of acute ischemic stroke in the anterior circulation was identified by 2 experienced neurologists (>10 years' experience) on the basis of the clinical and the imaging findings.[15] MR imaging for carotid arteries was performed within 1 week after neurovascular symptom onset.

Carotid MR Imaging Protocol

All patients were imaged with a 3T MR imaging scanner (Achieva; Philips Healthcare, Best, the Netherlands) by using an 8-channel Chenguang carotid coil (Chenguang Medical Technologies, Shanghai, China). A standardized imaging protocol was performed to obtain multicontrast cross-sectional MR images including TOF, T1-weighted, T2-weighted, and MPRAGE imaging[16] for bilateral carotid arteries centered on the bifurcation of the index carotid artery. The "index carotid artery" was defined as the artery responsible for the neurologic symptoms. The MR imaging parameters were as follows: 3D TOF: TR/TE, 20/5.1 ms; flip angle, 20°; quadruple inversion recovery[17] T1-weighted sequence: TR/TE, 800/10 ms; T2-weighted sequence with multi-double inversion recovery[18]: TR/TE, 4000/50 ms; 3D MPRAGE sequence: TR/TE, 9.2/5.5 ms; flip angle, 15°. All MR axial images were acquired with a section thickness of 2 mm, FOV of 14 × 14 cm, matrix size of 256 × 256, and an in-plane resolution of 0.54 × 0.55 mm. The longitudinal coverage of black-blood (T1-weighted, T2-weighted, and 3D MPRAGE) and bright-blood (3D TOF) sequences was 32 mm (16 sections) and 44 mm (22 sections), respectively. Fat saturation was applied to the acquisition of black-blood sequences to enhance the tissue contrast between the carotid vessel wall and the surrounding tissues. Maximum-intensity-projection MRA images were reconstructed from the 3D TOF images.

Carotid MR Image Interpretation

All MR images of the index carotid arteries were reviewed by 2 trained reviewers in consensus, blinded to clinical information and stroke status (first-time or recurrent stroke) by using the custom-designed software Cascade (University of Washington, Seattle, Washington).[19] Image quality was rated per axial location on a 4-point scale (1, poor; 2 marginal; 3, good; 4, excellent) depending on the overall signal intensity–to-noise ratio and the clarity of the vessel wall boundaries; images with an image quality of 1 were excluded from this study. For all MR images with acceptable image quality, the LA, WA, TVA, and the mean and maximum WT were measured for each axial location. Carotid plaque burden measurements, including mean LA, mean WA, mean WT, mean TVA, and PWV (PWV = Wall Volume/Total Vessel Volume × 100%) for each artery, were also determined. The degree of carotid stenosis was measured by using NASCET criteria (Percentage Stenosis = 100% × [1 − Luminal Diameter at the Point of Maximal Narrowing/Diameter of the Normal Distal Internal Carotid Artery]). The presence or absence of carotid plaque compositional features, such as calcification, LRNC, and IPH and/or fibrous cap rupture, was identified according to previously published criteria.[9] The volume of calcification, LRNC, and IPH for each artery was measured.

Table 1: Patients demographic and clinical information[a]

	First-Time Stroke (n = 51)	Recurrent Stroke (n = 38)	P Value
Age (yr)	59.98 ± 10.55	67.05 ± 9.69	.002[b]
Sex, male	72.5%	78.9%	.489
Body mass index	24.06 ± 2.76	23.69 ± 2.93	.543
Total cholesterol (mmol/L)	4.50 ± 1.05	4.96 ± 0.91	.031[b]
High-density lipoprotein (mmol/L)	1.08 ± 0.27	1.14 ± 0.24	.346
Low-density lipoprotein (mmol/L)	2.74 ± 0.94	2.95 ± 0.69	.223
Hypertension	70.6%	86.8%	.069
Diabetes	37.3%	39.5%	.831
Smoking	58.8%	50.0%	.408
Coronary heart disease	17.6%	22.5%	.732

[a] Mean ± SD or %.
[b] $P < .05$.

Statistical Analysis

Patients were divided into 2 groups according to the stroke status, namely a first-time stroke group and a recurrent stroke group. The normality of each continuous variable was tested by using the Kolmogorov-Smirnov Z-test. Normal distribution data were described as the mean value ± SD. The Student t test or Mann-Whitney U test was used to compare the significance of differences of variables between the 2 groups. For adjusting the age-confounding factor, we used the analysis of covariance for age control to compare the significance of differences of variables between the 2 groups. The prevalence of plaque compositional features was presented and compared with the χ^2 test or Fisher exact test between the 2 groups. Statistical analyses were performed with the Statistical Package for the Social Sciences, Version 16.0 software (SPSS, Chicago, Illinois). All tests were 2-tailed, and P values < .05 were considered statistically significant.

