Title: Prediction of intracranial arterial stenosis progression in patients with moyamoya vasculopathy: contrast-enhanced high-resolution magnetic resonance vessel wall imaging

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Short title: Prediction of moyamoya vasculopathy stenosis progression.

ABSTRACT

Object: Moyamoya vasculopathy (MMV) is characterized by progressive stenosis of the intracranial arteries. MMV currently has no curative treatments, and cerebral ischemia and hemorrhage are the major outcomes. Evaluation of the stroke risk of each patient due to the progression of intracranial arterial stenosis is clinically important.

Methods: We prospectively reviewed patients with intracranial arterial stenosis and already-diagnosed MMV. High-resolution magnetic resonance imaging (HR-MRI) using contrast agent is the novel vessel wall imaging (VWI) technique for directly evaluating vascular walls and intracranial artery disease. All patients underwent HR-VWI and MR angiography at the time of registration, and follow-up MR angiography. Fisher's exact tests were used to assess associations between the degree of wall enhancement, and between stable and progressive intracranial arterial stenosis.

Results: A total of 24 patients (17 female; mean age, 36.1 ± 16.8 years, 3-67 year) with MMV were consecutively recruited to this study. Progression of stenosis was shown in 6 lesions (66.6%) on strong enhancement, 2 lesions (12.5%) on mild enhancement, and 1 lesion (4.3%) on lack of enhancement. Arterial vessel wall enhancement in MMV patients correlated closely with progression of intracranial arterial stenosis ($p=0.002$).

Conclusions: Arterial vessel wall enhancement in MMV patients was closely related to progression of intracranial arterial stenosis. Strong enhancement of the intracranial vessel wall was associated with intracranial arterial stenosis progression, and lack of enhancement correlated with the stability of intracranial arterial stenosis.

INTRODUCTION

Moyamoya vasculopathy (MMV) is characterized by progressive stenosis of the intracranial internal carotid artery (ICA) and its proximal branches.[1] MMV can manifest as moyamoya disease (MMD), unilateral MMD or quasi-MMD. MMD is usually idiopathic and bilateral. Unilateral MMD is defined as MMD with unilaterally affected vessels and no association with any other underlying conditions. Angiographic findings of bi- or unilateral MMD associated with a definite underlying disease, such as hyperthyroidism, or trisomy 21, are usually categorized as quasi-MMD.[2,3] Prevalences of MMD, unilateral MMD and quasi-MMD have been reported as 5.22/100,000, 0.66/100,000 and 0.34/100,000, respectively.[3] Cerebral ischemia and hemorrhage are the major outcomes of MMV.[4,5] In particular, pediatric MMD is clinically characterized by the onset of one or more cerebral ischemic events. No curative treatment is available for MMV. Surgical revascularization therapies can be actively considered as secondary prevention for patients with symptomatic MMV.[4]

Intracranial magnetic resonance (MR) vessel wall imaging (VWI) is one emerging technique for evaluating the morphologies of atherosclerotic plaques, arterial walls, and surrounding structures. Although various techniques for VWI have already been reported, high-resolution MR imaging (HR-MRI) using contrast agent is a new VWI technique for directly evaluating the vascular wall and intracranial artery disease.[6–8] Intracranial artery atherosclerosis, MMD, vasculitis, and reversible cerebral vasoconstriction syndrome can also be diagnosed and differentiated using HR-MRI. Previous studies of carotid artery stenosis patients have shown that vessel wall enhancement may reflect inflammation or neovascularization associated with disease stability and worsened clinical outcomes.[9–11] Wang et al. recently reported that intracranial vessel wall enhancement is associated with acute ischemic infarction in

patients with MMV.[12]

There are some MMV patients cases that intracranial arterial stenosis was progressed and this led transit ischemic attack or cerebral infarction for a long time follow up period. It is clinically important to evaluate the possibility of progress intracranial arterial stenosis before ischemic stroke events will occur. Using contrast-enhanced HR-MRI VWI, we evaluated the progression of intracranial arterial stenosis in patients with MMV.

