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Contrast-Enhanced High-Resolution MRI for Evaluating Time Course Changes in Middle Cerebral Artery Plaques

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Background and Purpose: It is clinically important to evaluate time course changes in symptomatic middle cerebral artery (MCA) stenotic plaques because of likely recurrence. The objective of this study is to determine whether contrast-enhanced high-resolution magnetic resonance imaging (MRI) is a feasible method for this purpose.

Methods: Contrast-enhanced, high-resolution, 3D turbo spin-echo images with low refocusing flip angle control (3D LOWRAT) applied to 7 patients with symptomatic MCA stenosis were evaluated at the initial (1 month after stroke onset) and follow-up (7 months after stroke onset) stages, and statistical variables, including plaque-to-thalamus signal intensity ratio, degree of stenosis, and stroke recurrence obtained at the 2 stages, were compared. Stenotic change at the initial stage was compared to that at the follow-up stage using MR angiography.

Results: In 4 of the 7 patients, the signal intensity ratio measured at the follow-up stage was lower than that measured at the initial stage and in 1 patient, the stenosis subsequently improved. We used a Chi-Square Test. In the other 3 patients, the signal intensity ratios did not differ between the 2 stages, and ischemic stroke occurred in 2 of these 3 patients.

Conclusion: Gadolinium contrast enhancement was found to be useful for effective evaluation of time course changes in the stability of symptomatic MCA stenotic plaques.

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Key words: ischemic stroke, intracranial stenosis, atherosclerosis, magnetic resonance imaging, middle cerebral artery

1. Introduction

Various features of plaque morphology, such as structure, composition, and volume, are targeted to identify the risk of ischemic stroke in the setting of middle cerebral artery (MCA) stenosis. Accurate evaluation of these features is relevant for the effective prediction of stroke. Non-invasive imaging modalities, such as high-resolution magnetic resonance imaging (MRI) and ultrasonography, that target inflammatory and thrombotic components of carotid atherosclerotic plaques, can be useful in the identification of symptomatic risk of MCA plaques[1]. Recently, many investigations performed on a large number of patients have focused on the clinical significance of gadolinium (Gd) enhancement of plaques in the setting of intracranial artery stenosis, as reported by Millon et al.[2], Skarpathiotakis et al.[3], Qiao et al.[4], Natori et al.[5], and Ryu et al.[6]. These papers have described that intracranial plaque enhancement on MRI can help identify lesions responsible for an ischemic event and can potentially serve as a marker of intracranial plaque instability and stroke risk[4]. It has also been described that plaque enhancement was significantly higher in patients with symptomatic

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plaques in accordance with the degree of stenosis[6]. Recently, three-dimensional contrast-enhanced, high-resolution, black-blood MRI has been applied to investigate atherosclerotic lesions, which not only accurately detects atheroma burden, but also gives information regarding atheroma composition such as necrotic core, intraplaque hemorrhage, inflammation, and neovascularization[7]. These plaque characteristics will help clinicians to estimate the vulnerability of the culprit lesion, and possibly to predict future vascular events[7,8]. Little data so far support the prognostic value of MRI to predict future stroke.

The natural course of intracranial vessel wall lesions in patients with ischemic stroke or TIA on 7.0-Tesla MRI has been investigated[9]. The investigators focused on differences between 1-week and 2-month images in the detection of the presence of lesions or changes in their enhancement patterns. However, no information is available regarding the natural course of plaque enhancement occurring at more than 2 months after the onset of cerebral ischemic stroke. The purpose of our study is to investigate whether contrast-enhanced high-resolution MRI can be used to determine longer time course changes in symptomatic MCA plaques.

