Right-to-left shunt and lacunar stroke in patients without hypertension and diabetes

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Abstract—We analyzed the frequency of cardiac embolic sources in 62 patients with acute lacunar stroke vs 50 controls. In post hoc analysis, 11 patients with lacunar stroke having neither hypertension nor diabetes mellitus (non-HDM group) had a higher frequency of right-to-left shunt (RLS) (82%) than patients with risk factors for lacunar stroke. RLS was also independently associated with the non-HDM group. Thus, RLS may contribute to lacunar stroke in patients without risk factors for lacunar stroke.

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Pathologic evidence suggests that lacunar stroke is caused by diseases of small perforating arteries, such as lipohyalinosis and microatheroma.¹ Hypertension and diabetes mellitus are the traditional risk factors for lacunar stroke and play an important role in its pathogenesis. However, an embolic mechanism is proposed as causing lacunar stroke,¹ and several studies provide supporting evidence.^{2,3} Conversely, right-to-left shunt (RLS), such as patent foramen ovale (PFO), is associated with cryptogenic stroke.⁴ In this study, we sought to identify embolic sources, including RLS, in lacunar stroke patients using transesophageal echocardiography (TEE) and to compare the clinical characteristics and potential embolic origins among patients with and without risk factors for lacunar stroke.

Methods. From September 2004 to November 2005, we prospectively enrolled consecutive patients with first-ever lacunar ischemic strokes within 48 hours of onset. All patients were admitted to the Kawasaki Medical School Hospital, a tertiary referral center. Immediately on admission, patients had MRI, including diffusion-weighted images, fluid-attenuated inversion recovery images, and MR angiography. TEE was done within 7 days of admission. The patients were divided into two groups: (1) the non-HDM group (patients having neither hypertension nor diabetes mellitus), and (2) the HDM group (patients having hypertension or diabetes, or both). We also recruited control subjects who were age matched and gender matched to the non-HDM group patients between September 2004 and February 2006. The embolic origins were defined according to the Trial of Org 10172 in Acute Stroke Treatment criteria of high- and medium-risk sources, and frequencies of them were compared among groups. The clinical characteristics of the non-HDM and HDM groups were also compared. Patients and their families gave their written informed consent to participate in the study, which was conducted in accordance with the Declaration of Helsinki.

Definitions of lacunar stroke. We defined lacunar stroke as an acute event that lasted >24 hours, that included focal neurologic deficits congruent with the classic lacunar syndromes, and that showed focal hyperintensity of ≤ 15 mm on MRI. Patients with brainstem lacunar infarction were excluded.⁵ Patients were also excluded if they had an ipsilateral arterial stenosis of >50% on MR angiography or carotid duplex ultrasonography.

Risk factors. We assessed the vascular risk factors as follows: (1) hypertension was defined as a history of using antihypertensive agents, systolic blood pressure ≥ 140 mm Hg, or diastolic blood pressure ≥ 90 mm Hg 14 days after stroke onset; (2) diabetes mellitus was defined as the use of oral hypoglycemic agents or insulin, or glycosylated hemoglobin $>6.4\%$; (3) hyperlipidemia was defined as the use of antihyperlipidemic agents or a serum cholesterol level >240 mg/dL; (4) current smoking; and (5) ischemic heart disease was defined as a history of ischemic heart disease.

TEE study. TEE was done using an HDI 5000 (Philips Medical Systems, Bothell, WA) with a 4- to 7-MHz wideband multipane probe. During the study, patients were awake; lidocaine spray, but no premedication, was used. RLS was assessed by giving agitated saline injection and having patients do the Valsalva maneuver (VM); the numbers of microbubbles with and without contrast agents were compared. The number of microbubbles transiting from the right atrium to the left atrium was also counted. On the basis of the maximum number of microbubbles in the left atrium, patients were subdivided into two groups: large RLS (≥ 20 microbubbles) and small RLS (<20 microbubbles).⁶ PFO was diagnosed when microbubbles were visualized in the left atrium within three cardiac cycles after the VM. The examinations were recorded on super VHS videotapes and reviewed by three experienced sonographers who were blinded to the clinical data.

To detect other potential embolic sources, all patients had 24-hour EKG monitoring and transthoracic echocardiography. We also did duplex ultrasound scanning in all patients to identify carotid plaques, which were diagnosed when the thickness of the intima-media complex was >1.5 mm, and in patients with RLS to identify deep venous thrombosis (DVT). A worsening of the neurologic manifestations was defined as an increase of at least one point in the NIH Stroke Scale score for motor function. The size and location of the infarcts, and the white-matter abnormalities

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Table 1 Frequency of potential embolic origins in non-HDM and HDM group patients and controls

	Non-HDM group, n = 11	HDM group, n = 51	Control group, n = 50	p Value for comparison		
				Non-HDM vs HDM	Non-HDM vs control	HDM vs control
RLS, no. (%)	9 (82)	21 (41)	16 (32)	0.035*	0.007*	0.339
Patent foramen ovale	8 (73)	18 (35)	16 (32)	0.052	0.031*	0.726
Atrial septal defect	1 (9)	3 (6)	0 (0)	0.777	0.402	0.248
Number of microbubbles						
Large RLS (≥ 20)	2 (18)	4 (8)	2 (4)	0.624	0.295	0.692
Small RLS (< 20)	7 (64)	17 (33)	14 (28)	0.126	0.057	0.561
Other embolic sources, no. (%)						
Atrial septal aneurysm	2 (18)	4 (8)	8 (16)	0.624	0.785	0.337
Intracardiac thrombus	0 (0)	2 (4)	0 (0)	0.785	—	0.484
Mitral valve prolapse	0 (0)	1 (2)	0 (0)	0.395	—	0.992
Atrial fibrillation	0 (0)	2 (4)	3 (6)	0.785	0.950	0.981

Chi-square test was used for comparison.