MATERIALS AND METHODS

Study design

The study protocol was approved by Medical Research Ethics Committee of Nagoya University Hospital (approval number: 2016-0547). All patients or their legal representatives provided written informed consent. Our study was carried out in accordance with the relevant guidelines and regulations. Patients with MMV were recruited in this study. After approval of the study protocol by the hospital research ethics board, we prospectively reviewed patients with intracranial arterial stenosis who had been diagnosed with MMD or quasi-MMD at Nagoya University Hospital between April 2016 and June 2017. MMD or quasi-MMD were diagnosed by the Research Committee on Moyamoya Disease of the Ministry of Health, Welfare, and Labor, Japan criteria. This diagnostic criteria requires all of the following findings: (1) steno-occlusive lesions around the terminal portions of the internal carotid arteries; (2) moyamoya vessels at the basal ganglia appearing as abnormal vascular networks on MRA; (3) findings 1 and 2 are present bilaterally (if findings 1 and 2 are shown bilaterally or unilaterally on conventional angiography, those cases can be diagnosed MMD); and (4) known diseases with similar angiographic findings are excluded, such

as atherosclerosis or irradiation to the head. So we included all moyamoya disease patients and quasi-moyamoya disease patients, though the patients who have atherosclerotic arterial changes in MR angiography were excluded. All patients underwent HR-MRI and MR angiography (MRA) at the time of registration, and follow-up MRA within 6 months. Two independent radiologists blinded to clinical and vessel wall MRI data reviewed consecutive luminal studies performed for all MMD subjects. For the detection of enhancement, a T1-weighted MRI sequence without contrast (precontrast) was used for comparison with the contrast-enhanced sequence (postcontrast). Comparing T1-weighted pre- and postcontrast imaging, lesions were assessed for the presence and intensity of enhancement. The degree of enhancement of MMV was then qualitatively graded depending on signal intensity on post-contrast images compared to the corresponding pre-contrast images[12,13]: grade 0, no enhancement (Figure 1); grade 1, mild enhancement, with signal intensity of the vessel wall less than that of the pituitary infundibulum (Figure 2); and grade 2, strong enhancement, with signal intensity of the contrast-enhanced vessel wall similar to or greater than that of the infundibulum (Figure 3). Intracranial arterial stenosis progression was evaluated on MRA. If the stenotic lesion was extended from proximal MCA to distal MCA on follow up MRA, we assessed the intracranial arterial stenosis progression as “progressed”. On the other hand, if the stenotic lesion was not extended on follow up MRA, we assessed the intracranial arterial stenosis progression as “stable”. Standard protocol time-of-flight MRA was referenced when assessing VWI lesions. The artery involved was also documented for each lesion.

Imaging protocol

Patients were scanned using a 3-T Siemens SkyraMR scanner (Siemens Healthcare, Ehrlangen, Germany). The MR VWI protocol included three-dimensional (3D) time-of-flight MRA (in-plane resolution, 0.5×0.5; slice thickness, 0.8 mm; repetition time/echo time, 23.0/3.81 ms; flip angle, 16°; field of view, 200×200 mm; time, 4:11 min), T1 (0.5×0.5 in-plane resolution; slice thickness, 5 mm; repetition time/echo time, 500/11 ms; averages, 4; matrix, 384×384 pixels; field of view, 200×200 mm; Generalized Auto calibrating Partial Parallel Acquisition (GRAPPA) factor, 1; turbo factor, 1; time, 1:38 min), pre- and postcontrast high-resolution VWI performed in multiple planes to obtain at least two planes for each lesion, axial and orthogonal 3D T1-weighted high-resolution VWI (in-plane, 0.6×0.6; slices, 0.8 mm; field of view, 200×200 mm; matrix, 320×320; repetition time/echo time, 580/5.6 ms; averages, 1; GRAPPA factor, 2; turbo factor, 40; time, 4:16 min), and 3D T2-weighted Sampling Perfection with Application optimized Contrast using different flip angle Evolution (SPACE) (0.5×0.5 mm in-plane resolution; slice thickness, 1.0 mm; field of view, 200×200 ms; repetition time/echo time, 4000/545 ms; slice oversampling, 37.5%; slices, 104; matrix, 384×384 mm; turbo factor, 555; time, 3:02 min) sequences.

Statistical methods

SPSS for Windows version 20.0 (IBM, Chicago, IL, USA) was used for all statistical analyses. Fisher's exact tests were used to assess associations between the degree of wall enhancement, and between stable and progressive intracranial arterial stenosis. Binary logistic regression analysis was used to determine the risk factor for intracranial arterial stenosis. Data are given as odds ratios (ORs) with 95% confidence intervals (CIs). Inter- and intra-reader agreement for grading the intracranial vessel wall enhancement was assessed using Cohen's Kappa analysis before reader consensus to

settle disagreements. A k value of less than 0.40 was considered poor agreement; a k value of 0.4–0.75 was characterized as fair to good agreement; a k value of greater than 0.75 indicated excellent agreement. Statistical significance was set at the level of $P<0.01$.

