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Stroke mechanisms and their correlation with functional outcome in medullary infarction

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ABSTRACT

Purpose: To study the stroke mechanism of medullary infarction (MI) and their correlation with prognosis.
Methods: We collected 81 consecutive patients with acute isolated MI including 50 patients with lateral MI (LMI), 30 with medial MI (MMI) and one with combined MI. The stroke mechanisms were defined as follows: 1. Large artery atherosclerotic occlusive disease (LAOD): with severe stenosis (> 50%) or occlusion on the relevant arteries. 2. Penetrating artery disease (PAD): occlusion of penetrating arteries that arise from vertebral artery or basilar artery with no significant stenosis of the vertebro-basilar artery. 3. Dissection: angiographic findings met the criteria. 4. Cardiogenic embolism: abrupt onset with atrial fibrillation. The poor outcome was defined as a condition that includes the mRS ≥2 and/or dysphagia at one year after onset.
Results: There were 20 patients with PAD (40%), 18 with dissection (36.0%) and 11 with LAOD (22.0%) in LMI and 17 with PAD (56.6%), 10 with LAOD (33.3%) in MMI. LAOD and dissection compared with PAD were independently correlated with poor outcome in LMI (OR: 12.8, p = 0.029 and OR: 14.9, p = 0.035). LAOD was significantly correlated with poor outcome in MMI (OR: 13.4, p = 0.014).
Conclusions: PAD was the most predominant stroke mechanism in MI and generally showed favorable outcome. Patients with LAOD and dissection showed worse outcome than those with PAD.

1. Introduction

Numerous studies on medullary infarction (MI) have been performed on the symptoms and signs that correlate with complicated nervous structures in the medulla oblongata [1]. However, a limited number of studies have focused on the stroke mechanisms of MI [2–4]. Although vertebral artery occlusive disease has been considered as a major stroke mechanism in lateral medullary infarction (LMI), it is not uncommon that magnetic resonance angiography (MRA) appears normal in patients with LMI [5–7]. Diagnostic imaging has now progressed, it may be worthy of study to clarify the accurate prevalence of stroke mechanism in patients with MI.

Moreover, the prognosis of MI has not been fully understood. Further, the relationship between stroke mechanism and prognosis has seldom been discussed [9–11]. Nonetheless, the prognosis is presumed to depend on the nature of the underlying vascular lesions. We, herein, conducted the present study to explore the stroke mechanism and its correlation with functional outcome of MI including LMI and medial medullary infarction (MMI).

2. Methods

2.1. Subjects

We selected 81 patients with acute isolated medullary infarction including 50 patients with LMI that was caused by circumferential artery occlusion, 30 with MMI that was caused by paramedian artery occlusion and one with both LMI and MMI from the registration of 3061 consecutive acute ischemic stroke patients. Nineteen patients who had cerebellar infarcts in addition to medullary infarction were excluded. The definition of LMI and MMI were adopted from the previous study [12]. Patients were prospectively registered who entered hospital

Abbreviation: LMI, lateral medullary infarction; MMI, medial medullary infarction; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale; LAOD, large artery occlusive disease; PAD, penetrating branch disease; DIS, dissection; CE, cardiogenic embolism; VA, vertebral artery; OR, odds ratio; CI, confidential interval

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within 5 days of onset in the Kyoto Second Red Cross Hospital from January 2009 through September 2017. Isolated medullary artery infarction was defined as any new neurological symptom with acute ischemic stroke relevant to the lesions detected by diffusion weighted image. The Institutional Review Board of Kyoto Second Red Cross approved this study and informed consent was obtained from all patients.

3. Date collection

We collected the following data: age, sex, vascular risk factors, clinical features, anatomic location on DWI, National Institute of Health Stroke Scale (NIHSS) on admission, symptom progression after admission and modified Rankin Scale (mRS) on discharge, which was suggested to be highly correlated with the Barthel Index [13]. Hypertension was defined as a history of antihypertensive agents use, a systolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg during chronic period of the stroke. Dyslipidemia was defined as a history of lipid lowering agents or a serum level of total cholesterol ≥220 mg/dl, or a serum level of low density lipoprotein ≥140 mg/dl. Diabetes mellitus was defined as the use of insulin or oral hypoglycemic drugs, HbA_{1c} ≥ 6.5%, fasting blood glucose ≥126 mg/dl, or non-fasting blood glucose ≥200 mg/dl. Smoking is defined as current or past usage.

