ORIGINAL

Prognostic factors for acute large vessel occlusion with NIHSS 5 or lower

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Abstract : Background : Intravenous recombinant tissue plasminogen activator (IV rt-PA) and endovascular treatment have been performed for severe large vessel occlusion (LVO) and the results have been reported at high levels of evidence. However, acute treatment for LVO with mild symptom remains controversial. We retrospectively examined prognostic factors for LVO with mild symptoms. Method : We studied retrospectively the patients within 24 h of onset with large vessel occlusion with NIHSS score ≤5. Outcomes were evaluated by modified Rankin Scale (mRS) at 90 days, with 0–2 defined as a good outcome and 3–6 as a poor outcome. Clinical characteristics of each case were examined. Result : Participants comprised 76 patients. Of the 76 patients. ICA occlusion showed good outcome in 17/19 cases (90%), whereas MCA occlusion showed good outcome in 36/54 cases (67%). Among the 14 cases showing positive results for distal intraarterial signal (d-IAS), outcomes were good in 6 cases (43%). On the other hand, the 32 d-IAS-negative cases showed good outcome in 28 cases (88%). Outcomes were thus significantly poorer for d-IAS-positive cases. Conclusion : MCA occlusion is associated with poor prognosis, even with NIHSS score ≤5, and d-IAS may provide a predictor. J. Med. Invest. 70 : 22-27, February, 2023

Keywords **:** *large vessel occlusion with mild symptoms, susceptibility vessel sign, distal intraarterial signal*

INTRODUCTION

Nowadays revascularization with mechanical thrombectomy (MT) is the standard of care for anterior circulation emergency large vessel occlusion (LVO) presenting with National Institutes of Health Stroke Scale (NIHSS) score ≥6 during the first 6 h after symptom onset (1). However, the effect of MT for LVO with mild symptoms of NIHSS ≤5 or lower is unclear and controversial. The effect of MT for LVO with mild symptoms is reportedly no different from that of medical treatment, because the natural course of LVO with mild symptoms itself is good (2). On the other hand, MT has also been reported as more effective than pharmacotherapy for internal carotid artery (ICA) occlusion or proximal middle cerebral artery (MCA) occlusion (3). In these studies, diagnosis of the occlusion site and evaluation of collateral circulation are mainly performed using computed tomography angiography (CTA), and measurement of ischemic cores using the Alberta Stroke Program Early CT Score (ASPECTS). No studies have been conducted using magnetic resonance imaging (MRI).

We considered that factors related to exacerbation of LVO with mild symptoms should be examined to determine indications for MT in LVO showing NIHSS score ≤5. Our group uses MRI in principle to diagnose acute stroke. We retrospectively investigated findings from MRI and the course of LVO with mild symptoms.

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METHODS

Study selection and data collection

The study was approved by the Clinical Research Ethics Committee at Tokushima University Hospital (approval number : 1934-2). We studied retrospectively. This retrospective study included patients admitted to the Tokushima University Hospital stroke care unit (SCU) from January 2011 to August 2018 diagnosed with acute LVO within 24 h of onset of NIHSS score ≤5, and age ≥18 years. LVO was defined as ICA occlusion, proximal MCA (M1 or M2) occlusion or anterior cerebral artery (ACA) occlusion.

Exclusion criteria were occlusion of the basilar artery (BA) or vertebral artery (VA), pre-onset modified Rankin Scale (mRS) score ≥2, or no performance of MRI on admission.

MRI imaging

On admission, MRI was imaged and evaluated in principle. We measured ASPECTS-diffusion-weighted imaging (DWI), and diagnosed the occlusion site on magnetic resonance angiography (MRA). We checked for the susceptibility vessel sign (SVS) at the obstruction site using T2*-weighted imaging and distal intraarterial signal (d-IAS) in the artery distal to the occlusion site on fluid-attenuated inversion recovery (FLAIR) imaging (Figure 1).