RESULTS

Characteristics of patients with MMV

Between April 2016 and June 2017, a total of 24 patients with MMV (17 female; mean age, 36.1 ± 16.8 years, 3-67 year) were consecutively recruited to this study. Of the 48 sides in these 24 patients, 16 sides showed transient ischemic attack, 3 showed hemorrhagic stroke, 9 showed ischemic stroke, and 20 were asymptomatic. Patients with symptomatic intracranial stenosis underwent 3-Tesla MRI/MR angiography at a median interval of 66 months after symptom onset. Patient characteristics are summarized in Table 1. Intracranial vessel wall stenosis in the terminal ICA (internal carotid artery) and/or M1 segment of the MCA (middle cerebral artery) was identified in all patients. After contrast administration, 9 sides (18.8%) showed grade 2 enhancement and 16 sides (33.3%) displayed grade 1 enhancement (Table 2). All patients underwent follow-up 3-Tesla MR angiography within 6 months. Nine lesions (18.8%) showed progression of stenosis (Figure 4).

Relationship between intracranial vessel wall enhancement and progression of intracranial arterial stenosis

Progression of stenosis was shown in 6 lesions (66.6%) on grade 2 enhancement, 2 lesions (12.5%) on grade 1 enhancement, and 1 lesion (4.3%) on grade 0 enhancement (Table 3; $p=0.002$).

Univariate and multivariate risk factor for intracranial arterial stenosis

Univariate risk factor for intracranial arterial stenosis was assessed. ORs and p value of all variables tested are listed in Table.4 Only vessel wall enhancement was identified to be a risk factor for intracranial arterial stenosis (Table.4). To rule out possible collinearities, multivariate analysis was performed. Vessel wall enhancement was of significant independent predictive value (p=0.006) (Table.4).

Reproducibility

Inter-reader agreement between the two readers for enhancement of the MMV vessel wall was good (weighted $\kappa = 0.917$).

The relationship to radiographical progression and clinical feature

There were some patients to be taken a revascularization therapy due to the progression of intracranial arterial stenosis. Their cerebral blood flow at rest state was significantly down and some clinical neurological deficit, including transit ischemic attack, was shown.

DISCUSSION

This investigation found that arterial vessel wall enhancement in MMV patients was closely related to progression of intracranial arterial stenosis. Grade 2 enhancement of the intracranial vessel wall was associated with intracranial arterial stenosis progression within 6 months, and grade 0 enhancement correlated with the stability of intracranial arterial stenosis.

The main pathological changes of the narrow segment in MMV are fibrous thickening of the intima, irregular undulation of the internal elastic lamina, medial thinness, and a decrease in outer diameter.[14–18] The cause of fibrous thickening of the intima was proliferation of the cells making up the vessel wall, activation of angiogenesis, and matrix accumulation. HR-MRI studies of patients with MMD have recently

demonstrated constrictive remodeling in affected segments, concentric enhancement of symptomatic segments, intimal hyperplasia, and medial thinning.[15,19–22]

The pathophysiological mechanisms underlying contrast uptake in the intracranial arterial walls of MMV remain obscure. Previous studies have indicated that intracranial vessel wall enhancement reflects disease activity. Under contrast-enhanced HR-MRI, aneurysmal wall enhancement was related to the aneurysm state, with circumferential aneurysmal wall enhancement observed more frequently in unstable (ruptured, symptomatic, or undergoing morphological modification) aneurysms than in stable (incidental and nonevolving) aneurysms.[23] Qiao et al. showed that contrast enhancement of intracranial atherosclerotic plaque is associated with the likelihood of recent ischemic events and may serve as a marker of stability.[13] Contrast enhancement of the atherosclerotic lesion may occur with more generalized or focal inflammation of the vessel wall, together with neovascularization and endothelial contrast leakage,[24] or as a result of vasa vasorum in the plaque. Skarpathiotakis et al. reported that pathological enhancement of a vessel plaque supplying a stroke territory has been observed within 4 weeks of ischemic stroke, and the strength of enhancement is closely related to the time between stroke and assessment of the vessel wall.[25] The degree of enhancement is thought to correlate closely with the level of inflammatory activity, presumably as a result of neovascularization and increased endothelial permeability.[26] Wang et al. reported that strong enhancement of the intracranial vessel wall is independently associated with acute ischemic infarction in patients with MMV.[12] Chmelova et al. found that angiogenetic factors in the intima and vascular endothelial growth factor (VEGF) in the endothelium of moyamoya-affected arteries showed greater expression than in controls.[16] This suggests an active angiogenetic process in the enhanced vessel