4. Magnetic resonance imaging and computed tomography angiography (CTA)

All patients had MRI and magnetic resonance angiography (MRA). MRI scans were performed using 1.5-T superconducting magnets (Gyroscan Intera Achieva 1.5 Pulsar, Philips). Each MRI was performed within 3 days after stroke. Diffusion-weighted scans (TR 1861 ms/TE 69 ms, EPI factor 37) and fluid attenuated inversion recovery (FLAIR) scans (TI 2000 ms, TR 6000 ms, TE 120 ms) were obtained at a slice thickness of 5 mm. Three-dimensional time-of flight images were acquired in the axial plane with a repetition time of 25 ms, echo time of 6.9 ms, flip angle of 18°, 210-mm field of view, partition of 64, 219 9512r acquisition matrix and one signal average, for a total imaging time of 4 min 33 s.

CTA was performed for five patients with dissection. The patient receives an intravenous injection of contrast and then the head and neck were scanned using a high speed CT scanner. When vessel imaging was unclear, digital subtraction angiography was performed for three patients with.dissection.

5. Extracranial atherosclerotic disease

Extracranial vertebral artery disease was examined by cervical MRA. More than 50% diameter reduction or occlusion was considered to be significant atherosclerotic disease.

6. Cardiologic evaluation

A 12-lead ECG was performed on all patients. Echocardiography and 24-h Holter monitoring was performed on 62 and 8 patients, respectively.

7. Distribution of the lesions on DWI

Lesions of LMI detected by DWI were classified in terms of both rostral-caudal and horizontal aspects according to the classification by Kim et al. [3]. First, the lesions were rostral-caudally classified into four groups, as follows: 1. the rostral medulla, 2. the middle medulla, 3. the caudal medulla and 4. Involvement of two segments of aforementioned three groups. Second, the lesions were horizontally detected based on the horizontal map devised by Kim et al. [3]. They were discriminated into 5 segments according to the microanatomy of lateral medulla as follows: A; diagonal band-shaped lesions restricted to the descending trigeminal tract, B; nucleus ambiguus, C; ascending trigeminal tract, D; tracts restricted to the most dorsal or dorsolateral portion, E; lesions, usually at the caudal medulla, restricted to the lateral, superficial area without extending dorsally. Based on this topographical discrimination, we created three axial grades depend on the segment of A to E as follows: Grade 1; only one segment was involved, Grade 2; two segments were involved, Grade 3; more than three segments were involved.

As the majority of lesions in MMI were located in the rostral medulla, lesions were ventro-dorsally classified into 3 groups according to the diagram by Kim et al. [4] as follows: ventral (V); ventral part, presumably containing the pyramid, middle (M); middle part, presumably including the medial lemniscus, and dorsal (D); dorsal part, presumably including the medial longitudinal fasciculus in a lesion extending to the dorsal surface of the medulla. We also created three axial grades depend on the segment of V, M and D as follows: Grade 1; only one segment was involved, Grade 2; two segments were involved, Grade 3; more than three segments were involved.

When lesions were unclear despite medullary syndrome on initial DWI, we performed a second MRI. Patients whose lesion was not detected even on the second MRI were excluded.

8. Evaluation of vascular lesions and presumed stroke mechanism

Vascular lesions were assessed on MRI, MRA, computed tomography angiography or conventional angiography. The stenosis degree in the relevant arteries such as vertebral, basilar artery, or posterior inferior cerebellar arteries (PICA) on the affected side was categorized into 4 groups: Normal, mild stenosis (< 50% diameter reduction), severe stenosis (≥50% diameter reduction) and occlusion (non-visualization of artery). According to the previous reports, dissection was diagnosed when such imaging findings were found as double lumen, intimal flap, intramural hematoma, pearl and strings or fusiform or irregular aneurysmal dilation with rapid change in morphology [14].