2. Methods

2.1. Patients

This study was approved by the institutional ethics committee, and informed consent was obtained from every patient. The study was based on data clinically obtained from patients with symptomatic MCA stenosis who were admitted to the Department of Neurological Science at Nippon Medical School Hospital from January 1st, 2014 to December 31st, 2014. In all of the patients, cerebral ischemic stroke, including transient ischemic attack (TIA), was diagnosed. These patients had intracranial stenosis of at least 70% in the M1 segment of the MCA, as found by MR angiography and/or catheter angiography[10]; the patients also had recent ischemic stroke or TIA in the territory of the affected artery. Exclusion criteria consisted of contraindications to Gd-containing contrast agents (n=1), evidence of non-atherosclerotic intracranial vascular disease (dissection, n=2), and intraplaque hemorrhage. The remaining 7 patients qualified for analysis (**Fig. 1**). Subacute and chronic stages were evaluated by initial and follow-up contrast-enhanced high-resolution MRI.

We considered the following ischemic stroke risk factors: age, sex, hypertension, hyperlipidemia, diabetes, premedication with statins, coronary vascular disease, ischemic stroke or TIA history, atrial fibrillation, and history of smoking tobacco. We administered an antiplatelet agent and rosuvastatin to all 7 patients. In every patient, we administered 100 mg of aspirin.

2.2. Magnetic Resonance Imaging

Cross-sectional imaging was performed using a 3-Tesla whole-body clinical imager (Achieva TX, Philips Healthcare; Best, Netherlands). Each patient underwent 3D turbo spin-echo with refocusing flip angle control (Low Refocusing flip Angle Turbo spin-echo; LOWRAT) at 1 and 7 months (median time point) after disease onset in accordance with previously published methods[11,12]. The imaging parameters for 3D LOWRAT, modified axial 3D-T1-weighted imaging (T1WI)-TSE with flow sensitizing were as follows: field of view (FOV)=160×160 mm^2, actual voxel size 0.63×0.63×1.00 mm (reconstructed voxel size 0.50×0.50×0.50 mm), 80 slices, repetition time (RT)= 420 ms, effective echo time (TE_{eff})=9.2 ms, flip angle=75°, refocus flip angle=30°, echo train length=22, and acquisition time=5 min and 58 s. Post-contrast imaging was performed at 2 min after intravenous injection of a Gd-based contrast agent at a dose of 0.10 mmol/kg (gadopentetate dimeglumine or gadodiamide). The black-blood phenomenon was obtained, both along in-plane and through-plane directions, with high spatial resolution achieved. The imaging contrast and signal-to-noise ratios were similar to 2D-SE T1WI. A wide FOV was used in the process of creating imaging slices. A relatively short scan time of 6 min was found to be suitable for the clinical work-up.

2.3. Image Analysis

The images were reviewed by an independent neurologist (M.H-A.), who was blinded to the patients' clinical information, with the aid of a neuroradiologist who had 10 years experience (T.S.). The T1 images obtained before and after contrast injection with 3D LOWRAT were magnified up to 300%, and the regions of interest were set at the MCA stenotic and thalamic sites to measure signal intensity (SI), as previously described by Kanda et al.[13]. Regions of interest were drawn as in **Figure 1** to measure the signal intensity of the MCA stenotic and thalamic sites. The contrast ratio (CR) was calculated as:

CR=(post-CE T1 SI−pre-CE T1 SI)/post-CE thalamic SI, where CE is contrast enhancement, T1 is T1-weighted image, and SI is signal intensity. The CRs of the initial and follow-up stages were compared. In addition, stenosis grade was evaluated by MRA, not by LOWRAT. The evaluation of stenosis was based on the formula: % stenosis=[1−(D stenosis/D normal)]×100. D stenosis is