MRI examinations were performed with a 3-tesla MRI scanner (Discovery MR 750 ; GE Healthcare, Milwaukee, WI) equipped with an 8-channel phased-array head coil. All patients were examined with DWI, MRA and T2*WI. The imaging sequences and parameters were as follows : DWI (FOV : 24 cm, matrix : 128 × 128, TR : 6000 ms, TE : 65 ms, slice thickness : 5 mm, gap : 0 mm, number of slices : 30, b-factor : 1000, NEX = 2, and acceleration factor : 2), MRA (FOV : 22 cm, matrix : 512 × 224, TR : 30 ms, TE : 2.8 ms, flip angle : 17°, slice thickness : 1.2

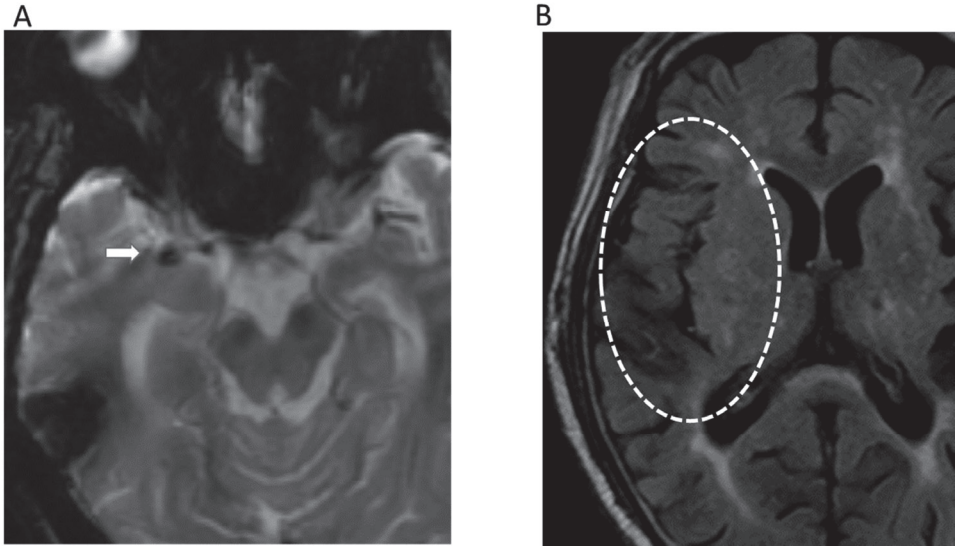

Figure 1. Representative MRI of middle cerebral artery occlusion due to cardioembolism (A : T2* ; B : FLAIR) Arrows in A indicate susceptibility vessel sign (SVS). Dotted circle in B indicates distal intraarterial signal.

mm, and number of slices : 66) and T2*WI gradient echo (FOV : 24 cm, matrix : 320 × 192, TR : 400 ms, TE : 28 ms, flip angle : 28°, slice thickness : 6 mm, gap : 1.5 mm, and number of slices : 18), FLAIR (FOV : 24 cm, matrix : 320 × 192, TR : 6200 ms, TE : 120 ms, flip angle : 28°, slice thickness : 6 mm, gap : 1.5 mm, and number of slices : 18).

Outcomes and statistical analysis

Outcome at 90 days after onset was evaluated by mRS, with mRS 0–2 regarded as a good outcome, and mRS 3–6 as a poor outcome. And we investigated the correlation between prognosis and patient characteristics.

Continuous data are presented as the mean (standard deviation [SD]) or median (interquartile range [IQR]), and categorical data are presented as counts (%). Comparisons were conducted using the t-test or the Mann–Whitney U test. Statistical analysis was performed using R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria.) and 2-tailed values of $P < 0.05$ were considered statistically significant.

RESULTS

Patients Characteristics

A total of 1,166 ischemic stroke cases were admitted to the SCU in Tokushima University Hospital during the study period. Of these, 76 patients (age, 73.1 ± 8.4 years ; 53 males and 23 females) were included. Etiology was atherothrombotic brain infarction in 42 patients (55%) and cardioembolic infarction in 25 patients (34%). Risk factors included a history of hypertension in 32 patients (42%), atrial fibrillation in 13 (17%), lipid abnormalities in 11 (14%), and current smoking in 30 (39%). Median NIHSS score on admission was 3.

As acute treatment, pharmacotherapy was administered in 59 cases (77%), intravenous recombinant tissue plasminogen activator (IV rt-PA) in 6 cases (8%), MT in 8 cases (11%), and combination IV rt-PA/MT in 3 cases (4%). For secondary prevention after stroke, 49 patients (65%) were treated with antiplatelets, 23 patients (30%) with anti coagulants, and 4 patients (5%) with a combination of antiplatelets and anticoagulants.