Based on the aforementioned vascular imaging, the presumed stroke mechanisms based on vascular lesions were defined as follows: 1. Penetrating artery disease (PAD); intrinsic artery disease or branch atheromatous occlusion of penetrating arteries that arise from the vertebral artery or basilar artery [15]. When the vertebral artery on the affected side was normal or mild stenosis (< 50%), PAD was diagnosed (Fig. 1a, c). 2. Large artery occlusive disease (LAOD); when severe atherosclerotic stenosis or occlusion on the vertebral artery or PICA in the affected side (Fig. 1b). 3. Dissection; when angiographic findings of the vertebral artery consistent with dissection (Fig. 1d). 4. Cardiogenic embolism (CE); when there was atrial fibrillation without large artery occlusive disease and symptoms occurred abruptly.

9. Functional evaluation and neurological sequelae

All of the patients were initially evaluated for neurological severity based on the NIHSS on admission. Functional outcomes were evaluated using the mRS on discharge and one year after onset. Dysphagia was evaluated by the methods developed by Motsch et al. and diagnosed when patients showed level 3 or more, i.e. dysphagia for soft diet [16]. Progression or worsening in acute phase was defined as > 1 point increase on NIHSS during 5 days after admission. Although dysphagia is not counted into mRS, it may be one of the serious neurological sequelae that afflict patients. We thus set the significant neurological sequela index as a condition that includes the mRS ≥2 and/or dysphagia. Those who showed the mRS ≥2 and/or dysphagia at one year after onset were defied as poor outcome. Most patients' outcomes were confirmed by their outpatient clinic, transferred hospital or private attending doctor.