wall in patients with MMV. Meanwhile some reports have shown that adult-onset autoimmune diseases are associated with MMV in pediatric populations, but not adults, potentially lending credence to the hypothesis that inflammation is involved in the pathogenesis of MMV.[27–29] These results suggested that enhancement of intracranial vessels in patients with MMV may indicate active angiogenetic process and inflammatory response in patients with MMV.

Stence et al. recently reported that the strong enhancement of intracranial vessel walls is related to stenosis progression in pediatric patients with intracranial arteriopathies.[30] He concluded that if strong vessel wall enhancement is detected in children with arterial ischemic stroke, more aggressive therapies such as steroids or antivirals could be considered to ameliorate the risk of worsening arteriopathy.

Regardless of symptomatic or asymptomatic, the population of intracranial arterial stenosis progression with MMD was about 20%, and half of those patients occurred TIA/cerebral infarction or intracranial hemorrhage.[31] So to evaluate intracranial arterial stenosis progression with MMD is quite important clinically.

The present study has some limitations. One of the limitations of our study was the small size of the cohort. The other limitations of our study were the existence of confounders. When we are talking about the underlying mechanisms of contract-enhancement, there are quite a lot of confounders. Larger cohorts are needed to prospectively follow presumably stable intracranial arterial stenosis with MMV to confirm the clinical use of contrast HR-MRI VWI to predict clinical instability, before contrast HR-MRI VWI can be introduced into routine clinical practice.

To the best of our knowledge, the natural history and progress of MMV, as seen with contrast-enhanced studies, have not yet been established. The exact mechanisms

accounting for intracranial vessel wall enhancement remain unknown. More studies of molecular contrast agents may be helpful to elucidate this mechanism. We continue to investigate more intracranial arterial stenosis patients and follow up them. If the degree of vessel wall enhancement will change in the future, new findings may be obtained.

CONCLUSIONS

Arterial vessel wall enhancement in MMV patients was closely related to progression of intracranial arterial stenosis. Strong enhancement of the intracranial vessel wall was associated with intracranial arterial stenosis progression, and lack of enhancement correlated with the stability of intracranial arterial stenosis.

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Figure 1. Grade 0 enhancement of MMV.

A) A transverse-section post-contrast T1-weighted isotropically reconstructed turbo spin echo acquisition image does not show the enhancement of ICA and MCA stenosis bilaterally. B) MRI CISS (Constructive Interference Insteady State) image can confirm the intracranial vascular structure precisely.

Figure 2. Grade 1 enhancement of MMV.

A) A transverse-section post-contrast T1-weighted isotropically reconstructed turbo spin echo acquisition image shows the mild vessel wall enhancement of left MCA stenotic lesion, but less than that of pituitary infundibulum (white arrowhead). B) MRI CISS image can confirm the intracranial vascular structure precisely.

Figure 3. Grade 2 enhancement of MMV.

A) A transverse-section post-contrast T1-weighted isotropically reconstructed turbo spin echo acquisition image shows the strong vessel wall enhancement of left MCA stenotic lesion. This enhancement is greater than that of pituitary infundibulum (white arrowhead). B) MRI CISS image can confirm the intracranial vascular structure precisely.