DWI and MRA were performed in all 76 cases. Occlusion site was the right ICA in 7 cases (9%), left ICA in 12 (16%), right ACA in 3 (4%), right MCA in 36 (47%), and left MCA in 18 (24%).

Median ASPECTS-DWI on admission was 9, with scores of 6–8 in 32 cases (42%) and 9–10 in 42 cases (55%). T2*-weighted imaging was performed in 75 cases, revealing positive SVS in 15 cases (20%). FLAIR imaging was performed in 70 cases, showing positive d-IAS in 20 cases (29%) (Table 1).

Atherothrombotic brain infarction (ATBI) was identified in 16 cases (84%) and cardioembolic infarction in 3 cases (16%). Among the 19 cases of ICA occlusion, ATBI was seen in 16 cases, all of which were treated with pharmacotherapy, while cardioembolic infarction was seen in 3 cases, 2 of which were treated with MT.

Of the 54 patients with MCA occlusion, ATBI was seen in 25 cases (46%) and cardioembolic infarction in 21 cases (38%). MT was performed in 4 of the 25 cases of ATBI following MCA occlusion. Two cases received IV rt-PA and 4 cases underwent MT among the 21 cases of cardioembolic infarction with MCA occlusion.

Outcomes

Good outcome was seen in 56 of all 76 cases (73%). By etiology, good outcome showed no significant difference in frequency between ATBI (30 of 42 cases, 71%) and cardioembolic infarction (18 of 25 cases, 72%, $P = 0.96$). The good outcome cases of medication without IV rt-PA is 45 of 57 cases (76%), while IV rt-PA or MT achieved good outcome in 11 of 17 cases (64%), again showing no significant difference.

Among cases with ASPECTS-DWI score 9–10, good outcome was seen in 35 of 42 cases (83%), compared to 22 of 34 cases with score ≤8 (65%). Higher ASPECTS-DWI score was associated with significantly better outcome ($P = 0.04$) (Table 2).

By occlusion site, good outcome was seen in 17 of 19 cases (90%) with ICA occlusion, and 36 of 54 cases (67%) with MCA occlusion. Outcomes were thus significantly worse for cases of MCA occlusion ($P = 0.01$).

Table 1. Patient Charactaeristics

Variables	n = 76
Age, mean (SD)	73.1 ± 8.4
Sex	men 53 women 23
Hypertension	32 (42%)
Atrial fibrillation	13 (17%)
Diabetes	26 (34%)
Hyperlipidemia	11 (14%)
Smoking	30 (39%)
Admission NIHSS median (IQR)	3 (1-4)
0	8 (11%)
1	17 (23%)
2	16 (21%)
3	14 (18%)
4	14 (18%)
5	7 (9%)
Acute treatment	
medication without rt-PA	59 (77%)
IV-rtPA	6 (8%)
MT	8 (11%)
IV-rtPA + MT	3 (4%)
Stroke subtype	
ATBI	42 (55%)
CI	25 (34%)
Other	8 (11%)
Antithrombotic agent after stroke	
SAPT	28 (37%)
DAPT	21 (28%)
Anticoagulant	23 (30%)
Antiplatelet + anticoagulant	4 (5%)
Occlusion site	
ICA	19
right	7 (9%)
left	12 (16%)
ACA	3 (4%)
right	3 (4%)
left	0
MCA	54 (71%)
right	36 (47%)
left	18 (24%)
DWI-ASPECTS, median (IQR)	9 (7-9.25)
≤5	2 (3%)
6-8	32 (42%)
9-10	42 (55%)
SVS	15/75 (20%)
D-IAS	20/70 (29%)

NIHSS : National Institutes of Health Stroke Scale, IQR : interquartile range, IV rt-PA : intravenous recombinant tissue-plasminogen activator, MT : mechanical thrombectomy, ATBI : atherothrombotic brain infarction, CI : cardioembolic infarction, SAPT : single antiplatelet therapy, DAPT : dual antiplatelet therapy, ICA : internal carotid artery, ACA : anterior carotid artery, MCA : middle carotid artery, DWI-ASPECTS : diffusion-weighted imaging - Alberta Stroke Program Early CT Score, SVS : susceptibility vessel sign, d-IAS : distal intraarterial signal

