(P = .027). The incidence of sICH was significantly lower in the MDM-P group (MDM-P group 3.4%, MDM-P group 20.0%; P = .009). The time from the onset was 3-8 hours in 29 patients in the MDM-P group and in 7 patients in the MDM-N group. Favorable outcomes were seen in 12 patients (41.4%) in the MDM-P group and 2 patients (28.6%) in the MDM-N group, with no significant difference between the 2 groups. No patients had sICH. The patients admitted 8 hours or more after the onset were all MDM-P. Five patients (55.6%) had a favorable outcome. *Conclusions:* This study demonstrated the safety and efficacy of EVT in MDM-P patients within 3 hours of symptom onset. Although the ratio of patients who had a favorable outcome was high in the MDM-P patients admitted 3-8 hours after the onset, the difference was not significant. **Key Words:** Magnetic resonance angiography (MRA)—diffusion weighted imaging (DWI) mismatch—endovascular treatment—acute cerebral infarction—cerebral large vessel occlusion.

Introduction

The results of randomized controlled trials regarding the usefulness of endovascular treatment (EVT) for acute ischemic stroke were reported recently; however, none of them showed the usefulness of EVT compared with intravenous recombinant tissue plasminogen activator (rt-PA) therapy.[1-3] Meanwhile, the results of the Recovery by Endovascular Salvage for Cerebral Ultra-acute Embolism (RESCUE)-Japan Registry, a multicenter registry study conducted in Japan on acute-phase therapy for patients with cerebral large vessel occlusion that occurred within 24 hours, showed that EVT provided significantly better outcomes in patients with proximal vessel occlusion, such as the internal carotid artery (ICA), compared with patients for whom intravenous rt-PA failed and ineligible patients.[4] The most important factor in performing reperfusion therapy for patients with acute cerebral infarction is the presence of the penumbra area.[5,6] Studies have been conducted to evaluate the usefulness of diffusion-weighted imaging (DWI)-perfusion mismatch and showed that the difference in abnormal areas between high-intensity areas in DWI and perfusion images was a predictor of the presence of this penumbra area, with clinical–DWI mismatch showing a dissociation between clinical symptoms and DWI findings, and magnetic resonance angiography (MRA)–DWI mismatch (MDM) combining the presence or absence of major artery lesions in MRA and DWI findings for selecting patients for acute-phase cerebral infarction and prognosis prediction.[7-10] We have also reported the possibility that the presence or absence of MDM using the DWI-Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) may be useful in determining the prognosis of patients receiving intravenous rt-PA therapy or EVT after recanalization.[11,12] In the present study using the RESCUE-Japan Registry, the treatment results were evaluated by the presence or absence of MDM using the DWI-ASPECTS in patients with cerebral large vessel occlusion who achieved recanalization with EVT.[4]

Methods

Of 1442 patients registered in the RESCUE-Japan Registry (http://www.rescue-japan.jp), a multicenter, prospective study that evaluated acute-phase treatment results in patients with cerebral large vessel occlusion within 24 hours of symptom onset between July 1, 2010 and June 30, 2011, 188 patients with occlusion in the ICA or middle cerebral artery (MCA) who had complete recanalization after thrombolysis in cerebral infarction grades 2B and 3 with EVT were included. Of these 188 patients, there were 143 patients within 3 hours of symptom onset for whom intravenous rt-PA therapy was indicated. Of these, 71 patients also underwent EVT because intravenous rt-PA therapy did not achieve recanalization. On pretreatment MRA, the occluded vessel was the MCA (M1 segment) in 88 patients, the M2 segment in 22 patients, and the ICA in 78 patients.

Intravenous Tissue Plasminogen Activator, EVT

Intravenous t-PA was performed as the first-line treatment within 3 hours of symptom onset according to the standard protocol in Japan (.6 mg/kg dose, 10% bolus, 90% continuously infused over 60 minutes).[13] EVT was defined as including catheter procedures such as clot removal/aspiration, balloon angioplasty, intra-arterial thrombolysis using a clot retriever, balloon angioplasty, microcatheter, and stenting.

MRA-DWI Mismatch

With ASPECTS, the MCA region is divided into 10 zones, and the presence or absence of early ischemic changes is quantified into points in each zone.[14] The DWI-ASPECTS of 6 was set as the cutoff value. The MDM-positive (MDM-P) group was defined as "major artery lesion (+) and the DWI-ASPECTS of 6 or more," and the MDM-negative (MDM-N) group was defined as "major artery lesion (+) and the DWI-ASPECTS of less than

6." Major artery lesions (+) were defined as ICA occlusion and MCA occlusion/stenosis.[11]

Evaluation of Clinical Outcome and Symptomatic Intracranial Hemorrhage

Patient outcomes were evaluated using the modified Rankin scale (mRS) on admission and 90 (±10) days after the onset. A favorable outcome was defined as an mRS score of 0-2. In this study, intracranial hemorrhage within 24 ± 8 hours after the onset was evaluated on follow-up imaging. Symptomatic hemorrhage was defined according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition[15]: local or remote parenchymal hematoma type 2 on the follow-up imaging scan, plus neurologic deterioration, as indicated by a score on the NIHSS score that was higher by 4 points or more than the baseline value or the lowest value between baseline and 24 hours, or hemorrhage leading to death.

Statistical Analysis

For statistical analysis, IBM SPSS Statistics 20 software (IBM Corporation, Armonk, NY) was used. The significance of intergroup differences was assessed using the Wilcoxon rank sum test and the Fisher exact test (2-sided). Values of P less than .05 were considered significant.

Results

Of the 188 patients analyzed, the time from the onset to hospital presentation was within 3 hours in 143 patients, 3- 8 hours in 36 patients, and 8 hours or more in 9 patients. Table 1 presents the baseline characteristics of the MDM-P and MDM-N patients within 3 hours of the onset. Overall, 118 patients were MDM-P and 25 were MDM-N. The median DWI-ASPECTS was 8 in MDM-P patients and 4 in MDM-N patients, and the infarct region was significantly larger in MDM-N patients. With regard to the median

Table 1. *Patients' characteristics by group based on the presence of MRA-DWI mismatch within 3 hours of the onset*

	MRA-DWI mismatch (+)	MRA-DWI mismatch (−)	
	DWI-ASPECTS ≥ 6 (n = 118)	DWI-ASPECTS < 6 (n = 25)	*P* value
Age, mean ± SD, y	71 ± 10	68 ± 11	.276*
Sex, female, n (%)	36 (31)	10 (40)	.357†
Hypertension, n (%)	62 (53)	16 (64)	.378†
Diabetes mellitus, n (%)	19 (16)	8 (32)	.089†
Hyperlipidemia, n (%)	20 (17)	3 (12)	.290†
Atrial fibrillation, n (%)	63 (53)	13 (52)	1.000†
Coronary heart disease, n (%)	10 (8)	3 (12)	.700†
Congestive heart failure, n (%)	10 (8)	1 (4)	.689†
Smoking, n (%)	19 (16)	2 (8)	.533†
Systolic BP, mean ± SD, mm Hg	135 ± 20	133 ± 18	.719*
Diastolic BP, mean ± SD, mm Hg	74 ± 15	71 ± 14	.414*
NIHSS score, median (range)	17 (0-37)	19 (9-38)	.060*
Stroke subtype			
Cardiogenic embolism, n (%)	89 (75)	19 (76)	1.000†
Atherothrombosis, n (%)	21 (18)	1 (4)	.125†
Others/unclassified, n (%)	8 (7)	5 (20)	.052†
rt-PA therapy	52 (44)	12 (48)	.826†
Onset to admission, mean ± SD, min	84 ± 55	80 ± 57	.709*
Onset to recanalization of EVT	331 ± 157	288 ± 72	.188*
DWI-ASPECTS, median (range)	8 (6-10)	4 (1-5)	<.001*
Occluded vessel			
ICA			
Extracranial ICA, n (%)	26 (22)	9 (36)	.198†
Intracranial ICA, n (%)	22 (19)	3 (12)	.568†
MCA			
Proximal M1, n (%)	29 (25)	7 (28)	.800†
Distal M1, n (%)	26 (22)	4 (16)	.598†
M2 or distal, n (%)	15 (13)	2 (8)	.737†

Abbreviations: BP, blood pressure; DWI-ASPECTS, diffusion-weighted image–Alberta Stroke Program Early Computed Tomography Score; EVT, endovascular treatment; ICA, internal carotid artery; MCA, middle cerebral artery; MRA-DWI, magnetic resonance angiography–diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue-type plasminogen activator.