Figure 4. Enhancement of the intracranial vessel wall was associated with progression of intracranial arterial stenosis for moyamoya vasculopathy

A 3-year-old girl without vascular risk factors presented with transit ischemic attack (TIA) localized to the left middle cerebral artery (MCA) territory. ~~left transit ischemic attack caused by left middle cerebral artery (MCA) stenosis.~~ She had already been

diagnosed moyamoya disease. **A)** Transverse time-of-flight magnetic resonance angiography (TOF-MRA) shows distal internal carotid artery (ICA) stenosis bilaterally, and proximal anterior cerebral artery (ACA) and MCA stenosis. **B)** MRI CISS image can confirm the intracranial vascular structure precisely. **C)** A transverse-section post-contrast T1-weighted isotropically reconstructed turbo spin echo acquisition image shows enhancement of only a left MCA stenosis (white arrowhead). Enhancement in the left MCA lesion exceeds that of the pituitary infundibulum (grade 2 enhancement), whereas no enhancement is evident in the right internal carotid artery (grade 0 enhancement). **D)** Six months after first vessel wall imaging, TOF-MRA shows progression of only left MCA stenosis

Table 1. Demographics of patients with moyamoya vasculopathy

Pt ID	Age (y)	Sex	Initial Symptom		Suzuki stage		Diagnosis	Period between symptom onset and VWI examination (m)
			Right	Left	Right	Left		
1	24	F	TIA	TIA	4	3	Quasi-MMD hyperthyroidism	84
2	48	F	None	None	3	3	MMD	-
3	3	F	CI	CI	3	3	MMD	6
4	18	F	TIA	TIA	1	-	Unilateral MMD	6
5	40	F	CI	None	1	-	Unilateral MMD	66
6	44	F	TIA	None	4	5	MMD	312
7	13	F	TIA	TIA	3	3	MMD	216
8	34	M	None	CI	1	1	MMD	13
9	67	M	None	CI	3	3	MMD	240
10	47	F	CI	TIA	4	3	MMD	6

11	8	F	TIA	None	3	3	MMD	9
12	14	M	CI	None	-	1	Unilateral MMD	15
13	52	F	None	TIA	3	3	MMD Ulcerative colitis	28
14	49	M	None	TIA	-	1	Unilateral MMD	10
15	48	F	None	TIA	-	1	Unilateral MMD	72
16	36	M	None	IVH	3	3	MMD	288
17	67	M	None	CI	3	3	Quasi-MMD Sjögren's syndrome	243
18	47	F	None	CI	4	4	MMD	23
19	32	F	None	TIA, ICH	4	4	MMD	420
20	24	F	TIA	TIA	4	3	Quasi-MMD Hyperthyroidism	90
21	27	M	None	None	3	5	MMD	-
22	42	M	IVH, ICH	None	5	4	MMD	6

23	32	F	None	TIA, ICH	4	4	MMD	420
24	50	F	ICH	None	3	4	MMD	1

Pt, patient; M, male; F, female; MRA, magnetic resonance angiography; CI, cerebral infarction; TIA, transient ischemic attack; IVH, intraventricular hemorrhage; ICH, intracranial hemorrhage; MMD, moyamoya disease; VWI, vessel wall imaging

Table 2. Relationship between intracranial vessel wall enhancement and intracranial arterial stenosis progression

Pt ID	Initial VWI enhancement		Follow-up MRA Intracranial arterial stenosis	
	Right	Left	Right	Left
1	0	2	Progressed	Progressed
2	2	1	Progressed	Stable
3	0	1	Stable	Progressed
4	1	0	Progressed	Stable
5	1	0	Stable	Stable
6	1	0	Stable	Stable
7	1	1	Stable	Stable
8	0	2	Stable	Progressed
9	1	0	Stable	Stable
10	2	0	Progressed	Stable
11	0	0	Stable	Stable
12	0	0	Stable	Stable
13	2	1	Progressed	Stable
14	0	0	Stable	Stable
15	0	1	Stable	Stable
16	1	0	Stable	Stable
17	2	0	Stable	Stable
18	1	0	Stable	Stable

19	0	0	Stable	Stable
20	1	2	Stable	Progressed
21	0	2	Stable	Stable
22	1	1	Stable	Stable
23	0	0	Stable	Stable
24	2	1	Stable	Stable