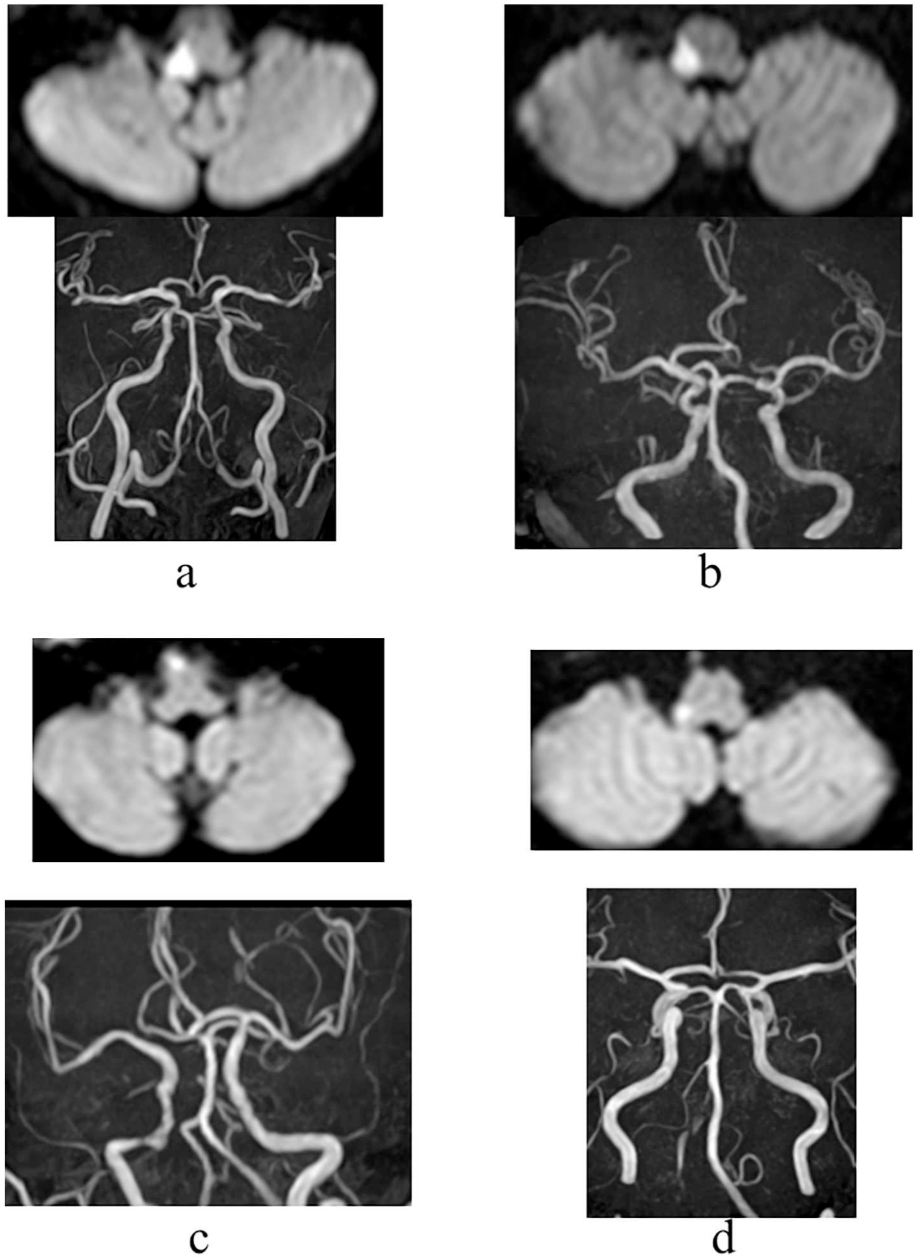

Fig. 1. Diffusion weighted images and magnetic angiography of four patients with different stroke mechanisms.
a. LMI type infarct presumably caused by penetrating artery disease (PAD).
b. LMI type infarct accompanied with right vertebral artery occlusion (LAOD).
c. MMI type infarct presumably caused by penetrating artery disease (PAD).
d. LMI type infarct accompanied with right vertebral artery dissection (Dissection).

9.1. Statistical analysis

Pearson's chi-square test, Fisher's exact test, an independent *t*-test or the Wilcoxon signed rank test were used, as appropriate, to compare the covariates between patients with LMI and MMI. Pearson's chi-square test and Kruskal-Wallis test were performed to compare the lesion locations and functional evaluations between different stroke mechanism groups. Logistic regression analysis was performed to evaluate how vascular risk factors, infarct volume, infarct location and underlying vascular lesions contribute to the final disability. Age (≥60 years versus < 60 years, for LMI group and ≥70 years versus < 70 years, for MMI group) and sex adjusted odds ratio of such factors for poor outcome was calculated. Factors that were significant in the age and sex adjusted odds ratios were put into a multivariate analysis. P-values < 0.05 were considered statistical significant. All statistical analyses were performed using JMP 12 software (SAS Institute Inc., Cary, NC).

10. Results

10.1. Patient characteristics

The characteristics in both groups with LMI and MMI were given in Table 1. Compared with the LMI group, higher age and prevalence of diabetes mellitus and more frequent rostral lesion were found in the MMI group. Dissection and middle lesion were significantly frequent in the LMI than in the MMI group.

Table 1
Characteristics in patients with LMI and MMI.

	LMI (n = 50)	MMI (n = 30)	P value
Age	61.5 (15.6)	71.1 (10.5)	< 0.01
Male	32 (64.0)	22 (73.3)	0.39
Hypertension	41 (82.0)	27 (90.0)	0.33
Diabetes mellitus	12 (24.0)	16 (53.3)	< 0.01
Dyslipidemia	25 (50.0)	17 (56.7)	0.56
Smoking	18 (36.0)	10 (33.3)	0.81
Atrial fibrillation	1 (2.0)	4 (13.3)	0.06
NIHSS on admission	2 (0–8)	3 (0–14)	0.09
Progression	13 (26.0)	14 (46.7)	0.06
mRS at discharge	1 (0–4)	1 (0–5)	0.58
mRS ≥2 at discharge	23 (46.0)	11 (36.7)	0.41
Stroke mechanism			
PBD	20 (40.0)	17 (56.6)	0.14
LAOD	11 (22.0)	10 (33.3)	0.26
DIS	18 (36.0)	2 (6.7)	0.0034
CE	1 (2.0)	1 (3.3)	1
Rostral-caudal classification			
rostral	12 (24.0)	20 (66.7)	< 0.01
middle	32 (64.0)	8 (26.7)	< 0.01
caudal	6 (12.0)	2 (6.7)	0.7

Age is expressed as mean (standard deviation). NIHSS on admission and mRS at discharge were expressed as median (range). Other items mean number (%).