*Wilcoxon rank sum test.

†Fisher exact test (2-sided).

NIHSS score on admission, the severity was higher in MDM-N patients, but the difference was not significant. No significant differences were noted in other items between the 2 groups. Table 2 presents the baseline characteristics of the MDM-P and MDM-N patients admitted 3-8 hours after the onset; 29 patients were MDM-P and 7 were MDM-N. The median NIHSS score on admission was 14 in MDM-P patients and 21 in MDM-N patients, showing a higher severity in MDM-N patients. The median DWI-ASPECTS was 8 in MDM-P patients and 4 in MDM-N patients, and the infarct region was significantly larger in MDM-N patients. No significant differences were noted in other items between the 2 groups. Figure 1A presents the clinical outcomes of the patients who had onset within 3 hours. The mRS scores at 90 days were 0-2 in 63 patients (53.4%) and 3-6 in 55 patients (46.6%) in the MDM-P group and 0-2 in 7 patients (28.0%) and 3-6 in 18 patients (72.0%) in the MDM-N group, showing significantly more favorable clinical outcomes in the MDM-P group (P = .027). In both MDM-P and MDM-N patients, the performance or nonperformance of intravenous rt-PA therapy before EVT did not result in differences in clinical outcome (MDM-P patients receiving rt-PA, mRS scores 0-2 in 34 patients [65.2%] and 3-6 in 24 patients [34.8%]; MDM-P patients not receiving rt-PA, mRS scores 0-2 in 29 patients [48.3%] and 3-6 in 31 patients [51.7%]; MDM-N patients receiving rt-PA, mRS scores 0-2 in 5 patients [38.5%] and 3-6 in 8 patients [61.5%]; and MDM-N patients not receiving rt-PA, mRS scores 0-2 in 2 patients [16.7%] and 3-6 in 10 patients [83.3%]). Symptomatic intracranial hemorrhage (sICH) occurred in 4 MDM-P patients (3.4%) and 5 MDM-N patients (20%), occurring in significantly fewer MDM-P patients (P = .009). Figure 1B presents the clinical outcomes of the patients admitted 3-8 hours after the onset. No significant differences were observed between the 2 groups (MDM-P, mRS scores 0-2 in 12 patients [41.4%] and 2-6 in 17 patients [58.6%]; MDM-N,

Table 2. *Patients' characteristics by group based on the presence of MRA-DWI mismatch at 3-8 hours from the onset*

	MRA-DWI mismatch (+)	MRA-DWI mismatch (−)	
	DWI-ASPECTS ≥ 6 (n = 29)	DWI-ASPECTS < 6 (n = 7)	*P* value
Mean age, y, mean ± SD	70 ± 12	73 ± 12	.447*
Sex, female, n (%)	13 (45)	3 (43)	1.000†
Hypertension, n (%)	19 (66)	5 (71)	1.000†
Diabetes mellitus, n (%)	6 (21)	3 (43)	.333†
Hyperlipidemia, n (%)	5 (17)	1 (14)	1.000†
Atrial fibrillation, n (%)	13 (45)	3 (43)	1.000†
Coronary heart disease, n (%)	3 (10)	1 (14)	1.000†
Congestive heart failure, n (%)	3 (10)	0	1.000†
Smoking, n (%)	3 (10)	1 (14)	1.000†
Systolic BP, mean ± SD, mm Hg	159 ± 25	181 ± 57	.135*
Diastolic BP, mean ± SD, mm Hg	87 ± 17	86 ± 35	.523*
NIHSS score, median (range)	14 (0-34)	21 (14-28)	.020*
Stroke subtype			
Cardiogenic embolism, n (%)	18 (62)	4 (57)	1.000†
Atherothrombosis, n (%)	8 (28)	2 (29)	1.000†
Others/unclassified, n (%)	3 (10)	1 (14)	1.000†
Onset to admission, mean ± SD, min	287 ± 82	253 ± 51	.326*
Onset to recanalization of EVT	478 ± 147	480 ± 124	.595*
DWI-ASPECTS, median (range)	8 (6-10)	4 (3-5)	<.001*
Occluded vessel			
ICA			
Extracranial ICA, n (%)	7 (24)	1 (14)	1.000†
Intracranial ICA, n (%)	4 (14)	3 (43)	.116†
MCA			
Proximal M1, n (%)	9 (31)	1 (14)	.645†
Distal M1, n (%)	6 (21)	1 (14)	1.000†
M2 or distal, n (%)	3 (10)	1 (14)	1.000†

Abbreviations: BP, blood pressure; DWI-ASPECTS, diffusion-weighted image–Alberta Stroke Program Early Computed Tomography Score; EVT, endovascular treatment; ICA, internal carotid artery; MCA, middle cerebral artery; MRA-DWI, magnetic resonance angiography–diffusion-weighted imaging; NIHSS, National Institutes of Health Stroke Scale; rt-PA, recombinant tissue-type plasminogen activator.

*Wilcoxon rank sum test.

†Fisher exact test (2-sided).

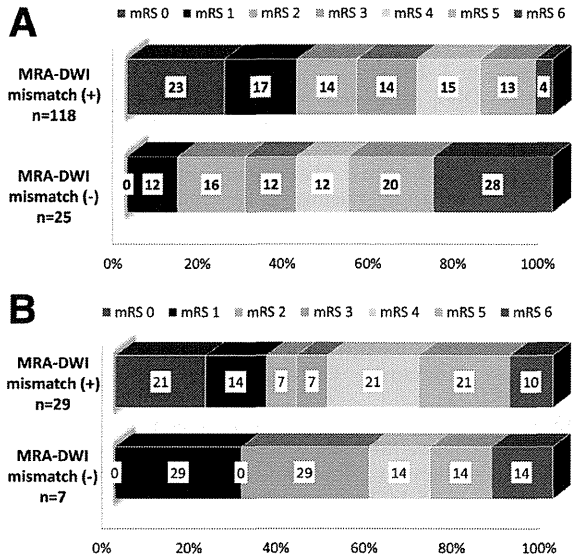

Figure 1. *(A) Clinical outcome for the MRA-DWI mismatch groups within 3 hours of onset. (B) Clinical outcome for the MRA-DWI mismatch groups at 3-8 hours from the onset. Abbreviations: MRA-DWI, magnetic resonance angiography–diffusion-weighted imaging; mRS, modified Rankin Scale. (Color version of figure is available online.)*

mRS scores 0-2 in 2 patients [28.6%] and 3-6 in 5 patients [71.4%]; $P = .681$). No patients had sICH. The patients admitted 8 hours or more after onset were all MDM-P. The mRS scores at 90 days were 0-2 in 5 patients (55.6%) and 3-6 in 4 patients (44.4%).

Discussion

The results of this study demonstrated that, among patients with acute cerebral artery occlusion who presented to the hospital within 3 hours of symptom onset and achieved recanalization with EVT, MDM-P patients had significantly more favorable outcomes than MDM-N patients. Meanwhile, the proportion of patients who had a favorable outcome was high in the MDM-P patients admitted 3-8 hours after the onset; however, the difference between the 2 groups was not significant, and the proportion of patients with mRS scores 5-6, which are considered severe, was slightly higher in MDM-P patients. This is considered to be associated with the time from the onset to recanalization. Yoshimura et al also pointed out that the delay in starting EVT may have greatly affected the results of the Interventional Management of Stroke III and Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy studies.[4] In the present study, the mean time from the onset to recanalization was 323 minutes when the time from the onset was within 3 hours, and 484 minutes when the time of the onset was 3-8 hours. The proportion of MDM-P patients with a comparatively small infarct region with DWI-ASPECTS of 8 or more was 66.9% among those who presented within 3 hours of the onset, but 51.7% in those who presented 3-8 hours after the onset, a comparatively lower figure. For MDM-P patients with poor development of collateral circulation, if recanalization took some time, the infarct site might have spread to the entire region supplied by that vessel even after recanalization was achieved. Therefore, we consider that it is necessary to aim for more prompt recanalization by paying attention to differences in the timing of completion of the infarct region in individual patients with acute ischemic stroke. General anesthesia (GA) is also considered to be an issue. To safely perform EVT, patients who are unable to follow instructions need to be managed under GA. However, several reports state that EVT for patients with acute ischemic stroke under GA is associated with a worse outcome than with conscious sedation.[16-18] Froehler et al reported that the causes include hemodynamic instability and hypotension, delays in treatment, prolonged intubation, and neurotoxicity of the anesthetic agent itself.[18] The present study did not differentiate between those patients who underwent GA and those who did not, and the degree to which this had an effect is therefore unknown, but it may possibly have affected the outcome. In addition, the number of MDM-N patients admitted 3-8 hours after the onset was small, which was likely to have affected the results. All MDM-P patients admitted 8 hours or more after the onset underwent EVT. Because the number of patients admitted 8 hours or more after the onset was small, further studies with a larger patient population are necessary to evaluate the efficacy of EVT by the presence or absence of MDM.

sICH was significantly less common in MDM-P patients admitted within 3 hours of the onset. This finding was attributed to the size of the infarct region. Previous studies have reported that the DWI-ASPECTS of 5 or less is associated with sICH after reperfusion with regard to relationships between the DWI-ASPECTS and sICH after acute reperfusion therapy,[19] that the frequency of sICH increases as the DWI-ASPECTS decreases, and that the DWI-ASPECTS is an independent predictor of sICH after acute reperfusion therapy.[20] In the present study, sICH associated with reperfusion was thought to be more common in MDM-N patients with extensive infarction than in MDM-P patients because of major artery occlusion.