Results

Of the total of 94 consecutive subjects recruited from August 2009 to November 2010, 5 were excluded from this study due to poor MR image quality of the carotid artery. Of the remaining 89 subjects, the mean age was 63.00 ± 10.73 years (range, 31–82 years) and 67 (75.2%) were male. First-time stroke and recurrent stroke were found in 51 and 38 subjects, respectively. The mean age of patients with recurrent stroke was significantly greater than that of patients with first-time stroke (67.05 ± 9.69 years versus 59.98 ± 10.55 years, P = .002). Patients with recurrent stroke showed a significantly higher level of total cholesterol compared with those with first-time stroke (4.96 ± 0.91 mmol/L versus 4.50 ± 1.05 mmol/L, P = .031). The demographics and clinical information of this study population are summarized in Table 1.

Comparison of Carotid Plaque Burden

Most of carotid atherosclerotic burden measurements, including mean WA, mean WT, and PWV, of patients with recurrent

Table 2: Comparison of carotid plaque burden after adjusting the age

Carotid Plaque Burden	First-Time Stroke ($n = 51$)	Recurrent Stroke ($n = 38$)	P Value
Mean LA (mm^2)	49.06 ± 14.06	45.46 ± 17.98	.292
Mean WA (mm^2)	26.16 ± 5.58	29.82 ± 9.78	.043[a]
Mean TVA (mm^2)	75.22 ± 16.09	75.28 ± 20.62	.988
Mean WT (mm^2)	0.96 ± 0.22	1.13 ± 0.42	.043[a]
PWV (%)	35.49 ± 7.36	40.66 ± 11.86	.021[a]

[a] $P < .05$.

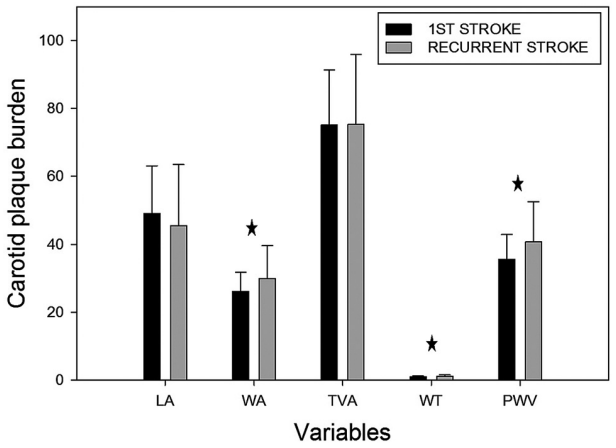

Fig 1. Comparison of carotid plaque burden in first-time and recurrent stroke after adjusting the age. The star indicates a significant difference ($P < .05$) between adjacent data.

stroke were significantly greater than those of patients with first-time stroke after adjusting the age (all P values $< .05$) (Table 2 and Fig. 1). No significant differences were found in mean LA (45.46 ± 17.98 mm^2 versus 49.06 ± 14. 06 mm^2, $P = .292$) and mean TVA (75.28 ± 20.62 mm^2 versus 75.22 ± 16.09 mm^2, $P = .988$) between patients with recurrent stroke and those with first-time stroke (Table 2 and Fig. 1). Additionally, the prevalence of lumen stenosis of >50% of patients with recurrent stroke was higher, but insignificant statistically, than that of patients with first-time stroke (15.8% versus 7.8%, $P = .315$).

Comparison of Carotid Plaque Compositional Features

Patients with recurrent stroke had a significantly higher prevalence of calcification compared with those with first-time stroke (44.7% versus 23.5%, $P = .035$) (Fig 2). The prevalence of LRNC (57.9% versus 49.0%, $P = .407$) and IPH and/or fibrous cap rupture (15.8% versus 3.9%, $P = .069$) in patients with recurrent stroke was greater, but statistically insignificant, than that of patients with first-time stroke. In the carotid arteries with LRNC, patients with recurrent stroke showed a significantly larger volume of LRNC compared with patients with first-time stroke (179.14 ± 254.81 mm^3 versus 71.65 ± 111.15 mm^3, $P = .027$). For carotid arteries with calcification, patients with recurrent stroke had a slightly larger volume of calcification compared with those with first-time stroke (32.60 ± 32.13 mm^3 versus 25.20 ± 27.98 mm^3, $P = .525$) (Figs 3 and 4).