Pt, patient; MRA, magnetic resonance angiography; VWI, vessel wall imaging

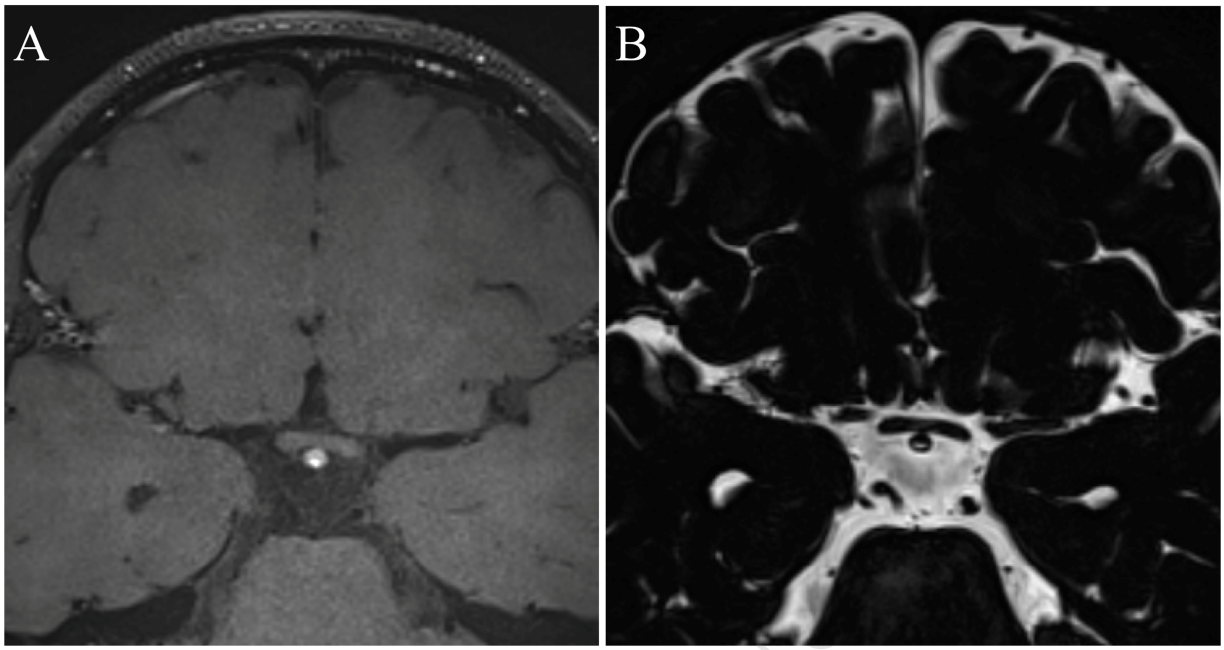
Table 3. Relationship between intensity of intracranial vessel wall enhancement and progression of intracranial arterial stenosis

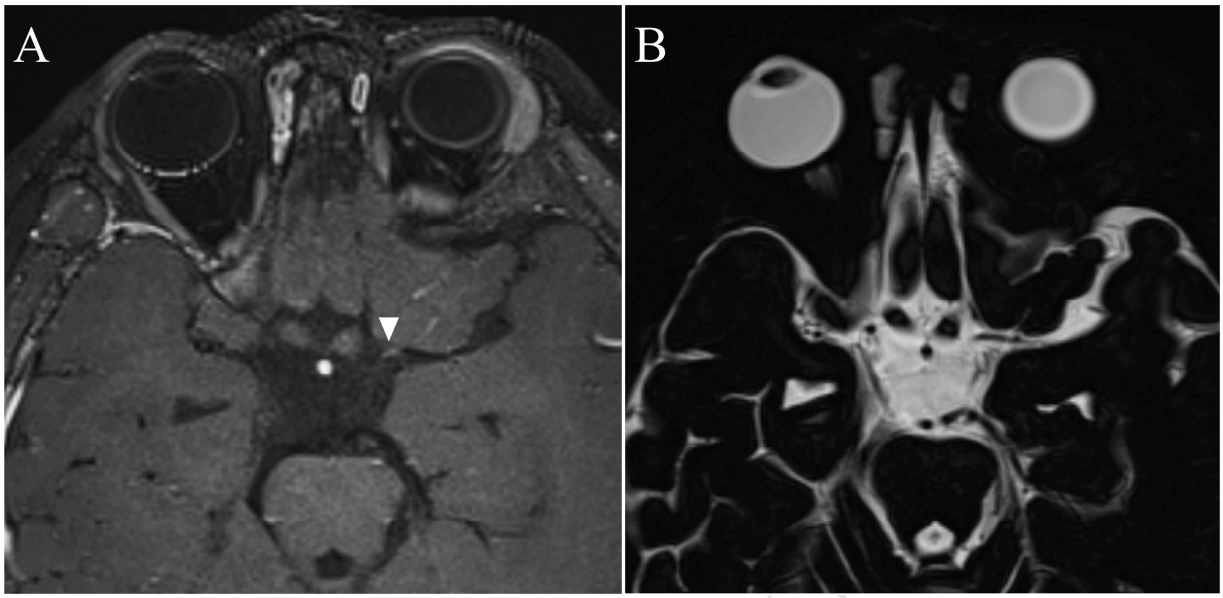
		Follow-up MRA Intracranial arterial stenosis	
		Progressed n=9	**Stable n=39**
Initial VWI enhancement	**Grade 2**	6	3
	Grade 1	2	14
	Grade 0	1	22