Table 2. Patients with NIHSS ≤5 stratified according to good outcome (mRS 0-2 vs 3-6)
mRS : modified Rankin Scale

	mRS 0-2	mRS 3-6	*P*
Total	56 (73%)	20 (27%)	
Stroke subtype			0.96
ATBI	30 (71%)	12 (29%)	
CI	18 (72%)	7 (28%)	
Acute treatment			0.41
Medication without IV rt-PA	45 (76%)	14 (24%)	
MT or IV rt-PA	11 (64%)	6 (36%)	
Occlusion site			0.01
IC	17 (89%)	2 (11%)	
MCA	36 (67%)	18 (33%)	
ACA	3 (100%)	0	
DWI-ASPECTS			0.04
<9	22 (65%)	12 (35%)	
9, 10	35 (83%)	7 (17%)	

ATBI : atherothrombotic brain infarction, CI : cardioembolic infarction, IV rt-PA : intravenous recombinant tissue-plasminogen activator, ICA : internal carotid artery, ACA : anterior carotid artery, MCA : middle carotid artery, DWI-ASPECTS : diffusion-weighted imaging- Alberta Stroke Program Early CT Score

Imaging of MCA occlusion

Imaging findings for cases of MCA occlusion were examined. Of the 54 cases of MCA occlusion, T2*-weighted imaging was performed in 52 cases. Twelve of those cases (23%) were SVS-positive. Of the 12 SVS-positive cases, good outcome was seen in 5 cases (42%), compared to 30 of the 40 SVS-negative cases (75%). This tendency was not significant (P = 0.06).

FLAIR imaging was performed for 46 cases of MCA occlusion. Among the 14 d-IAS-positive cases, 6 (43%) showed good outcomes. On the other hand, good outcome was seen in 28 of the 32 d-IAS-negative cases (88%), showing significantly poorer outcomes in d-IAS-positive cases (P <0.01) (Table 3, Figure 2).

Mechanical Thrombectomy

Comparisons were made between 59 patients in the group treated conservatively for acute LVO with mild symptoms and 17 patients in the revascularization group who underwent IV rt-PA or MT. Mean age was 71.4 ± 7.3 years in the conservative treatment group and 75.1 ± 9.3 years in the revascularization group, showing no significant difference. Median NIHSS score was 2 in the conservative treatment group and 4 in the revascularization group, showing significantly higher score in the revascularization group (P = 0.01). In the conservative treatment and revascularization groups, respectively, ICA occlusion was seen in 15 cases (25%) and 4 cases (24%), MCA occlusion in 42 cases (71%) and 12 cases (71%), and ACA occlusion in 2 cases (4%) and 1 case (5%).

In terms of MRI findings, median ASPECTS-DWI score was 8 for both.

Positive SVS was seen in 7 cases (12%) in the conservative treatment group and 8 cases (47%) in the revascularization group (P = 0.02). Positive d-IAS was seen in 14 patients (26%) in the conservative treatment group and 6 patients (35%) in the revascularization group, showing no significant difference (P = 0.51) (Table 4).

MT was performed in 11 cases, 9 of which were treated after 2015.