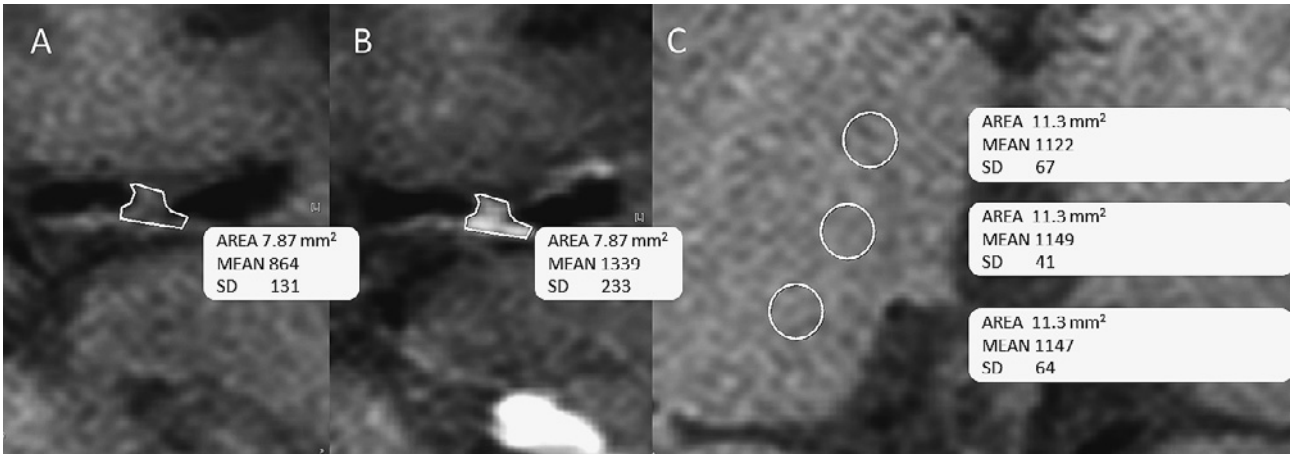

Fig. 1 Regions of interest (ROIs) were ovoid or linear and were placed to cover the plaques in a manner that was consistent with the stenotic segment of the middle cerebral artery on axial 3-dimensional-T1-weighted image-turbo spin-echo by a neuroradiologist. To increase the reliability of the ROIs, the rater measured the signal intensity (SI) 3 times with an ROI drawing and then averaged the SI values. ROIs in the thalamus were measured in 3 different regions in the same area and the SI values averaged. (Patient C in Fig. 3). The contrast ratio (CR) was calculated as: CR=(post-CE T1 SI–pre-CE T1 SI)/post-CE thalamic SI, where CE is contrast enhancement, T1 is T1-weighted image, and SI is signal intensity. SD is defined as standard deviation.

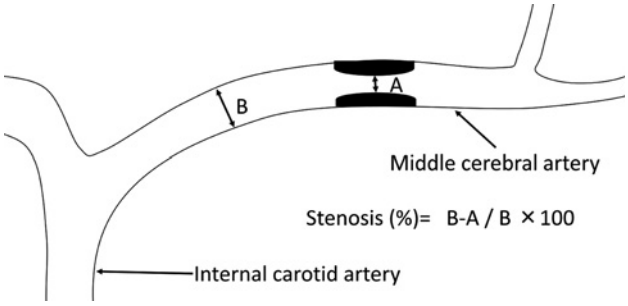

Fig. 2 Time-of-flight magnetic resonance (MR) angiography image is compared with the minimum lumen-narrowing diameter (A) to obtain the proximal, non-plaque lumen diameter (B). Thus, the stenotic change at the initial stage is compared to that at the follow-up stage using the formula (B–A)/B×100.

A and D normal is B[10] (**Fig. 2**).

3. Results

We studied the 7 patients (**Table 1**), who were all found to have focal enhancement at the stenotic region (**Fig. 3 and 4**). The enhancement after follow-up decreased in 4 patients (**Fig. 3**), while no such decrease was seen in the other 3 patients (**Fig. 4**). Only 1 of the 4 patients, whose focal enhancement decreased, showed improvement in M1 stenosis (**Fig. 5**), whereas no such improvement was found in 3 patients. Two of the 3 patients without focal enhancement had recurrence of ischemic stroke, while the other patient had no further ischemic stroke.