There are some unresolved issues related to the DWI-ASPECTS, including the following: a very small lesion with high intensity in each area and a lesion extending the entire area are both treated as 1 lesion in a similar manner; and how to treat very faint signal changes. However, the results of the present study demonstrated that the presence or absence of MDM using the DWI-ASPECTS could be a predictor of clinical outcome in patients with major cerebral artery occlusion after achieving recanalization with EVT. It will be extremely important to shorten the time to recanalization to ensure better outcomes for MDM-P patients in the future, by various means including new devices.

Acknowledgment: The authors would like to thank all the RESCUE-Japan registry investigators.

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CASE SERIES

Asymptomatic moderate carotid artery stenosis with intraplaque hemorrhage: onset of new ischemic stroke

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Received 26 August 2014
Revised 14 November 2014
Accepted 24 November 2014

ABSTRACT

Background The degree of stenosis of carotid arteries is recognized as an important risk factor for ischemic stroke. However, high-grade stenosis does not always cause cerebrovascular events, whereas low- to moderate-grade stenosis may often cause strokes. It has been reported that there is an association between carotid intraplaque hemorrhage (IPH) and new brain ischemic events.

Case presentation We present three patients with asymptomatic moderate carotid artery stenosis and carotid IPH who underwent both neurological and MRI at baseline and after at least 1 year's follow-up. These patients were admitted to our hospital (after 15–35 months of follow-up) because of neurological deficits. Diffusion-weighted MRI of the brain showed ipsilateral new ischemic lesions due to carotid artery plaques. The patients were treated with carotid artery stenting and discharged uneventfully.

Conclusions Whether plaques with severe stenosis already had severe stenosis at the onset of events or plaques with moderate stenosis progressed owing to an acute change, such as growth of an IPH, remains unclear, because no carotid imaging was carried out just before the events. This is the first case report which presents neurological symptoms and MRI at both baseline and follow-up in patients with asymptomatic moderate carotid artery stenosis and carotid IPH.

BACKGROUND

Carotid artery stenosis is one of the major causes of ischemic stroke. Several large randomized controlled trials have established that carotid endarterectomy (CEA) or carotid artery stenting (CAS) significantly reduces stroke risk compared with medical treatment in patients with high-grade stenosis, but does not reduce stroke risk in those with low- to moderate-grade stenosis.[1–5] Assessment of the risk of stroke and the criteria for surgical intervention in these randomized controlled trials have been based on the degree of stenosis.[6 7] However, it has been reported that intraplaque hemorrhage (IPH) is associated with accelerated plaque growth, luminal narrowing, and development of symptomatic events.[8 9] Whether plaques with severe stenosis after the onset of events already had severe stenosis at the onset of events or whether plaques with moderate stenosis progressed owing to acute change, such as the growth of IPH remains unclear, because no carotid imaging was available just before the events.

In this report, we describe three patients with asymptomatic carotid plaques with moderate stenosis and IPH who later presented neurological deficits after 15–35 months of follow-up.

CASE PRESENTATION

Case 1

An 82-year-old man was referred to our department for evaluation of carotid artery stenosis. He showed no neurological deficit. He had a history of hypertension and hyperlipidemia. He was receiving a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin), a calcium channel blocker, and an angiotensin II receptor blocker (ARB). No acute infarction was seen on diffusion-weighted MRI (DW-MRI) and no stenotic lesions in the intracerebral arteries on three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA). A 3D-TOF-MRA maximum intensity projection (MIP) image of the neck showed 50% stenosis according to North American Symptomatic Carotid Endarterectomy Trial criteria with IPH in the left internal carotid artery.[3] According to the guidelines for the management of asymptomatic carotid stenosis,[6 10] the patient was treated with antiplatelet medication and a statin in an outpatient clinic. His compliance with this treatment was good.

After 35 months, he was admitted to our hospital with a history of right hemiparesis and an low-density lipoprotein (LDL) cholesterol level of 83 mg/dL. DW-MRI of the brain showed acute infarctions in the left cerebral hemisphere. 3D-TOF-MRA of the brain showed no stenotic lesions. A 3D-TOF-MRA MIP image and digital subtraction angiography (DSA) of the neck showed 80% stenosis. The degree of stenosis appeared to have progressed compared with that seen 35 months earlier. After admission, according to the guidelines for the management of symptomatic carotid stenosis,[4–6 10] the patient was treated with CAS, and discharged uneventfully (Figure 1).

Case 2

An 82-year-old woman was referred to our department for evaluation of carotid artery stenosis. She showed no neurological deficit. She had a history of hypertension and hyperlipidemia. She was receiving a statin, calcium channel blocker, and ARB. There was no acute infarction on DW-MRI and no stenotic lesions in the intracerebral arteries on 3D-TOF-MRA. A 3D-TOF-MRA MIP image of

To cite: Yamada K, Kawasaki M, Yoshimura S, *et al. J NeuroIntervent Surg* Published Online First: [*please include* Day Month Year] doi:10.1136/neurintsurg-2014-011317