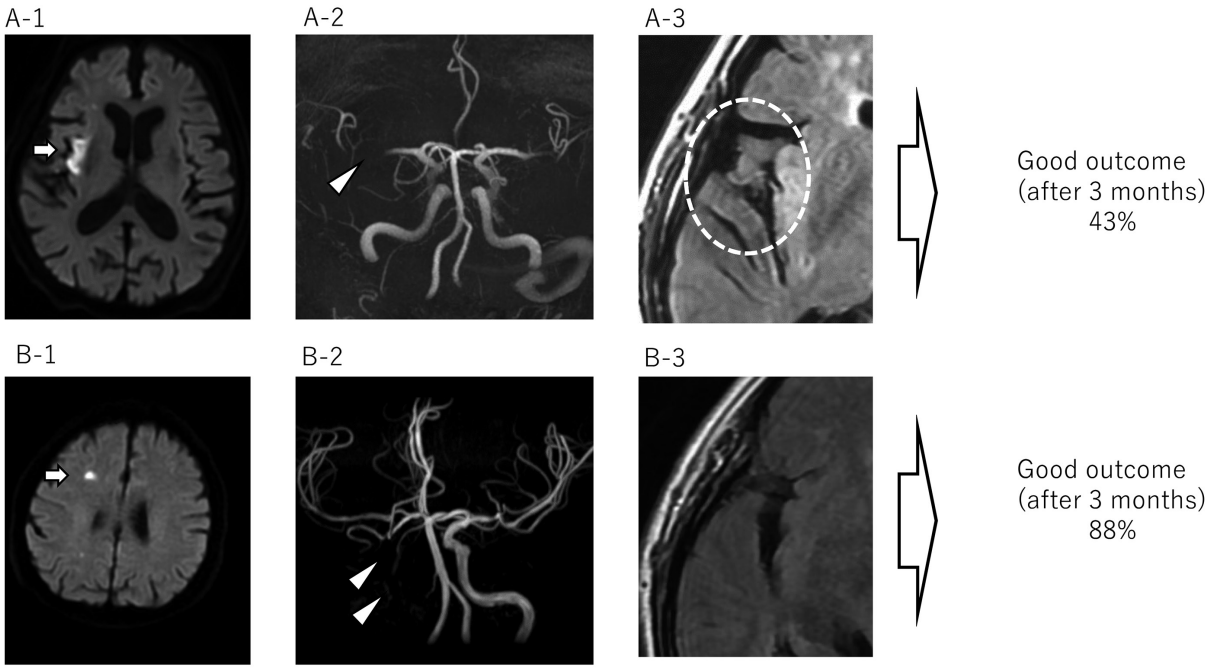

Figure 2. Regarding distal intraarterial signal (d-IAS), the schematic diagram that combined with brain MRI of acute LVO and the Result part. Arrows in A-1 and B-1 indicate the brain infarction on DWI. Arrowheads in A-2 and B-2 indicate LVO on MRA. Dotted circle in A-3 indicates d-IAS, and no signal in B-3 on FLAIR.

Table 3. Concerning MRI : Patients with MCA occlusion stratified according to good outcome (mRS 0-2 vs 3-6)

	mRS0-2	mRS3-6	*P*
Total	36 (67%)	18 (33%)	
SVS			0.06
positive	5 (42%)	7 (58%)	
negative	30 (75%)	10 (25%)	
d-IAS			0.01
positive	6 (43%)	8 (57%)	
negative	28 (88%)	4 (12%)	

mRS : modified Rankin Scale, SVS : susceptibility vessel sign, d-IAS : distal intraarterial signal

Table 4. Differences in characteristic medication without IV rt-PA or revascularization (mechanical thrombectomy or IV rt-PA)

	Medication without IV rt-PA	MT or IV rt-PA	*P*
Total	59	17	
Age, mean (SD)	71.4 ± 7.3	75.1 ± 9.3	0.21
NIHSS, median (IQR)	2 (1-3)	4 (2-5)	0.01
Occlusion site			0.91
ICA	15 (26%)	4 (24%)	
MCA	42 (71%)	12 (71%)	
ACA	2 (4%)	1 (5%)	
ASPECTS-DWI median (IQR)	8 (7-9)	8 (7-9.5)	0.5
SVS positive	7/58 (12%)	8/17 (47%)	0.02
D-IAS positive	14/53 (26%)	6/17 (35%)	0.51

IQR : interquartile range, ICA : internal carotid artery, ACA : anterior carotid artery, MCA : middle carotid artery, ASPECTS-DWI : Alberta Stroke Program Early CT Score – diffusion-weighted imaging, SVS : susceptibility vessel sign, d-IAS : distal intraarterial signal

DISCUSSION

LVO with mild symptoms and revascularization

Other studies have reported good outcome at 90 days after pharmacotherapy for acute LVO with NIHSS score ≤5 in 54.4–88.4%, compared to 55.7–96.7% using MT (2-5). Some reports have described MT as better than pharmacotherapy, although differences exist between the reports. Dargazanli *et al*. reported that for LVO with NIHSS score ≤8, good outcome was seen with MT in 78.1% and with medication in 76.7% (6).

Recently, using RAPID (RApid processing of Perfusion and Diffusion) software for measuring infarct volume, we have been able to determine indications for revascularization. In the EXTEND-IA (7), SWIFT-PRIME (8), and DAWN trials (9), ischemic mismatch was measured using RAPID, and good results were obtained by MT for LVO. At present, no large randomized controlled trials have measured ischemic mismatch with RAPID for LVO with mild symptoms, and this issue should be addressed

in the future.