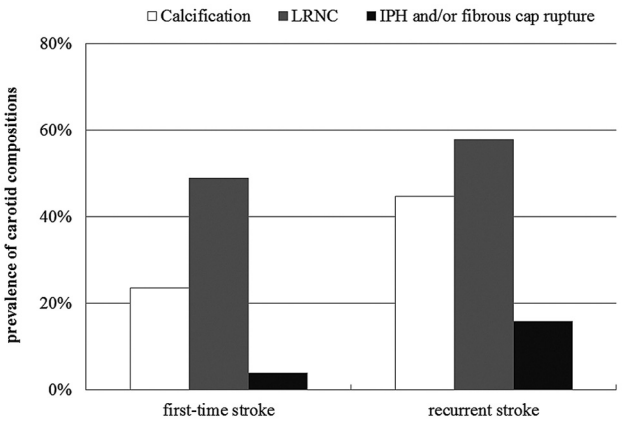

Fig 2. The prevalence of MR imaging–defined carotid plaque compositions (ie, calcification, LRNC, and IPH and/or fibrous cap rupture) in patients with first-time stroke compared with those with recurrent stroke. A high prevalence of calcification, LRNC, and IPH and/or fibrous cap rupture was found in the patients with recurrent stroke.

Discussion

This study is one of the first to compare the characteristics of carotid atherosclerotic plaques determined by high-resolution black-blood MR imaging between patients with first-time and recurrent acute ischemic stroke. We found that patients with recurrent stroke had significantly greater carotid atherosclerotic plaque burden. A higher prevalence of calcification and IPH and/or fibrous cap rupture in the carotid arteries was observed in patients with recurrent stroke compared with those with first-time stroke. In addition, the volume of LRNC was markedly larger in patients with recurrent stroke than in patients with first-time stroke.

In this study, patients with recurrent stroke were found to have similar traditional risk factors to those in patients with first-time stroke except for age and total cholesterol level. It has been shown that ischemic stroke is related to modifiable risk factors that have multiplied and compounded for many years. A number of studies have documented that the risk factors for recurrent stroke are the same as those for the first stroke.[2,20] The findings of our study are consistent with previous findings that no significant differences can be found between these 2 groups of patients in hypertension, diabetes, smoking, and history of coronary heart disease. Moreover, a very recent study investigated the carotid atherosclerotic plaques of 1385 subjects undergoing carotid endarterectomy and demonstrated that plaque vulnerability and risk of stroke increase gradually with age.[21] In our study, the total cholesterol level was significantly higher, and there was a trend in low-density lipoprotein toward hyperlipidemia in patients with recurrent stroke. Given the recent results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial[22] demonstrating that aggressive medical management is very important in prevention of a secondary event, the prevention of hyperlipidemia may also protect patients from a recurrent stroke.

For carotid atherosclerosis in this study population, we found that patients with recurrent stroke exhibit larger plaque burdens compared with those with first-time stroke, even after adjusting the age factor. In this study, the PWV was used to measure the plaque burden because it can fully exploit the 3D data acquisition inherent in carotid MR imaging and is the

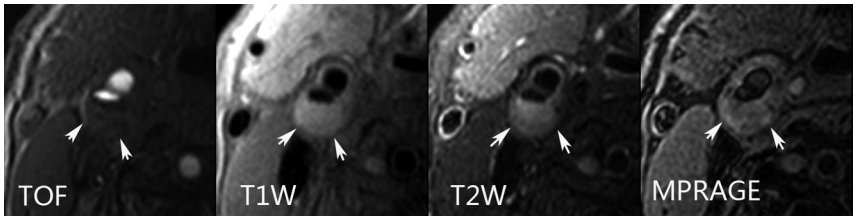

Fig 3. An atherosclerotic plaque with a large LRNC was found in the right internal carotid artery of a 65-year-old male patient who had ipsilateral first-time acute ischemic stroke. The plaque exhibits an intact surface and typical signal-intensity patterns of LRNC (*arrows*) on TOF, T1-weighted, and T2-weighted images. No high signal intensity was present on the MPRAGE image representing IPH.

