ON-LINE APPENDIX

Supplemental Methods

Subjects. This retrospective case control study was performed on all patients admitted to 2 hospital stroke centers from April 2007 to November 2012 who were clinically diagnosed with acute ischemic stroke by neurologists and managed in the stroke care unit. The inclusion criteria were the following: 1) presentation within 3 hours of symptom onset and treatment with IV rtPA according to Japanese guidelines,[1] and 2) acute ischemic regions within the MCA territory on DWI and occlusion of the proximal MCA (M1 or M2 segment) on MRA. All patients routinely underwent brain MR imaging before rtPA, and the median time from symptom onset to initial MR imaging was 91 minutes (IQR, 72–103 minutes). Median time from symptom onset to IV rtPA was 135 minutes (IQR, 123.5–154.3 minutes). To assess the flexibility of collateral signs, we included patients who underwent follow-up MR imaging (median, 6 days; IQR, 3–8 days). In 2 hospital stroke centers included in the study, follow-up MR imaging was usually achieved in patients with proximal MCA occlusion treated with rtPA, though follow-up MR imaging was not performed in some cases, due to the patient's general condition, including severe infectious disease, agitation, or early hospital discharge.

Follow-up brain CT was performed on all patients after stroke onset (median, 9 days; IQR, 6–12 days) to assess the infarct extent. Demographic data and information on cardiovascular risk factors, medical history, and the results of diagnostic tests were collected at the time of admission. The institutional review boards of both centers approved this study. In accordance with the standard protocol of our institutions for patients with ischemic stroke, neurologic deficits were evaluated daily by stroke neurologists or stroke nurses by using the NIHSS score. The Modified Rankin Scale score was collected 3 months after stroke. We assessed ENI, defined as a decrease in NIHSS score of ≥10 or an NIHSS score ≤2 at 24 hours from rtPA treatment.[2-6]

MR Imaging Protocol and Imaging Analysis

Pretreatment and follow-up MR imaging were performed on 1.5T machines (Signa HDxt 1.5T Optima Edition, GE Healthcare; Magnetom Avanto, Siemens; or Symphony, Siemens). MR imaging included spin-echo DWI, T2 FLAIR, and 3D-TOF MRA sequences acquired in the axial plane. The protocol and scan parameters were the following: DWI (TR/TE, 10,000/75.0–90 ms; section thickness/gap, 5 /1 mm; FOV, 21–23 cm; matrix size, 98 × 128 to 160 × 160; b-value, 1000 s/mm^2); FLAIR (TR/TE, 9000–9202/105–124.9 ms; TI, 2300 ms; matrix, 256 × 192; FOV, 22; 20 contiguous sections taken 5 mm apart with a gap of 1.5 mm); and 3D time-of-flight angiography (TR/TE, 27–30/6.8–7.0 ms; flip angle, 20°; FOV, 16–24 cm; matrix size, 256 × 128 to 160; section thickness, 0.8–1.2 mm). Readers (E.I. and M.I.) blinded to all clinical information assessed the presence of PCA laterality and HVs on FLAIR. PCA laterality was considered present if ≥1 segmental extent was observable on axial stereoscopic images (Fig 1*A*), as described in our previous study.[7,8] If signal from both PCAs ended in the same segment, laterality was defined as negative. HVs were defined as linear or serpentine hyperintense signals relative to gray matter distal to the Sylvian fissure.[9]

To quantify the degree of HV, we analyzed 10 FLAIR MR imaging sections, from 2 sections below to 7 sections above the first M1 segment in which the MCA appeared (Fig 1*B*).[10] The resulting HV score ranged from 0 to 10. A large reduction in the HV score was defined as a decrease of ≥5 on follow-up MR imaging. The "development of collaterals" was defined as positive PCA laterality and/or an HV score of ≥5 on initial MR imaging. The disappearance of PCA laterality or the reduction of the HV score by ≥5 on follow-up MR imaging or both were defined as the "flexibility of collaterals." Interrater reliability for the presence of PCA laterality and HV score grading between 2 observers was estimated; in the event of discrepancies between readers, the final result was reached by consensus.