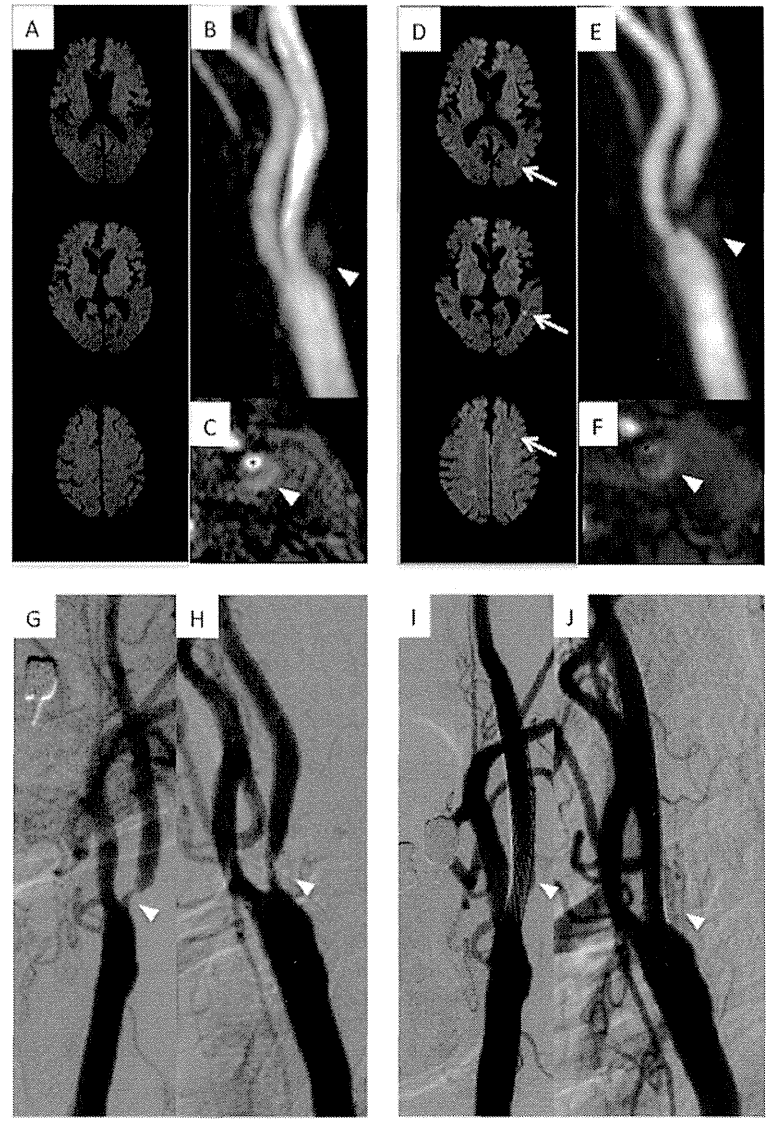

Figure 1 MRI images at baseline (A–C) and after 35 months of follow-up (D–F). Angiogram of precarotid artery stenting (CAS) (G, H) and post-CAS (I, J). (A) Diffusion-weighted MRI (DW-MRI) of the brain showed no acute ischemic lesion. (B) A three-dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) maximum-intensity projection (MIP) image of the left carotid artery showed moderate-grade stenosis (50%). It also illustrates a hyperintense signal indicating intraplaque hemorrhage (IPH) (arrow head). (C) An axial 3D-TOF source image demonstrates signal hyperintensity in the plaque indicating IPH (arrowhead). *Lumen of internal carotid artery. (D) DW-MRI of brain showed acute ischemic lesions (arrows). (E) A 3D-TOF-MRA MIP image of the left carotid artery changed from moderate-grade to high-grade stenosis (80%). It also illustrates a hyperintense signal indicating IPH. (F) An axial 3D-TOF source image demonstrates signal hyperintensity in the plaque indicating IPH (arrowhead). The lumen of the internal carotid artery (*) is apparently narrowed comared with that of baseline. (G) Frontal view and (H) lateral view of the pre-CAS angiogram showed high-grade left carotid artery stenosis. (I) Frontal view and (J) lateral view of the post-CAS angiogram. The left carotid artery was successfully dilated.

the neck showed 50% stenosis with IPH in the right internal carotid artery. The patient was treated with antiplatelet medication in an outpatient clinic.

After 32 months, she was admitted with a history of left hemiparesis and dysarthria and an LDL cholesterol level of 88 mg/dL. DW-MRI of the brain showed acute infarctions in the right cerebral hemisphere. 3D-TOF-MRA of the brain showed no stenotic lesions. A 3D-TOF-MRA MIP image and DSA of the neck showed 56% stenosis with IPH in the right internal carotid artery. After admission, the patient was treated with CAS and discharged uneventfully (Figure 2).

Case 3

A 78-year-old man was referred to our department for evaluation of carotid artery stenosis. He showed no neurological deficit. He had a history of hypertension and hyperlipidemia. He was receiving a statin and an ARB. There was no acute infarction on DW-MRI and no stenotic lesions in the intracerebral arteries on 3D-TOF-MRA. A 3D-TOF-MRA MIP image of the neck showed 50% stenosis with IPH in the right internal carotid artery. The patient was treated with antiplatelet medication in an outpatient clinic.

After 15 months, he was admitted to our hospital with a history of left hemiparesis and an LDL cholesterol level of 102 mg/dL. DW-MRI of the brain showed acute infarctions in the right cerebral hemisphere. A 3D-TOF-MRA MIP image of the brain showed no stenotic lesions. A 3D-TOF-MRA MIP image and DSA of the neck showed 54% stenosis. After admission, the patient was treated with CAS and discharged uneventfully (Figure 3).

DISCUSSION

Strokes remain a leading cause of morbidity and mortality. Carotid artery stenosis is one of the major causes of ischemic stroke. However, treatment decisions are still based on the degree of stenosis. Current criteria for surgical intervention in asymptomatic patients requires 70–80% stenosis, and the benefit of CEA or CAS is controversial even in patients with asymptomatic carotid artery stenosis.[11] According to the Asymptomatic Carotid Atherosclerosis Study, the stroke rate in patients with ≥60% asymptomatic carotid stenosis is about 2%/

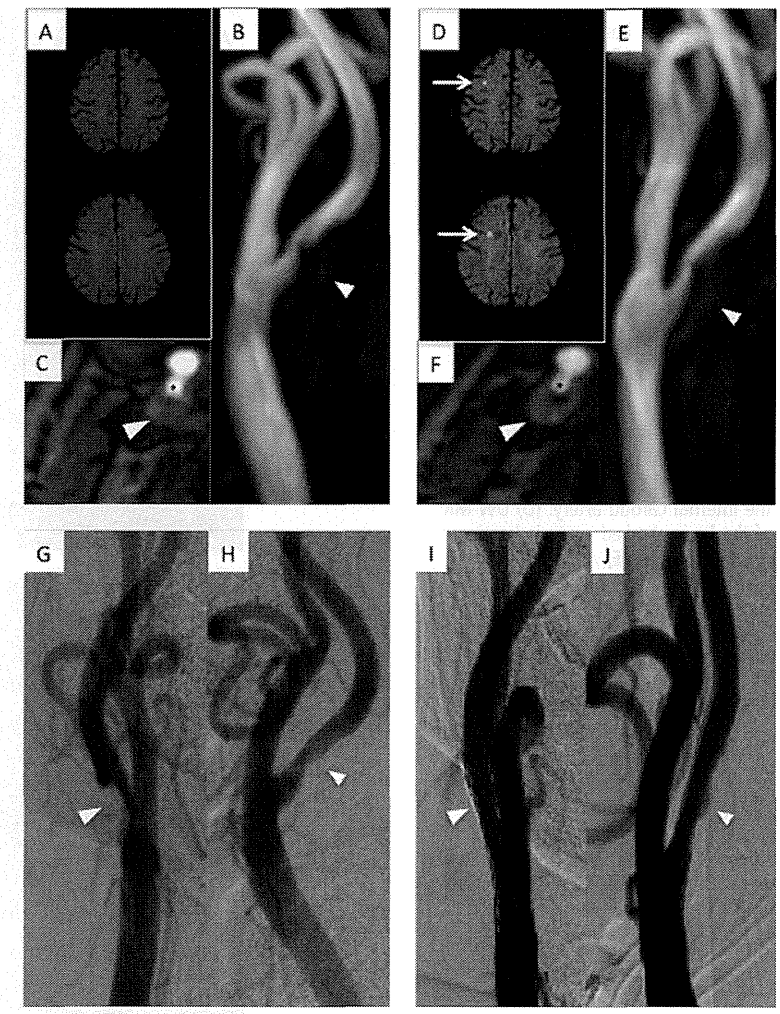

Figure 2 MRI images at baseline (A–C) and after 32 months of follow-up (D–F). Angiogram of precarotid artery stenting (CAS) (G, H) and post-CAS (I, J). (A) Diffusion-weighted MRI (DW-MRI) of brain showed no acute ischemic lesion. (B) A three dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) maximum intensity projection (MIP) image of the right carotid artery showed moderate-grade stenosis (50%). It also illustrates a hyperintense signal indicating intraplaque hemorrhage (IPH) (arrow head). (C) An axial 3D-TOF source image demonstrates signal hyperintensity in the plaque indicating IPH (arrowhead). *Lumen of the internal carotid artery. (D) DW-MRI of brain showed acute ischemic lesions (arrows). (E) A 3D-TOF-MRA MIP image of the right carotid artery shows slight change of stenosis from 50% to 56%. It also illustrates a hyperintense signal indicating IPH. (F) An axial 3D-TOF source image demonstrates signal hyperintensity in the plaque indicating IPH (arrowhead). *Lumen of internal carotid artery. (G) Frontal view and (H) lateral view of the pre-CAS angiogram showed moderate-grade right carotid artery stenosis. (I) Frontal view and (J) lateral view of the post-CAS angiogram. The right carotid artery was successfully dilated.

year.[1] However, in cases of asymptomatic moderate carotid artery stenosis, a low stroke rate (0.6%/year) was reported during a mean follow-up of 48 months in 198 patients.[12] The average annual rate of ipsilateral strokes in patients with asymptomatic carotid stenosis receiving medical treatment, such as antiplatelet drugs and statins, has fallen well below the rates in patients who undergo CEA.[13]

On the other hand, a growing body of literature suggests that tissue characterization of carotid plaques may provide a better means of predicting future ipsilateral cerebrovascular events than the degree of carotid artery stenosis.[8 9] Carotid IPH plays a critical role in the progression of carotid atherosclerotic disease. The presence of IPH in carotid atherosclerotic plaques has been associated with accelerated plaque growth and luminal narrowing.[8 9] We and other investigators reported that MRI of carotid plaque has a good sensitivity with a moderate-to-good specificity for the detection and quantification of IPH, using histology as a 'gold standard'.[14–17] According to these methods, IPH can be seen as a hyperintense signal on 3D-TOF source images and 3D-TOF-MRA MIP images of carotid plaques.