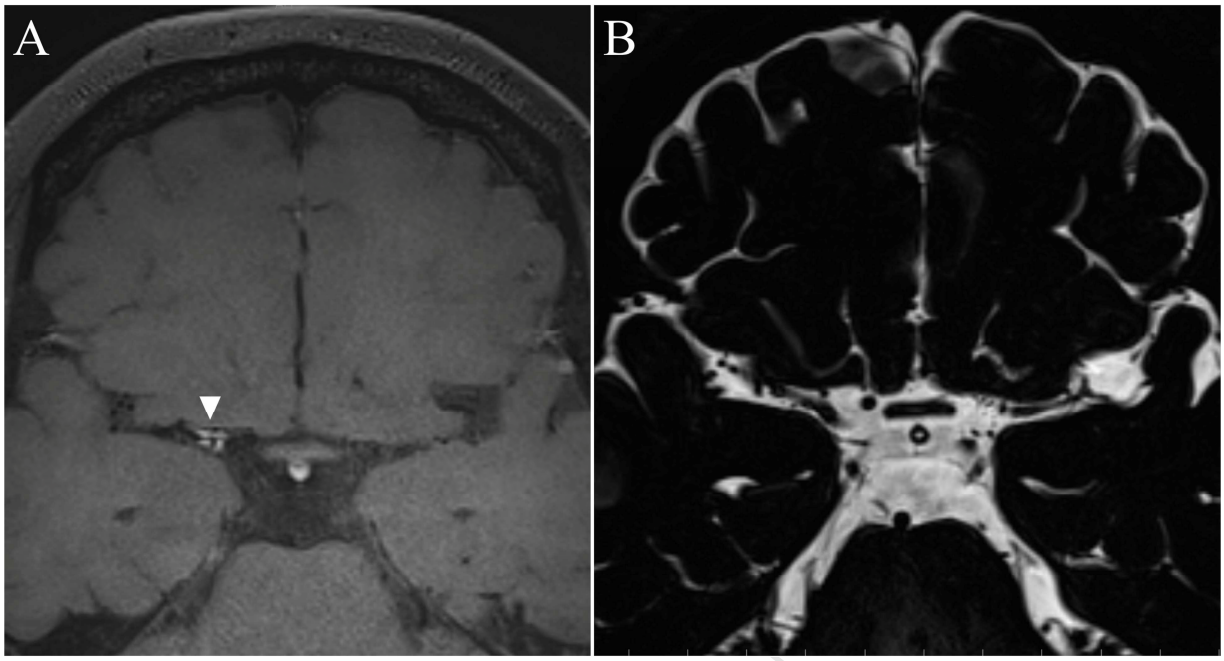
MRA, magnetic resonance angiography; VWI, vessel wall imaging