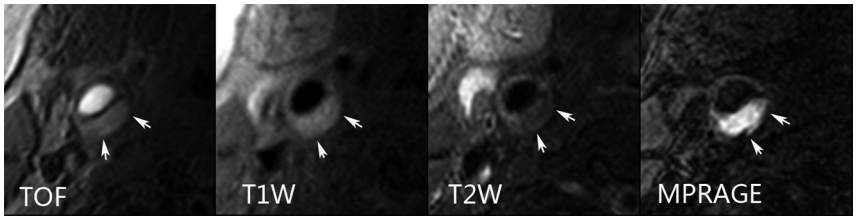

Fig 4. A large complicated plaque can be seen in the left common carotid artery of a 77-year-old male patient who experienced ipsilateral recurrent acute ischemic stroke. Inhomogeneous signal intensity (*arrows*) on TOF, T1-weighted, and T2-weighted images indicates LRNC with IPH and fibrous cap rupture. The hemorrhage was depicted more clearly by MPRAGE images.

most reproducible parameter to evaluate plaque burden among all the morphologic measurements by MR imaging.[23,24] Similarly, a previous study has shown that carotid plaque burden as measured by sonographic intima-media thickness is associated with recurrence of cardiovascular events including stroke.[25] Additionally, we found that there was no significant difference in the prevalence of carotid lumen stenosis of >50% between the 2 patient groups, indicating that the degree of arterial stenosis alone is a relatively poor predictor of recurrent neurologic events. This finding can be explained by the positive remodeling effect of the arterial wall.[26] Recent studies have shown that plaque burden measurements, such as PWV, are better indicators than luminal stenosis for evaluating the severity of atherosclerotic disease in the carotid artery.[7] The findings of this study imply that measures of carotid plaque burden by using vessel wall imaging techniques might be more effective indicators than the degree of luminal stenosis for assessing the risk of developing recurrent stroke for those symptomatic patients.

The prevalence of carotid calcification was found to be associated with recurrent stroke in this study. Our finding is consistent with that in a previous study by Wattanakit et al.[25] However, the role of calcification in carotid plaque vulnerability and its relation to the risk of developing ischemic stroke remains controversial. A previous systematic review suggested that clinically symptomatic carotid plaques have a lower degree of calcification than asymptomatic plaques.[27] In contrast, studies have demonstrated that the presence of carotid calcified plaque is an effective predictor for initial and recurrent vascular events.[25,28] In this study, the greater prevalence of calcification in patients with recurrent stroke may be attributable to the older age of subjects and the increasing presence of calcification from intermediate-to-advanced atherosclerotic lesions (American Heart Association types IV-VIII).[9] Investigators have observed that calcifications at superficial regions of the plaque[29] or in the fibrous caps[30] increase the risk of developing IPH or fibrous cap rupture. This phenomenon may be due to the increases in the mechanical stress at the interface between noncalcified and calcified compositions.[31,32] As such, for evaluation of the role of calcification of atherosclerosis in plaque stability and vascular events in symptomatic subjects, location may be key.[33]

Compared with patients with first-time stroke, a larger volume of carotid LRNC was seen in patients with recurrent stroke in this study. In a prospective study, Takaya et al[34] demonstrated that the size of the LRNC is associated with subsequent ischemic cerebrovascular events. These findings can be explained by the hypothesis in a prospective investigation that LRNC size may govern the risk of future surface disruption.[35] Previous studies have shown that the LRNC of carotid atherosclerosis regresses after treatment with lipid-lowering drugs.[36] For symptomatic patients, therefore, early detection of LRNC size by using accurate MR imaging techniques and receiving systemic lipid-lowering therapy may be helpful for prevention of recurrent stroke.

The prevalence of IPH and/or fibrous cap rupture tended to be higher in patients with recurrent than in those with first-time stroke in this study. This finding is in accordance with those of a number of previous studies that have demonstrated that carotid IPH[37-39] and fibrous cap rupture[40] are correlated with recurrent cerebrovascular events. Accordingly, early identification of high-risk plaque features may be necessary for prevention of secondary ischemic stroke.

Because a longer scanning time can lower the overall image quality due to poor cooperation of patients with severe diseases, most of our patients had mild-to-moderate ischemic stroke with few IPHs. Moreover, only MR images of at least average quality were considered for review, and patients with poor image quality were excluded, including 5 patients with image quality scores of 1. Development of new MR imaging protocols with shorter scanning times for the analysis of carotid atherosclerotic disease may broaden the use of carotid MR imaging in research and clinical work. Although the sample is small, this study represents a promising future regarding the potential value of MR imaging of plaque for secondary

stroke prevention. However, larger and prospective studies are needed to confirm the findings of this study.

Conclusions

Our study reveals significant differences in carotid atherosclerotic plaque features between patients with first-time and recurrent acute ischemic stroke. Patients with recurrent stroke tend to develop more advanced carotid atherosclerotic lesions and more high-risk plaque features compared with those with first-time stroke. Monitoring of carotid atherosclerosis may be needed, and MR imaging seems to represent a promising tool for secondary stroke prevention.

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