4. Discussion

In our study, all 7 patients with symptomatic M1 stenosis had focal enhancement, which we considered to be due to the presence of unstable plaques[14]. Strong enhancement of severe stenosis may result from inflammatory changes that occur within plaques during their growth. In this context, a histopathologic-radiologic correlation study of the extracranial carotid artery has shown that Gd enhancement is significantly associated with neovascularization, macrophage infiltration, and loose fibrosis occurring within plaques[2]. This indicates that focal enhancement takes place in the presence of unstable plaques. No reference is available. Several recent studies reported that plaque enhancement is more commonly observed in symptomatic intracranial artery stenosis, suggesting its vulnerability[15,16]. Another study reported that enhanced plaque is more commonly associated with multiple arterial embolic infarctions compared to a non-enhanced plaque which tends to go with a single infarction, implicating its structural weakness[17].

Van der Kolk et al.[7] reported the natural course of intracranial vessel wall lesions in patients with ischemic stroke or TIA on 7.0-Tesla MRI. The authors noted that the change in enhancement patterns over a 2-month follow-up period was observed in 11 of 28 patients with ischemic stroke or TIA (29%) and in 14 of 84 lesions (16.5%). Of these, 6 lesions showed improvement on both TOF-MRA and magnetization-preparation inversion recovery turbo spin-echo (MPIR-TSE), 3 lesions showed

Table 1 Patient characteristics

Patient	Sex/ Age (y)	HTN	Hyper-lipidemia	DM	Smoking status	AF	CAD	Prior stroke or TIA	Premedi-cation with statin	Sub-type	Initial MR imaging after onset (days)	Follow-up MR imaging after onset (days)	Clinical course
A	F/48	Yes	Yes	No	No	No	No	TIA	No	TIA	28	119	No recurrence
B	F/70	Yes	Yes	No	No	No	No	No	No	CI	71	169	No recurrence
C	F/69	Yes	Yes	No	Yes	No	No	No	No	CI	29	389	No recurrence
D	M/71	Yes	Yes	No	Yes	No	No	No	No	TIA	35	202	No recurrence
E	M/67	Yes	Yes	No	Yes	No	No	No	No	CI	45	126	No recurrence
F	F/38	Yes	Yes	No	Yes	No	No	No	No	TIA	32	300	TIA recurrence
G	F/68	Yes	Yes	No	No	No	No	No	No	CI	33	370	CI recurrence

Abbreviations: AF, atrial fibrillation; CAD, coronary artery disease; CI, cerebral infarction; DM, diabetes mellitus; HTN, hypertension; MCA, middle cerebral artery; MR, magnetic resonance; TIA, transient ischemic attack