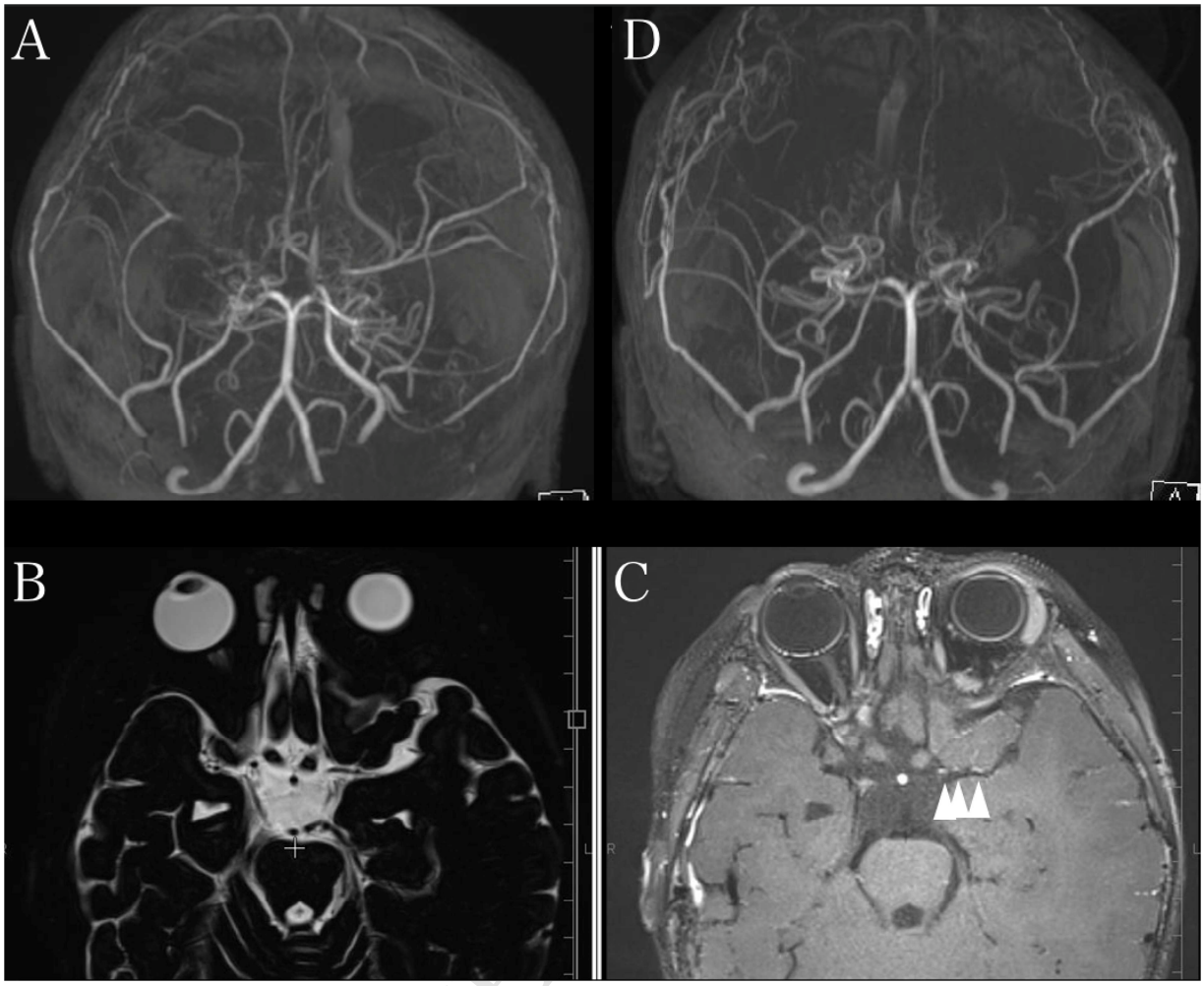
Table.4 Univariate and multivariate risk factor for intracranial arterial stenosis

Risk Factors	OR	95% CI	p Value
Possible relevance for intracranial arterial stenosis			
Age	0.976	0.934-1.019	0.271
Sex	5.000	0.567-44.084	0.147
Initial symptom	1.250	0.205-7.615	0.809
Suzuki grade	1.004	0.599-1.685	0.987
Vessel wall enhancement	7.817	2.109-28.969	**0.002**
Period between symptom onset and VWI examination (m)	0.992	0.980-1.004	0.172
Analysis of significant factors			
Vessel wall enhancement	36.215	2.761-475.028	**0.006**









- Arterial vessel wall enhancement in MMV patients was closely related to the progression of intracranial arterial stenosis.
- Strong enhancement of the intracranial vessel wall was associated with the progression of intracranial arterial stenosis.
- The lack of enhancement was associated with the stability of intracranial arterial stenosis.

ACA (anterior cerebral artery), CI (cerebral infarction), CISS (Constructive Interference Insteady State), HR-MRI (high-resolusion magnetic resonance imaging), ICA (internal carotid artery), ICH (intracranial hemorrhage), IVH (intraventricular hemorrhage), MCA (middle cerebral artery), MMD (moyamoya disease), MMV (moyamoya vasculopathy), TIA (transient ischemic attack), TOF-MRA (Transverse time-of-flight magnetic resonance angiography), VWI (vessel wall imaging)