11. Neurological sign and symptoms

Neurological sign and symptoms in both groups with LMI and MMI have been shown in Table 2.

12. Stroke mechanism and lesion location

The breakdown of stroke mechanism is given in Table 3. In LMI group, PAD accounted for 40%, LAOD for 22% and dissection for 36%. Among 11 patients with LAOD, 8 patients had vertebral artery occlusion, 2 had ipsilateral vertebral artery stenosis and one had PICA stenosis. Among 20 patients with PAD, 7 patients had mild vertebral artery stenosis in affected side. In MMI group, PAD accounted for 56.6%, LAOD for 33.3% and dissection for 6.6%. Among 10 patients with LAOD, 6 patients had ipsilateral vertebral artery occlusion, 3 had vertebral artery stenosis and one had basilar artery stenosis. One patient's condition with hemi-MI was caused by bilateral vertebral artery dissection [17]. The relationships between stroke mechanisms and rostral-caudal location or horizontal extension were displayed in Table 3. There were no significant differences between groups.

Table 2
Neurological symptoms and signs in groups with LMI and MMI. Number (%).

LMI (n = 50)		MMI (n = 30)	
Sensory disturbance	43 (86)	Motor weakness	27 (90)
Horner's sign	35 (70)	Dysarthria	16 (53)
Truncal ataxia	28 (56)	Sensory disturbance	14 (47)
Vertigo/dizziness	28 (56)	Deep sensory disturbance	4 (13)
Dysphagia	26 (52)	Facial palsy	9 (30)
Limb ataxia	23 (46)	Nausea/ vomiting	7 (23)
Dysarthria	23 (46)	Nystagmus	6 (20)
Headache	21 (42)	Tongue paralysis	5 (17)
Nystagmus	17 (34)	Vertigo/ dizziness	5 (17)
Nausea/ vomiting	14 (28)	Limb ataxia	4 (13)
Facial palsy	7 (14)	Headache	4 (13)
Eye movement disorder	6 (12)	Dysphagia	4 (13)
Hiccups	4 (8)	Diplopia	3 (10)
Diplopia	4 (8)	Eye movement disorder	3 (10)
Respiration management by intubation	3 (6)	Respiration management by intubation	1 (3)
Gaze deviation	1 (2)		
Motor weakness	1 (2)		

13. Functional disability

Functional disabilities were expressed by NIHSS on admission, and mRS and dysphagia at discharge and one year after onset. Functional disabilities in different stroke mechanism are given in Table 4. There were significant differences in dysphagia (LAOD versus PAD, $p = 0.028$ and dissection versus PAD, $p = 0.011$) and in the mRS ≥2 and/or dysphagia one year after onset (LAOD versus PAD, $p = 0.015$).

14. Predictors for poor outcome

The results of logistic regression are displayed in Table 5. In LMI group, LAOD versus PAD (OR: 14.9, $p = 0.035$) and dissection (OR: 12.8, $p = 0.029$) persisted significant in multivariate analysis. In MMI group, only LAOD versus PAD was significantly correlated with poor outcome (OR: 13.4, $p = 0.014$).

15. Discussion

The present study demonstrated that PAD was the most prevalent stroke mechanism of MI both in groups with LMI and MMI, accounting for 40% and 56.6%, respectively. The second most prevalent mechanism in LMI group was dissection accounting for 36%, succeeded by LAOD for 22%. In MMI group, LAOD was the second most frequent cause accounting for 33.3%. Patients with PAD showed better functional outcome than those with LAOD and dissection. In both groups, LAOD compared with PAD was independently correlated with poor outcome ($p = 0.035$, $p = 0.014$). In LMI group, dissection compared with PAD showed independent correlation ($p = 0.029$).

Fisher found vertebral artery occlusion for 75% in 16 autopsied patients with LMI [6]. Subsequently, Norrving et al. and Sacco et al. reported that vertebral artery occlusive disease accounted for 72% and 73%, respectively [7,8]. The largest study by Kim et al. in patients with LMI reported LAOD in 50%, arterial dissection in 15% and small vessel infarction in 13% [3]. The latest study by Lee et al. found LAOD in 44.2%, arterial dissection in 22.1% and small vessel infarction in 18.2% [5]. As the era is new, the prevalence of LAOD tends to decrease and that of PAD tends to increase. Similar trend is also seen in patients with MMI [18]. The highest prevalence of PAD in the present study can be explained by the advent of MRI technology using DWI that enables small infarcts sensitively visible.