Among our cases, the degree of stenosis apparently progressed in one case and did not progress in the other two during a follow-up of 15–35 months. However, ipsilateral stroke occurred in all three cases. This suggests that the presence of carotid IPH does not always cause luminal narrowing that precedes the onset of ipsilateral stroke, and ipsilateral stroke can occur without plaque growth and luminal narrowing when carotid plaques have IPH. Therefore, it is clear that there are two types of carotid plaques that have IPH associated with ipsilateral ischemic stroke. One is the plaque with moderate stenosis after the onset of ischemic stroke, and the other is the plaque with severe stenosis after the onset of ischemic stroke. For coronary artery disease, it has been reported that the progression of coronary artery lesions can be classified into two types: type 1 vessels are characterized by sudden appearance of marked progression due to large thrombi and bleeding in plaques after plaque rupture or endothelial damage; type 2 vessels are characterized by continuous slight progression of stenosis due to plaque growth or small thrombi and bleeding in plaques after plaque rupture. Acute myocardial infarction occurs only in type 1 vessels. This process is different from carotid artery stenosis and is a unique process. It provides new insight into the mechanism of carotid artery disease.[18 19]

Two previous studies using MRI have reported an association between new cerebrovascular events and carotid IPH at baseline in patients with asymptomatic moderate carotid artery stenosis. Takaya *et al*[20] reported that 14 cerebrovascular events (3.0%/year) occurred (four transient ischemic attacks, six strokes, and four amaurosis fugax) during a mean follow-up of 38 months in 154 patients with asymptomatic moderate carotid artery stenosis with IPH at baseline. Singh *et al*[21] reported that six ipsilateral carotid events (8.3%/year) occurred (four transient ischemic

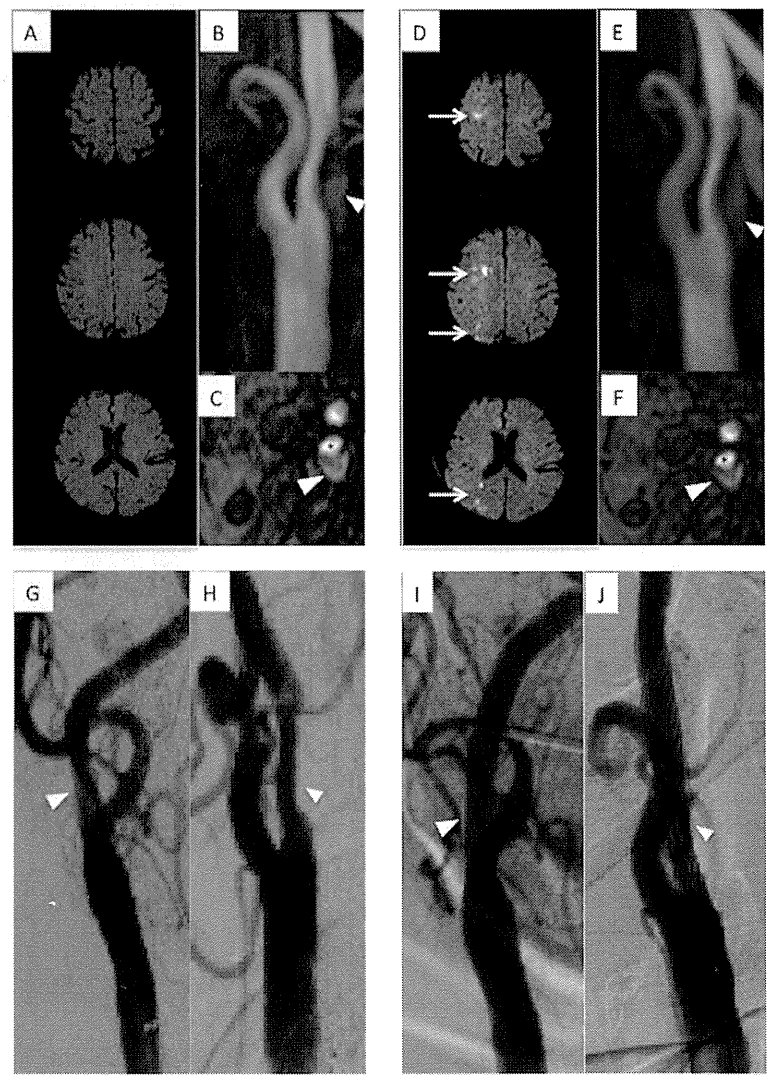

Figure 3 MRI images at baseline (A–C) and after 15 months of follow-up (D–F). Angiogram of precarotid artery stenting (CAS) (G, H) and post-CAS (I, J). (A) Diffusion-weighted MRI (DW-MRI) of brain showed no acute ischemic lesions. (B) A three dimensional time-of-flight magnetic resonance angiography (3D-TOF-MRA) maximum intensity projection (MIP) image of the right carotid artery shows moderate-grade stenosis (50%). It also illustrates a hyperintense signal indicating intraplaque hemorrhage (IPH) (arrow head). (C) An axial 3D-TOF source image demonstrates signal hyperintensity in the plaque indicating IPH (arrowhead). *Lumen of the internal carotid artery. (D) DW-MRI of the brain showed acute ischemic lesions (arrows). (E) A 3D-TOF-MRA MIP image of the right carotid artery shows slight change of stenosis from 50% to 54%. It also illustrates a hyperintense signal indicating IPH. (F) An axial 3D-TOF source image demonstrates signal hyperintensity in the plaque indicating IPH (arrowhead). *Lumen of the internal carotid artery. (G) Frontal view and (H) lateral view of the pre-CAS angiogram showed moderate-grade right carotid artery stenosis. (I) Frontal view and (J) lateral view of the post-CAS angiogram. The right carotid artery was successfully dilated.

attacks and two strokes) in 36 patients with asymptomatic moderate carotid artery stenosis and IPH, whereas there were no clinical events in the carotid arteries without IPH during a mean follow-up of 24 months. Both studies have shown that IPH at baseline is associated with future ipsilateral cerebrovascular events with HRs of 3.6[21] and 5.2,[20] suggesting that IPH is a promising predictor of future cerebrovascular events in patients with moderate carotid stenosis. However, both studies only discussed the association between the presence of carotid IPH at baseline and new ischemic stroke, and did not discuss the stenotic change or stenotic process. In our report, we showed plaques with asymptomatic moderate stenosis and IPH both at baseline and at the onset of neurological deficits.

Whether plaques with severe stenosis after the onset of ischemic stroke already had severe stenosis at the onset of stroke or whether plaques with moderate stenosis progressed owing to acute change, such as growth of IPH at the onset of an event, remains unclear, because no carotid imaging was carried out just before the events. However, this is the first case report presenting neurological symptoms and MRI at both baseline and follow-up in patients with asymptomatic moderate carotid artery stenosis and carotid IPH.

The study has limitations, because the patients were studied retrospectively and the number of cases is small, therefore, larger prospective studies are warranted to determine the value of carotid IPH in predicting strokes in patients with asymptomatic moderate carotid artery stenosis.

CONCLUSION

We have described three patients who had asymptomatic moderate carotid stenosis with carotid IPH and who subsequently experienced ipsilateral stroke after 15–35 months despite treatment with antiplatelet drugs and statins. Unlike coronary artery disease, two types of carotid plaque were seen where IPH was associated with ipsilateral ischemic stroke. One was plaque with moderate stenosis after the onset of ischemic stroke, and another was plaque with severe stenosis after the onset of ischemic stroke. Although the complex mechanisms of onset of ipsilateral strokes are still unknown, these cases provide new insight into the carotid plaques that cause ipsilateral strokes.