In terms of indications for MT or IV rt-PA in cases of mild LVO, no clear guidelines have been provided, and the decision has been left to the judgment of each facility and operator. Griessenauer *et al*. undertook a systematic review and meta-analysis (10) of LVOs with NIHSS score ≤5, and compared characteristics between medication groups and IV rt-PA or MT groups. Patients with IV rt-PA or MT were younger (64.17 ± 1.25 years vs 70.26 ± 1.95 years ; P = 0.02) and had higher NIHSS (4 ± 0 vs 2.7 ± 0.58 ; P <0.01) and ASPECT score (8.82 ± 0.24 vs 9.56 ± 0.45 ; P = 0.001). Analyzing the occlusion site, ICA occlusion tended to be treated with medication rather than recalculation (17.3% vs 35.7% ; P <0.001), and M1 occlusion tended to be treated with IV rt-PA or MT rather than medication (56.8% vs 24.8% ; P = 0.003). In our study, IV rt-PA or MT was performed in 17 cases. As noted in the review by Griessenauer *et al*., NIHSS was higher in the revascularization group, but no significant differences in age, ASPECT score, or occlusion site were apparent. Our study also showed a significantly higher frequency of SVS-positive cases in the revascularization group. SVS on T2*-weighted imaging suggests the presence of deoxyhemoglobin-rich thrombus, considered highly likely to represent embolus in cardioembolic stroke (11). Therefore, even in LVO with mild symptoms, the presence of SVS may indicate possible emboli and may help determine whether to perform revascularization.

Occlusion site

The natural history of ICA occlusion is known to be poor, and the results of IV rt-PA, which is given priority in the hyperacute phase, are not particularly good (12). In general, because the ICA has a wide perfusion area, ICA occlusion often creates an extensive area of ischemia. In particular, occlusion of the ICA due to cardiogenic embolism displays poor prognosis (13, 14). However, LVO due to ATBI, because of the chronic, slowly progressive course compared with that due to cardioembolic stroke, is considered to involve much better collateral circulation, and outcomes may progress well (15). Therefore, although 84% of ICA occlusions in our study were ATBI and all cases of ATBI due to ICA occlusion were treated conservatively, 90% showed good outcome.

SVS and d-IAS

Many reports have described SVS in acute LVO. Kimura *et al*. (16) reported that IV rt-PA was poorly effective in SVS-positive cases of M1 occlusion, resulting in poor outcome. On the other hand, Bourcier *et al*. (17) reported that MT using a stent retriever performed better in SVS-positive M1 occlusion cases than in SVS-negative cases. This was because SVS-negative thrombus is fibrin-based, suggesting atherosclerotic plaque in the occluded part, and thus a risk of re-occlusion after MT.

A positive d-IAS in LVO suggests retrograde flow through the collateral circulation distal to the occlusion site (18, 19). Further, a d-IAS-negative finding in LVO may imply chronic atherosclerosis-related occlusion (20).

In addition, d-IAS in LVO represents slower flow distal to the occlusion site, and DWI-perfusion mismatch has been shown in the d-IAS region (21, 22). In other words, d-IAS may be associated with mild symptoms due to collateral flow, but may progress due to reduced perfusion. SVS and d-IAS in LVO have been reported as biomarkers for evaluating stroke subtype (20). However, our study suggested that SVS and d-IAS could be factors associated with outcomes in MCA obstruction with mild symptoms.

Limitations and strength

This study has some limitations that warrant consideration. First was the single-center retrospective study design with a relatively small number of cases, and implementation of MT and IV rt-PA left to the discretion of the clinician. Second, identification of SVS and d-IAS is susceptible to bone and motion artifacts and are not quantifiable. However, the notion that d-IAS may predict outcomes of LVO with mild symptoms is a new finding from the present study.

CONCLUSION

We retrospectively studied mild LVO with NIHSS score ≤5 and identified MCA occlusion as potentially associated with poor outcome. Positive d-IAS in MCA occlusion may also suggest poor outcome. Whether such cases of LVO with mild symptoms should undergo acute revascularization represents a challenge for the future.

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DECLARATIONS OF INTEREST

none

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