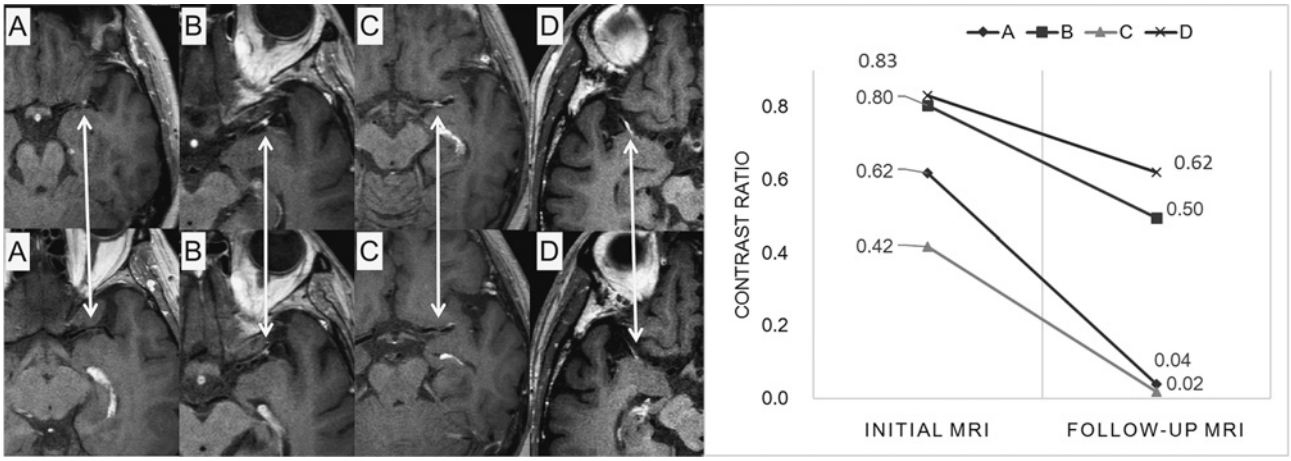

Fig. 3 Contrast-enhanced MR images obtained soon after the onset of disease and at the follow-up stage are shown for 4 patients (A–D). Arrows indicate focal contrast enhancement at the M1 segment of the middle cerebral artery (MCA) stenotic region. The graph shows the contrast ratios of the 4 patients at the initial and follow-up stages (Fig. 3). Focal enhancements are reduced.

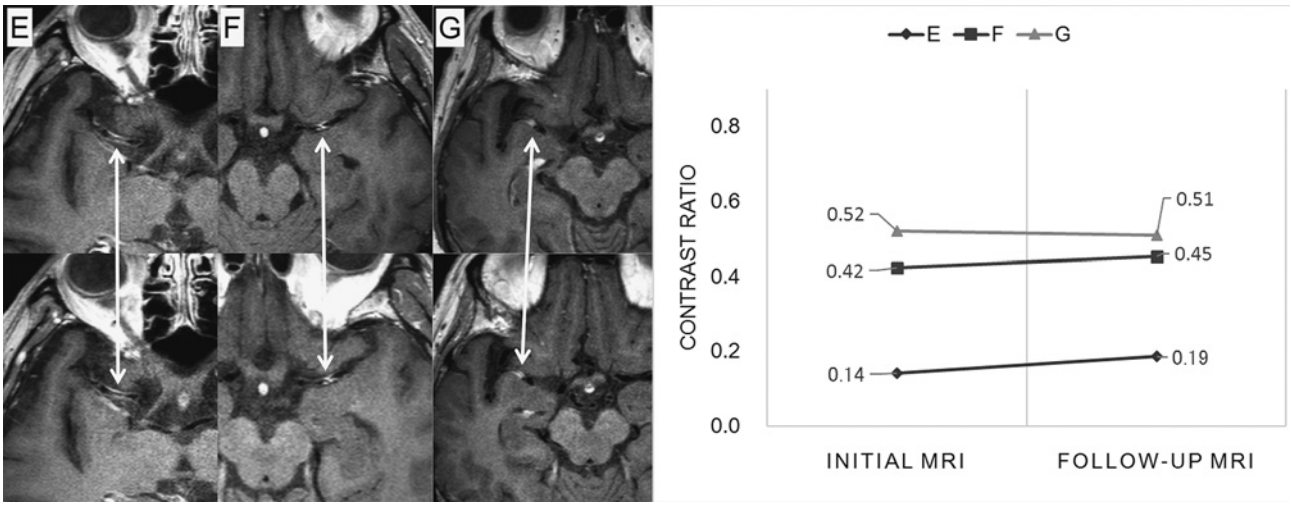

Fig. 4 Contrast-enhanced MR images at the initial stage and follow-up stage are shown for 3 patients, as in Figure 3. Arrows indicate focal enhancement at the M1 segment of the middle cerebral artery (MCA) stenotic region. Graphs on the right are the contrast ratios at the initial and follow-up stages. Focal enhancements are not reduced.