Contributors KY was responsible for the MR image review and interpretation of data, and preparation of the manuscript. MK assisted in data interpretation and revised the critical content of the manuscript. SY assisted in development of the study design and interpretation of data. YuS, SN, and YoS revised the manuscript. All authors read the manuscript and approved its submission.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics approval was provided by the local institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

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Asymptomatic moderate carotid artery stenosis with intraplaque hemorrhage: onset of new ischemic stroke

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J NeuroIntervent Surg published online December 9, 2014

SWIFT trial, TREVO 2 trial, SARIS

内田和孝　吉村紳一

SWIFT trial

1．試験のフルネーム

Solitaire Flow Restoration Device versus the Merci Retriever in Patients with Acute Ischemic Stroke

2．主たる結論

SWIFT trial は脳主幹動脈急性閉塞における Solitaire と Merci の多施設前向きランダム化比較試験である．手技の安全性は同等であったが，再開通率と予後は Solitaire 群で良好であった．

3．対象疾患と目的

A．対　象： 発症から 8 時間以内の急性期脳梗塞

B．目　的： Solitaire と Merci の効果と安全性を比較すること

4．試験のデザインと解析方法

A．デザイン： 多施設前向きランダム化比較試験

B．解析方法： Solitaire に慣れるため血管モデルにおける練習の後，2 症例で最初の 1 手技のみ Solitaire を使用する．これらはランダム化例と別に解析された．画像診断とイベント評価は独立したコアラボで行われた．

5．対象症例数と選択基準，除外基準

A．対象症例数： 113 人(Solitaire 群 58 人，Merci 群 55 人)

B．選択基準： 中等度～重症の神経学的脱落症状があり，発症から 8 時間以内の主幹動脈閉塞を伴った患者で，年齢は 22～85 歳，脳卒中重症度スケールである National Institutes of Health Stroke Scale (NIHSS) が 8 点以上，30 点以下で，rt-PA 静注療法の非適応または無効例が対象となった．

C．除外基準： コントロール不可能な高血圧，造影剤過敏症，CT もしくは MRI における頭蓋内出血，広範な脳梗塞(中大脳動脈領域の 1/3 の領域か，その他の領域で 100 mL 以上の組織が虚血性変化している場合)を認める症例．

6．試験の行われた施設

18 施設(米国 17 施設，フランス 1 施設)

7．主な結果

A．一時エンドポイント： 割り当てられたデバイスで手技後に症候性頭蓋内出血の合併がなく，3 施行回以内に割り当てられたデバイスのみで部分灌流〔Thrombolysis In Myocardial Ischemia (TIMI) scale 2〕もしくは末梢までの完全な灌流(TIMI scale 3)を得た症例数を比較した．結果は第三者機関で評価され，Solitaire 群で有意に優れていた(60.1% vs 24.1%，$p=0.0001$)．

割り当てられたデバイスで再開通が得られず追加治療が必要であった症例は Solitaire 群 12 人，Merci 群で 24 人と，Solitaire 群で有意に少なかった．90 日後の予後良好群〔modified Rankin Scale (mRS) 0-2〕は Solitaire 群に多く(58% vs 33%，$p<0.0001$)，90 日後の死亡率は Solitaire 群で少なかった(17% vs 38%，$p=0.001$)．デバイスや手技に関する重篤な合併症は 2 群間で有意差を認めなかった．

8．解釈と批判的コメント

A．解　釈： Solitaire 群では再開通率，安全性，臨床学的予後が Merci 群と比較して有意に良好であった．また，追加療法の必要性は Solitaire 群で有意に低かった．Solitaire は Merci リトリーバーよりも優れたデバイスであり，将来的に急性期脳虚血発作における主流デバイスとなる可能性がある．

B．批判的コメント： 急性期脳梗塞に対する機械的血栓回収の有効性が未だ証明されておらず，今後は rt-PA 静注療法や保存的療法とのランダム化試験が必要である．

9．エビデンスレベル(脳卒中ガイドライン参照)　Ib

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0289-0585/14/¥500/論文/JCOPY

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TREVO 2 trial

1．試験のフルネーム

Thrombectomy Revascularisation of Large Vessel Occlusions

2．主たる結論

Trevo と Merci を比較した多施設前向きランダム化比較試験．デバイス単独での再開通率の割合，90 日後の転帰良好例は Trevo 群で有意に優れていた．安全性，死亡率については有意差を認めなかった．

3．対象疾患と目的

A．対　象： 発症から 8 時間以内の急性期脳虚血病変

B．目　的： Trevo と Merci の効果と安全性を比較すること

4．試験のデザインと解析方法

A．デザイン： 多施設前向きランダム化比較試験

B．解析方法： 本試験は運営委員会，独立臨床イベント委員会，CT と MRI の中央判定委員会，血管撮影の中央判定委員会，独立安全モニタリング委員会(DSMB)によって研究データはモニターされ，解析された．

5．対象症例数と選択基準，除外基準

A．ランダム化された対象症例数： 178 例(Trevo 群 88 例，Merci 群 90 例)

B．選択基準： 主幹動脈閉塞を伴った急性期脳虚血発作の患者で，年齢は 18～85 歳，NIHSS が 8 点以上，29 点以下の，発症から 8 時間以内の患者である．rt-PA 静注療法の適応外または無効例で，発症前の日常生活が自立しており(mRS 0-1)，余命が 6ヵ月以上ある症例が対象となった．

C．除外基準： コントロール不可能な高血圧(収縮期 185 mmHg 以上，拡張期 110 mmHg 以上)，血糖の基礎値が 2.78 mmol/L(50 mg/dL)以下，22.20 mmol/L(400 mg/dL)以上の場合．出血素因，凝固因子の欠損があるもの，経口抗凝固薬内服中で INR が 3.0 以上のもの，ヘパリン治療中で APTT が通常の 2 倍以上のもの，血小板が 3 万/L 以下のもの，造影剤もしくはナイチノールで発疹以上のアレルギーがあるもの，妊娠中のもの．CT もしくは MRI で頭蓋内出血，広範な脳梗塞(中大脳動脈領域の 1/3 の領域か，その他の領域で 100 mL 以上の虚血性変化を認める場合)，正中偏位を伴う占拠性病変，頭蓋内腫瘍(小さな髄膜腫以外)，閉塞部の中枢側での高度狭窄病変やアプローチルートの極端な蛇行例．

6．試験の行われた施設

27 施設(米国 26 施設，スペイン 1 施設)

7．主な結果

一時エンドポイント： 割り当てられたデバイスのみでの部分灌流および完全灌流〔Thrombolysis In Cerebral Ischemia(TICI)scale 2-3〕を得た症例は Trevo 群で有意に多かった(86% vs 60%，$p<0.0001$)．

TICI scale 2-3 を得た症例の再開通までの時間は有意差を認めなかった．

また，Trevo 群 12 人，Merci 群 24 人で追加治療が行われた．

90 日後の予後良好例(mRS 0-2)は Trevo 群に多く(40% vs 22%，$p=0.013$)，手技に関する重篤な合併症は有意差を認めなかった．

8．解釈と批判的コメント

A．解　釈： Merci 群と比較して Trevo 群の方が再開通成功，安全性，臨床学的予後のいずれも良好であった．また，追加療法の必要性は Trevo 群で有意に低かった．

B．批判的コメント： 同型のデバイスである Solitaire などに優位性があるかどうかは不明である．

SWIFT trial と TREVO 2 trial の結果は，Solitaire と Trevo という新しい 2 つのデバイスが Merci よりも治療効果が高いことを示唆している．これらの研究結果を基に米国で承認を受け，現在のところ主流デバイスとなっている．

9．エビデンスレベル(脳卒中ガイドライン参照)　Ⅰb

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研究名	SWIFT		TREVO 2		SARIS
Used device	Solitaire (n=58)	Merci (n=55)	Trevo (n=88)	Merci (n=90)	(n=20)
Significant reperfusion	89%	67%	92%	77%	100%
Procedure-related complication	14%	16%	15%	23%	
Symptomatic ICH	2%	11%	7%	9%	5%
Favorable outcome (mRS 0-2)	58%	33%	40%	22%	60% (mRS 0-3)

SARIS

1．試験のフルネーム

Stent-Assisted Recanalization in Acute Ischemic Stroke

2．主たる結論

急性期脳血管閉塞症に対するステント留置による再開通療法は再開通率，予後共に良好な結果であった．

3．試験のデザインと解析方法

Nonrandomized, single-center 後ろ向きパイロット研究

4．対象症例数と選択基準，除外基準

A．選択基準： 主幹動脈閉塞を伴った急性期脳虚血発作の患者で，年齢は 18 歳以上，NIHSS score が 8 点以上で，脳血管撮影上の頭蓋内血管の閉塞が 14 mm 以下，発症から 8 時間以内の患者が選択された．rt-PA 静注療法の適応外，または投与後 1 時間で反応しなかった 20 例が対象である．

B．除外基準： 出血素因，凝固因子の欠損があるもの，血小板が 10 万/L 以下のもの，頭蓋内出血，血糖値 51 mg/100 mL 以下，CT で広範な脳梗塞（中大脳動脈領域の 1/3 の領域以上の虚血性変化を認める場合）．