Outcome studies of patients with MI have only been limited [7–11]. Norrving et al. studied 43 patients and found 5 patients died in acute phase and 2 strokes and 5 transient ischemic attacks occurred during 33 months [7]. After MRI era, Graf et al. followed 26 patients with LMI for 4 years and observed mRS got better after discharge [10]. Nelles et al. followed 18 consecutive patients with LMI and found remarkable improvement during inpatient rehabilitation and further improvement even after discharge [11]. All patients were discharged home and 85% were totally independent after a mean time of 1 year. The percentage of good outcome after one year in the present study was 80%, which is in line with Nelles's study [11]. As recent two studies suggested, we also observed functional improvement in patients with LMI continued after discharge. Especially in patients with PAD, significant neurological sequela represented by the mRS ≥ 2 and/or dysphagia at discharge mostly resolved one year after onset (Table 3).

In both groups, LAOD compared with PAD was significantly correlated with poor outcome. Lee et al. performed perfusion-weighted MRI in patients with LMI and found patients with LAOD and dissection showed delayed perfusion (60% and 75%, respectively), whereas all patients with PAD showed normal findings [5]. Continuous hypo-perfusion status for a long period may lead to more extensive ischemic insult. Patients with LAOD as well as dissection may be predisposed to chronic hypo-perfusion over a long period of time.

Moreover, the rostral lesion compared to the middle lesion location showed nearly significantly correlated with poor outcome ($p = 0.059$).

Table 3
Vertical location and horizontal extension of infarcts in different stroke mechanism. Number (%).

	LMI (n = 50)				MMI (n = 30)			
Stroke mechanism	PBD 20 (40.0)	LAOD 11 (22.0)	DIS 18 (36.0)	CE 1 (2.0)	PAD 17 (56.6)	LAOD 10 (33.3)	DIS 2 (6.6)	CE 1 (3.3)
Vertical classification								
Rostral	5 (25.0)	4 (36.3)	3 (16.6)	0	13 (76.4)	6 (60.0)	1 (50.0)	0
Middle	15 (70.0)	4 (36.3)	13 (72.2)	1 (100)	4 (40.0)	4 (40.0)	0	0
Caudal	1 (5.0)	3 (27.2)	2 (11.1)	0	0	0	1 (50.0)	1 (100)
Horizontal grade								
Horizontal grade 1	11 (55.0)	3 (27.2)	7 (38.8)	1 (100)	11 (64.7)	2 (20.0)	0	1 (100)
Horizontal grade 2	5 (25.0)	7 (63.6)	4 (22.2)	0	5 (29.4)	4 (40.0)	2 (100)	0
Horizontal grade 3	4 (20.0)	1 (9.09)	7 (38.8)	0	1 (5.8)	4 (40.0)	0	0

Table 4
Functional disability on admission, at discharge and one year after onset in different stroke mechanisms. NIHSS and mRS are expressed as median and range.