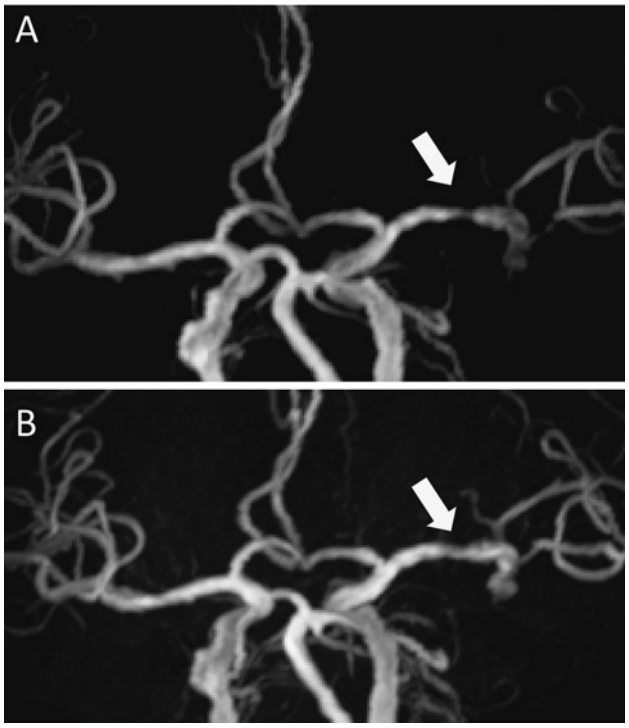

Fig. 5 (Patient C of Fig. 3); stenosis of the left M1 segment at the initial stage (upper) had improved at the follow-up stage (lower). In the other patients, stenosis between the initial and follow-up stage had not changed.

new enhancement, 3 lesions improved on MPIR-TSE but not on TOF-MRA, and 1 lesion improved on TOF-MRA but not on MPIR-TSE. The other 71 lesions (83.5%) showed no changes over time. In our study, however, focal enhancement was observed in 4 of 7 patients (57%) with symptomatic M1 segment stenosis at 1 month after disease onset, but this effect decreased at 7 months after. Our observation of the change in focal enhancement was higher than the data reported by van der Kolk et al.[7] (57% vs. 29%); there were differences in terms of numbers of patients (7 vs. 28), observation period (7 vs. 2 months), and MRI (3- vs. 7-Tesla).

In the present study, we observed focal enhancement reduction in 4 of 7 patients, while the other 3 patients showed no reduction. In 2 of those 3 patients, ischemic stroke recurrence occurred (patients F and G in **Fig. 4**). The patients experienced more recurrences due to the extended follow up period. MRA showed that stenosis improved in only 1 of the 4 patients who had attenuated plaque enhancement. A possible reason is that positive remodeling had already taken place in the artery and also that stenosis seemed to improve in association with plaque reduction[16,17]. No definitive information is available to confirm this. Despite this limitation, our finding may be noteworthy enough to add prospective data in the near future.

The current study has some additional limitations. First, we scanned our patients retrospectively. The lack of comparison between patients with asymptomatic and symptomatic MCA plaques is another limitation. Furthermore, one of our reviewers was a neurologist, not a neuroradiologist. Since patients with stenosis less than 70% were excluded, selection bias may have had an effect on our results. Our study suggests that longer follow-up periods may lead to more changes in Gd-contrast enhancement at the site of high-grade stenosis. Our findings may contribute to the understanding of the natural development of symptomatic MCA stenosis and may influence clinical evaluation as well as improve recurrence prediction. One patient had a decrease in plaque enhancement and consequent improvement of stenosis. This suggests that the reduction of intracranial artery plaques may be accurately observed by contrast-enhanced high-resolution 3T-MR images, although further studies with a prospective design, enrolling more patients, evaluated over a period of 6 months or longer will be required.

Conflict of Interest: One of the authors of this paper, Masami Yoneyama, works for Philips Electronics Japan, Tokyo, Japan.

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