5．試験の行われた施設

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6．主な結果

直接ステントを留置したところ全例で有意な再開通を認め，TIMI 3 が 60%，TIMI 2 が 40% であった．1ヵ月後の mRS 0-3 の割合は 60% であり，症候性脳出血は 5% で認めた．

7．解釈と批判的コメント

SARIS は症例数が少なく，ステント留置に対しては現時点では主流の治療ではないが，成績は良好であったため，本研究は患者数を増やして進行中である．

8．エビデンスレベル（脳卒中ガイドライン参照） III

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SWIFT, TREVO 2 trial はステント型血栓回収デバイス (Solitaire と Trevo) で Merci リトリーバーよりも良好な治療成績が得られることを示した．

今後これらのデバイスを用いて急性期脳梗塞に対する血管内治療の有効性が示されることが期待される．

脳梗塞の治療
超急性期治療

脳梗塞超急性期における血管内治療

Endovascular therapy for very acute ischemic stroke

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Key words：endovascular therapy, acute ischemic stroke

はじめに

2005年に組織プラスミノーゲンアクチベーター(recombinant tissue plasminogen activator: rt-PA)が我が国で認可され，以降，これまでに5万例以上に治療が行われてきた．また，ECASS III[1]の結果を受け，2012年9月より我が国でも発症4.5時間以内に適応が拡大され，ますます多くの症例がrt-PA静注療法の恩恵を受けることが予想される．

しかし，rt-PA静注療法は，脳主幹動脈閉塞例に対して無効例が多いことが問題視され始めており，その無効例に対する救済や時間的制約，禁忌事項に該当する適応外症例に対して，脳血管内治療による血栓回収療法が発症8時間以内の症例に対して行われている．古くはバルーンを用いた血栓破砕術やウロキナーゼを用いた経動脈的局所血栓溶解療法が行われてきた．最近では，新しい血栓回収デバイスが使用可能となり，3つのランダム化比較研究[2-4]が行われたが，いずれもその有効性を示すことはできなかった．

本稿では，この結果をふまえ，今後の超急性期脳梗塞に対する血管内治療の展望についても解説する．

1 経動脈的局所血栓溶解療法

米国で行われた遺伝子組換え型prourokinase(r-proUK)を用いた経動脈的局所血栓溶解療法についての臨床試験では，来院時のNIHSSが4-29で，CT上梗塞巣がなく，発症6時間以内に治療開始が可能な中大脳動脈塞栓性閉塞において有効であると報告[5,6]された．さらに我が国で行われたウロキナーゼを用いた経動脈的局所血栓溶解療法でも，来院時のNIHSSが4-22と中等症以下で，CT上梗塞巣がない，または軽微な所見にとどまり，発症6時間以内に治療開始が可能な中大脳動脈塞栓性閉塞において社会復帰率に優れると報告[7]された．

現在では，脳主幹動脈閉塞症例については後述の血栓回収デバイスが使用されることが多くなったものの，末梢の残存閉塞に対しては，経動脈的局所血栓溶解療法が盛んに行われている．しかし，出血性合併症を増加させる可能性もあり，rt-PA静注療法施行例や発症から時間が経過した例に対しては，そのリスクとベネフィットを十分に評価したうえでの使用が求められる．

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0047-1852/14/¥60/頁/JCOPY

表1 急性期脳梗塞に対する血管内治療のランダム化比較試験

	IMS III				MR RESCUE				SYNTHESIS expansion		
	血管内治療群	rt-PA治療群	p値		血管内治療群	通常治療群	p値		血管内治療群	rt-PA治療群	p値
患者数	434	222		患者数	34	34		患者数	181	181	
予後良好（mRS 0-2）	40.8％	38.7％	0.25	予後良好（mRS 0-2）	21.0％	26.0％	0.48	予後良好（mRS 0-1）	30.4％	34.8％	0.16
死亡率	19.1％	21.6％	0.52	死亡率	18.0％	21.0％	0.75	死亡率	8％	6％	0.53
症候性頭蓋内出血	6.2％	5.9％	0.83	症候性頭蓋内出血	9.0％	6.0％	0.24	症候性頭蓋内出血	6.0％	6.0％	0.99

2 現行の血栓回収デバイスによる治療

1）Merciリトリーバー

発症8時間以内の脳主幹動脈閉塞症例で，rt-PA静注療法の無効・非適応例に対して我が国でも2010年より認可された．本デバイスを血栓の遠位に誘導し，先端のコイル型ループで血栓を絡め取り，回収する．米国での前向き研究Multi MERCI trialにおいては，再開通率（Thrombolysis In Myocardial Infarction（TIMI）：2-3）は68％で，90日後の予後良好例（modified Rankin Scale（mRS）：0-2）は36％と報告[8]された．

一方で，Merciリトリーバーにおいては，出血性合併症が多いといわれている．国内15施設で行われた119例の初期周術期成績においては，画像上のくも膜下出血が21.9％に認められた[9]．症候性のものは2.6％であったが，強い屈曲部への堅いデバイスの使用は控えることが望ましい．

2）Penumbraシステム

本デバイスは，血栓を吸引することで再開通を得ることができ，2011年に我が国でも認可された．ペナンブラを用いた前向き研究においては，再開通率（TIMI 2-3）は82％で，予後良好例（mRS 0-2）は25％と報告[10]された．

本デバイスは，血管に適合したサイズを選択することが極めて重要である．目的血管と再灌流カテーテル先端部とのサイズ差が少なくなるほど吸引力も高まり，末梢塞栓も起こしにくくなる．最近では大口径のMAXシリーズが使用可能となり，治療結果の改善が期待されている．また，Penumbraシステムにおいては，治療後のくも膜下出血が少ない印象がある．

3 ランダム化比較試験の結果

2013年，ホノルルで開催されたInternational stroke conferenceにおいて，急性期脳梗塞に対する血管内治療に関する3つのランダム化比較試験の結果が公表され，New England Journal of Medicineに同日掲載された．

rt-PA静注療法に対する血管内治療の追加効果を検討するIMS III[2]，MRI画像診断を基に血管内治療の有効性を検討したMR RESCUE[3]，rt-PA静注療法と血管内治療を比較したSYNTHESIS expansion[4]である（表1）．各試験の結果について解説する．

1）IMS III[2]

この試験は，rt-PA静注療法に対して，血管内治療の追加効果を検討した多施設共同ランダム化試験である．1次エンドポイントは90日後のmRS 0-2に設定された．

1次エンドポイントは有意差なく（血管内治療群40.8％ vs rt-PA単独群38.7％），NIHSSスコアごとの層別化後のサブグループ解析（NIHSSスコア8-19，NIHSSスコア≧20）でも有意差は認めなかった．しかしIMS IIIは，登録された半分以上の症例で主幹動脈の閉塞を確認していない点やrt-PA静注療法から血管内治療まで平均で2時間以上経過している点，血管内治療の再開通率（Thrombolysis in Cerebral Infarction（TICI）：2b-3）が40％前後と低い点が問題とし

表2 新規血栓回収デバイスの治療成績

研究名	Multi MERCI trial (n=164)	Penumbra Pivotal stroke trial	SWIFT		TREVO 2	
使用デバイス	Merci	Penumbra	Solitaire (n=58)	Merci (n=55)	Trevo (n=88)	Merci (n=90)
再開通率(TIMI 2-3)	68 %	81.6 %	89 %	67 %	92 %	77 %
手技関連合併症	9.8 %	12.8 %	14 %	16 %	15 %	23 %
症候性頭蓋内出血	9.8 %	11.2 %	2 %	11 %	7 %	9 %
予後良好例(mRS 0-2)	36 %	25 %	58 %	33 %	40 %	22 %

て挙げられる.

以上の結果から, 特に再開通率と再開通までの時間を短縮することが重要であり, 血管内治療は脳主幹動脈閉塞をターゲットとすることが示唆された.

2) MR RESCUE[3]

この試験は, 発症8時間以内の脳主幹動脈閉塞症例(前方循環のみ)を血管内治療群と通常の内科的治療群に割り付け, 各症例におけるMR perfusionによるペナンブラ領域の大きさと血管内治療の有効性を検討したランダム化比較試験である. 90日後のmRSを転帰の指標とした.

結果は, 90日後のmRSの平均値は両群ともに3.9と差を認めなかった. またペナンブラ領域の有無に関わらず血管内治療の有効性は認められなかった. しかし, この試験にも発症から血管内治療開始まで平均で6時間以上経過していることや血管内治療の再開通率(TICI 2b-3)が27 %と低いことが問題点として挙げられる.