	LMI (n = 50)				p value	MMI (n = 30)				p value
Stroke mechanism, n (%)	PAD 20 (40.0)	LAOD 11 (22.0)	DIS 18 (36.0)	CE 1 (2.0)		PAD 17 (56.6)	LAOD 10 (33.3)	DIS 2 (6.6)	CE 1 (3.3)	
Functional severity during admission and 1 year after onset										
NIHSS on admission	2 (0–5)	2 (1–8)	3 (0–6)	1	0.33	2 (0–14)	5 (1–7)	3.5 (3–4)	2	0.25
Progression, n (%)	2 (10.0)	5 (45.5)	8 (44.4)	0	0.064	10 (58.8)	4 (40.0)	0	0	0.28
mRS at discharge	1 (0–4)	2 (0–3)	1 (0–4)	1	0.24	1 (0–3)	2.5 (0–5)	1 (1–1)	1	0.62
mRS ≥ 2 at discharge	8 (40.0)	7 (63.6)	8 (44.4)	0	0.57	5 (29.4)	6 (60.0)	0	0	0.21
mRS ≥ 2at 1 year after onset	1 (5.0)	2 (18.1)	3 (16.6)	0	0.76	2 (11.7)	5 (50.0)	0	0	0.11
Dysphagia at discharge	4 (22.2)	5 (71.4)	6 (33.3)	0	0.21	0	2 (20.0)	0	1 (100)	0.0067
Dysphagia at 1 year after onset	0	2 (20.0)	5 (27.7)	0	0.0301	0	1 (10.0)	0	1 (100)	0.0014
mRS ≥ 2 and/or dysphagia at discharge	9 (45.0)	8 (72.3)	9 (50.0)	0	0.33	5 (29.4)	6 (60.0)	0	1 (100)	0.15
mRS ≥ 2 and/or dysphagia at 1 year after onset	1 (5.0)	4 (36.3)	5 (27.7)	0	0.014	1 (5.8)	4 (40.0)	0	1 (100)	0.027

Table 5
Odds ratio and 95% confidential interval of each predictors for poor outcome.

	Univariate analysis			Multivariate analysis		P value
LMI group						
Age > 60vs ≤60	3.64	0.76–26.78	0.107	2.41	0.26–27.85	0.43
Male vs Female	1.03	0.24–4.91	0.96	0.55	0.065–4.21	0.56
Hypertension	1.34	0.14–29.46	0.804			
Diabetes mellitus	0.209	0.0104–1.39	0.11			
Dyslipidemia	0.61	0.13–2.58	0.508			
Smoking	1.35	0.25–6.92	0.708			
Alcohol	0.93	0.14–5.53	0.93			
PAD	1					
LAOD	12.7	1.40–295.7	0.022	14.9	1.18–489.6	0.035
Dissection	13.3	1.58–304.7	0.015	12.8	1.26–336.2	0.029
Horizontal grade 1	1					
Horizontal grade 2	3.11	0.56–25.70	0.22			
Horizontal grade 3	4.13	0.62–35.64	0.13			
Middle	1					
Caudal	2.66	0.108–35.74	0.32	1.44	0.047–25.71	0.80
Rostral	7.89	1.33–65.59	0.022	7.21	0.91–79.2	0.059
Two segments	11.2	0.91–167.6	0.058	9.77	0.61–180.5	0.103
MMI group						
Age ≥ 70 vs < 70	2.17	0.34–18.35	0.41			
Male vs Female	0.63	0.099–4.37	0.63			
PAD	1					
LAOD	13.4	1.62–303.59	0.014			
Horizontal grade 1	1					
Horizontal grade 2	1.09	0.16–6.94	0.92			
Horizontal grade 3	1.7	0.064–25.94	0.709			
Rostral	1					
Middle	1.65	0.21–11.94	0.61			
Caudal	4.68	0.15–149.25	0.33			

Dysphagia was pointed to be related to the nucleus ambiguus that located in the rostral medulla [19]. As we defined persistent dysphagia as significant sequelae, rostral lesion location may be associated with poor outcome.

Limitations of the present study should be addressed. First, the definition of poor outcome as mRS ≥2 and/or dysphagia may be arbitrary. However, dysphagia is also serious sequelae that afflict patients. Second, as we applied a simplified method instead of a videofluorographic test, diagnosis of dysphagia was insufficient. Third, some information of outcome was obtained from attending doctors or transferred hospital.

The present study showed PAD is the most predominant cause of medullary infarction and patients with PAD tended to showed favorable functional outcome than those with LAOD or dissection. Stroke mechanism of LAOD was independently correlated with poor functional outcome one year after onset in both groups of LMI and MMI. In patients with LMI, dissection and rostral lesion location compared with middle location was also correlated with poor outcome. Underlying vascular lesions predicted long term outcome in patients with MI.

Conflict of interest

We have no conflict of interest.

Author contributions

Naoki Makita, acquisition of data.
Yasumasa Yamamoto, study design.
Yoshinari Nagakan, statistical analysis.
Yasuhiro Tomii, reference search.
Toshiki Mizuno, supervision.

Author disclosures

All authors – Reports no disclosures.

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