We defined proximal MCA occlusion as an M1 or M2 segment

On-line Table: Univariate analyses and multivariate logistic regression analysis for prediction of favorable long-term functional outcome after IV rtPA in patients with proximal middle cerebral artery occlusion

	mRS Score 0–1 at 3 mo			Estimated OR (95% CI)		
	Yes (*n* = 24)	No (*n* = 24)	*P* Value	Crude	Adjusted[a]	*P* Value
Age (median) (IQR)	77.5 (73–81)	79.5 (67–85)	.81	1.00 (0.94–1.05)	1.00 (0.94–1.06)	.96
Male sex (No.) (%)	13 (54)	13 (54)	1	1.00 (0.32–3.14)	0.98 (0.24–4.03)	.98
NIHSS score at arrival (median) (IQR)	14 (9–22)	18 (15–24)	.09	0.93 (0.83–1.01)	0.90 (0.80–0.99)	.044[d]
Systolic blood pressure (mean) (mm Hg)	164.6 ± 26.1	151.2 ± 32.8	.11	1.02 (0.99–1.03)		
Diastolic blood pressure (mean) (mm Hg)	86.0 ± 25.7	80.0 ± 22.8	.39	1.01 (0.99–1.03)		
Temperature (°C) (mean)	36.2 ± 0.4	36.3 ± 0.7	.38	0.72 (0.24–1.97)		
Hypertension	15 (63)	13 (54)	.56	1.41 (0.45–4.55)		
Diabetes mellitus	7 (29)	3 (13)	.29	2.88 (0.69–14.98)		
Hyperlipidemia	5 (21)	6 (25)	.73	0.79 (0.20–3.07)		
Atrial fibrillation	18 (75)	16 (67)	.52	1.50 (0.43–5.46)		
Congestive heart failure	4 (17)	5 (21)	.71	0.76 (0.17–3.29)		
Previous stroke	6 (25)	6 (25)	1	1 (0.27–3.77)		
Smoking	7 (29)	11 (48)	.19	0.45 (0.13–1.47)		
MCA M1 occlusion (No.) (%)	18 (75)	17 (71)	1	1.24 (0.34–4.56)		
Initial DWI volume (mL) (median) (IQR)	19.8 (10.8–24.2)	36.1 (15.9–45.6)	.027[d]	0.97 (0.93–0.99)	0.97 (0.94–1.01)	.11
Time to rtPA administration	141.5 ± 25.1	131.4 ± 22.0	.13	1.02 (0.99–1.05)	1.02 (0.99–1.06)	.095
Development of collaterals at arrival[b] (No.) (%)	15 (63)	9 (38)	.08	2.78 (0.88–9.28)	2.74 (0.80–10.08)	.11
Reversion of collaterals[c] (No.) (%)	16 (67)	9 (38)	.042[d]	3.33 (1.05–11.38)	5.07 (1.38–22.09)	.013[d]

[a] Adjusted for age, sex, NIHSS score at arrival, and time to rtPA administration.

[b] The development of collaterals was defined as positive in the presence of PCA laterality positivity and an HV score of ≥5 on initial MRI.

[c] The reversion of collaterals was defined as positive in cases with disappearance of PCA laterality and/or a large reduction in the HV score.

[d] $P < .05$ was considered significant.

occlusion observed on MRA. An M1 occlusion was defined as the occlusion of the main MCA trunk before its bifurcation, and an M2 occlusion was defined as a branch occlusion after the bifurcation. Recanalization status after IV rtPA was assessed with a modified grading system based on the Thrombolysis in Myocardial Infarction grade.[11] Successful recanalization was defined as TIMI 3 on follow-up MRA, and the percentage of successful recanalization was used as the recanalization rate. The Alberta Stroke Program Early CT Score [12] was used to evaluate the initial DWI hyperintensity and final infarct extent on follow-up CT scans. Initial DWI volume was measured by using NIH Image.

Statistical Analyses

Continuous variables were described by using the median and IQR or mean and SD, as appropriate. Univariate parametric and nonparametric comparisons of clinical characteristics were performed by using the Mann-Whitney *U* test, the χ^2 test with or without the Yates correction, and the Fisher exact test as appropriate. Interrater reliability for the presence of PCA laterality and HV score grading between the 2 observers was estimated by using Cohen κ statistics. To identify potential prognostic factors for ENI and long-term functional outcome, we first performed univariate analyses with all potential variables, including demographic characteristics, neurologic markers, and radiologic markers to detect factors that showed a significant relationship with ENI and long-term outcome (Table 2 and On-line Table). A stepwise method was used to select the variables included in a multivariate regression model. A final adjustment for the reported ORs was made for the following variables for predicting ENI: age, a history of atrial fibrillation, NIHSS score at arrival, time to rtPA administration, and development of collaterals. We performed multivariate logistic regression analyses by using age, sex, NIHSS score at arrival, time to rtPA administration, and reversion of collaterals for predicting long-term functional outcome. All statistical analyses were performed by using JMP software (Version 9.02; SAS Institute, Cary, North Carolina) under the direction of a statistician (M.T.).

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