IMS IIIと違い, 本試験では割り付け前に主幹動脈の閉塞がMRAで確認されており, 我が国に近いプロトコールである. しかし, 血管内治療開始までに長時間を要しており, また再開通率が低かったため, 有効性が示されなかったと考えられる.

3) SYNTHESIS expansion[4]

この試験は, 発症4.5時間以内の急性期脳梗塞を血管内治療もしくはrt-PA静注療法のいずれかに割り付けたランダム化比較試験である. 1次エンドポイントは, 3カ月後のmRS 0-1と定義された.

結果は, mRS 0-1の転帰良好の割合は両群間で差を認めなかった(血管内治療群30.4 % vs rt-PA静注療法群34.8 %, p=0.16). 発症から治療開始までの時間は, 血管内治療群で3.75時間, rt-PA静注療法で2.75時間であり(p<0.001), 血管内治療群で1時間の遅れを認めた.

SYNTHESIS expansionの最大の問題点は, IMS IIIと同様, 割り付け前に主幹動脈の閉塞が確認されていない点である. このため, 1割弱が割り付け後に血管内治療を受けておらず, 行われた手技も2/3はrt-PAの動注療法であった.

以上から, 本試験はデザインが未完成であったと言わざるを得ない.

4 今後の展望

現在, 世界的に最も期待されているのはステント型血栓回収デバイスである. これらは閉塞部位に一時的にステントを展開して, そのままステントごと血栓を回収するデバイスである. 既に米国ではランダム化比較研究が行われ, Merciリトリーバーに対して優位性を示している[11,13]. 本デバイスは従来よりも高い再開通率が得られ, 手技時間の短縮も期待されるため, 今後の主流となるだろう. 主なデバイスとして, SolitaireとTrevoがあげられる. SolitaireとMerci(SWIFT試験)[11]およびTrevoとMerci(TREVO 2試験)[12]の多施設前向きランダム化比較試験の結果を示す(**表2**).

ステント型血栓回収デバイスによる再開通率はいずれも高率であり, また手技時間も短縮できるといわれている. 我が国においてもこれら

のデバイスの迅速な承認が期待される.

おわりに

手技時間のみならず, 発症から再開通までの時間全体の短縮が急性期脳梗塞における予後良好を増加させる鍵である. 30分の再開通の遅れが2割近くの死亡や予後不良を増加させたとも報告[13]されており, 搬送や画像診断, 治療までの時間をいかに短縮させるかが今後の課題となるであろう.

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脳梗塞急性期の血管内治療(IVR)を再考する

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rt-PA 静注療法は急性期脳梗塞に対してエビデンスの確立された治療法であるが，脳主幹動脈閉塞例では有効性が低いことがわかってきた．このため脳血管内治療に期待がかかっているが，欧米の3つのランダム化比較試験では有効性が示されなかった．ただし，その解析から近位主幹動脈閉塞例に対して早期に高い開通率が得られれば有効性が示される可能性が示唆され，新たな試験結果が待たれている．

KEY WORDS

急性期脳梗塞　rt-PA　脳血管内治療　ランダム化試験

はじめに

組織プラスミノーゲンアクチベータ（recombinant tissue plasminogen activator：rt-PA）静注療法は急性期脳梗塞に対してエビデンスの確立された治療法であり，2012年に適応が発症後4.5時間以内に拡大されたが，脳梗塞例全体の5%程度にしか実施されておらず，また脳主幹動脈閉塞例では再開通率が低く，予後良好例が少ないなどの問題点がある．このため，より適応時間が長く開通率の高い脳血管内治療に期待がかかるが，2013年に報告された3つのランダム化比較試験では，その有効性が示されなかった[1)~3)]．一方，わが国の前向き登録試験では近位血管における有用性が示唆されている[4)5)]．

本稿ではこれらの試験結果を振り返り，次世代型デバイスを用いたランダム化試験について考察する．

ランダム化試験の概要（表❶）と問題点

1）SYNTHESIS Expansion 試験[1)]

発症後4.5時間以内の急性期脳梗塞患者を，血管内治療群とt-PA静注療法群に無作為に割り付けた．治療開始までの時間は，血管内治療群が発作後6時間以内，t-PA静注療法群が無作為化直後（発作後4.5時間以内）とした．主要評価項目は90日後の無障害生存（modified Rankin Scale：mRS 0~1）で，t-PA静注療法群では34.8%，血管内治療群では30.4%であり，2群間に有意差は認めなかった（p=0.16）．

本研究では重症度を限定せず，画像診断で血管閉塞を

表❶ 2013年の3つのランダム化試験

	IMS III			MR RESCUE			SYNTHESIS Expansion		
	Endovascular therapy	t-PA only	p value	Endovascular therapy	Standard care	p value	Endovascular therapy	t-PA only	p value
Number of patiant	434	222		34	34		181	181	
Favorable outcome (mRS 0～2)	40.80%	38.70%	0.25	21%	26%	0.48	mRS 0～1 30.4%	34.80%	0.16
Motality at 90 days	19.10%	21.60%	0.52	18%	21%	0.75	8%	6%	0.53
Symptomatic ICH within 30 hrs	6.20%	5.90%	0.83	9%	6%	0.24	6%	6%	
Onset to puncture t-PA to puncture Reperfusion : TICI 2B-3	127minutes ICA : 38% M1 : 44%			370minutes Total : 53% ICA : 56% M1 : 60%			370minutes Total : 27%		

確認せずにランダム化するという試験デザインに問題があったと考えられる.

2) IMS III試験[2]

NIHSS 10点以上で発症後3時間以内の急性期脳梗塞患者に対し, rt-PA (0.6 mg/kg) を40分かけて投与し, その時点で改善が得られない場合, そのままrt-PA静注療法を続ける群 (rt-PA群) と血管内治療をおこなう群 (血管内治療群) に振り分けた. 血管内治療には血管内超音波カテーテルであるEKOS, Merciリトリーバー, Penumbraシステムなどが用いられた. 本試験では900例の登録を目標としていたが, 登録を継続しても有効性が見出せないと判断されたため, 656例で登録が中止された. 最終結果では予測通り, 予後良好, 死亡率, 症候性頭蓋内出血のいずれの項目においても両群間に有意差を認めなかった.

本研究では, 超音波カテーテルやMerciリトリーバーなどの旧式のデバイスが多く使用されたこと, rt-PA後に血管内治療を開始するまでに127分という長い時間がかかったことが問題であったと考えられている.

3) MR RESCUE試験[3]

NIHSS 6点以上で発症から8時間以内の, 前方循環の主幹動脈閉塞患者を, Merciリトリーバーまたは Penumbraシステムを用いた機械的血栓除去, もしくは標準療法の2群にランダムに割り付けた. また本試験ではMRI灌流画像を撮像しており, ①血栓除去を施行した患者の機能予後が改善する, ②広いペナンブラを確認できた患者 (ペナンブラ群) では機械的血栓除去への反応性が高い, の2つの仮説を検証する目的で実施された.

主要評価項目の90日後のmRSは, 血管内治療群で3.9, 標準療法群で3.9と, 有意差はみられなかった (p=0.99). また期待されたペナンブラ群でも, mRSは血管内治療群 (34例) で3.9 (95%CI : 3.3-4.4), 標準療法群 (34例) で3.4 (95%CI : 2.8-4.0) と, 有意差はみられなかった (p=0.23). 非ペナンブラ群では, mRSは血管内治療群で4.0 (95%CI : 3.4-4.6), 標準療法群で4.4 (95% CI : 3.6-5.2) と, 同様に差はみられなかった (p=0.32). 画像診断によるペナンブラパターンや, 治療法による交絡はみられなかった (p=0.14). 本研究で血管内治療の有効性が示されなかったのは, 穿刺までの平均時間が発症後6.2時間と長かったこと, 有効再開通率が低かったことが主因と考えられる. また論文では, 標準治療群でt-PA静注療法が施行された症例があったこと, 画像診断時にCTとMRIの両方が用いられたことなどもあげられている.

なぜ日本の治療成績は良かったか? —RESCUE-Japan Registry[4]

脳主幹動脈急性期閉塞症の前向き多施設登録研究 (RESCURE-Japan Registry) では, 発症後24時間以内に搬入された脳主幹動脈急性閉塞が1,400例以上登録された. 主要評価項目は, 発症90日後の予後良好 (mRS 0～2) とされた.

結果, 血管内治療を施行した442例全体では, mRS 0～2がt-PA静注療法単独群で125例 (42.2%), t-PA静注療法+血管内治療群で65例 (44.5%) と, t-PA静