* Significant at the $p < 0.05$ level; all other comparisons were not significantly different.

HDM = hypertension and/or diabetes; RLS = right-to-left shunt.

seen on MRI, were also evaluated.⁷ Plasma D-dimer levels were measured in all patients.

Statistical analysis. Group differences were analyzed using the χ^2 test and the Mann-Whitney test. Multiple logistic regression analysis was used to determine factors associated with the non-HDM group. All analyses were performed using the SPSS 11.0 software package for Windows.

Results. During the study period, 267 patients with acute ischemic strokes were admitted. Of the 126 patients with lacunar syndromes, 24 had large-vessel or multiple infarctions on MRI, 37 had infratentorial infarctions, and 3 declined to participate in the study. The remaining 62 patients were enrolled in this study; of these, 34 (55%) had embolic origins. The non-HDM group had 11 (18%) patients, and the HDM group had 51 patients (82%). The control group had 50 subjects. Table 1 lists the frequency of embolic sources among three groups. RLS was identified in 30 patients (48%) with lacunar stroke; RLS was more frequent in the non-HDM group than in the HDM group ($p = 0.035$) and controls ($p = 0.007$) in post hoc analysis. No significant differences in the number of microbubbles were seen among the groups.

Table 2 shows the clinical characteristics of the non-HDM and the HDM groups. DVT was more common in the non-HDM group than in the HDM group ($p = 0.033$). Plasma D-dimer levels were also higher in the non-HDM group ($p = 0.007$).

On multiple logistic regression analysis, the eight variables with p values < 0.3 on univariate analysis were studied. After adjustment, the only independent predictor associated with the non-HDM group was the frequency of RLS (OR, 7.43; 95% CI, 1.09 to 50.81; $p = 0.041$) (table 3).

Discussion. In this study, patients with lacunar stroke had a high frequency of potential embolic sources. A previous study speculated that embolic mechanisms might be present in patients with lacu-

nar stroke,¹ and evidence of the relationship between lacunar strokes and embolic mechanisms has been reported.^{2,3}

PFO is found in about 30% of the general population. Particularly in young adults, PFO is associated with cryptogenic strokes; the frequency of PFO in such patients is as high as 54%.⁴ In lacunar stroke patients, the frequency of atrial septal aneurysm, but not PFO, is higher than in patients with other causes of stroke.⁸ In our study, 48% of lacunar stroke patients had RLS; the percentage of RLS was higher in the non-HDM group than in controls. Moreover, RLS was strongly associated with the non-HDM group. Thus, lacunar stroke patients with neither hypertension nor diabetes mellitus should be investigated for RLS. Furthermore, hypertrophic changes in the left ventricle may prevent PFO by increasing left atrial pressure.⁹ Therefore, PFO may be more likely in patients without risk factors for lacunar stroke than in patients with risk factors. However, the number of microbubbles was not significantly increased in the non-HDM group. Therefore, anatomic and pathophysiological research needs to be done to explain these findings.⁶

DVT and elevated plasma D-dimer levels were more frequent in the non-HDM group. The patients with DVT and cardioembolic strokes tended to have high levels of plasma D-dimer. However, in lacunar stroke patients, the plasma D-dimer levels may not increase because their thrombi are too small to produce a detectable plasma D-dimer elevation.¹⁰

Our study has some limitations. First, our findings must be considered preliminary because the number of patients in the non-HDM group was

Table 2 Baseline characteristics of the non-HDM and HDM group patients

	All, <i>n</i> = 62	Non-HDM group, <i>n</i> = 11 (18%)	HDM group, <i>n</i> = 51 (82%)	<i>p</i> Value
Age, y†	66 ± 11	67 ± 14	65 ± 10	0.733
Female gender, <i>n</i> (%)	25 (40)	6 (55)	19 (37)	0.289
Family history, <i>n</i> (%)	19 (31)	5 (45)	14 (27)	0.240
Risk factors, <i>n</i> (%)				
Hypertension	43 (69)	0 (0)	43 (84)	
Diabetes mellitus	16 (26)	0 (0)	16 (31)	
Hyperlipidemia	25 (40)	3 (27)	22 (43)	0.526
Current smoking	23 (37)	2 (18)	21 (41)	0.277
Ischemic heart disease	4 (6)	0 (0)	4 (8)	0.777
Symptoms/signs				
NIHSS score on admission†	2.5 ± 1.5	1.5 ± 1.3	2.7 ± 1.6	0.032*
Neurological deterioration, <i>n</i> (%)	31 (50)	3 (27)	26 (51)	0.273
Lacunar syndromes, <i>n</i> (%)				0.845
Pure motor hemiparesis	28 (45)	6 (55)	22 (43)	
Pure sensory stroke	5 (8)	1 (9)	4 (8)	
Dysarthria and clumsy-hand syndrome	4 (6)	1 (9)	3 (6)	
Ataxic hemiparesis	4 (6)	1 (9)	3 (6)	
Sensory motor stroke	21 (34)	2 (18)	19 (37)	
MRI findings				
Size of infarcts, mm†	10.7 ± 2.9	10.5 ± 3	10.7 ± 3.0	0.854
Locations, <i>n</i> (%)				0.746
Deep white matter	37 (60)	5 (45)	32 (63)	
Internal capsule	21 (34)	5 (45)	16 (31)	
Basal ganglia	3 (5)	1 (9)	2 (4)	
Thalamus	1 (2)	0 (0)	1 (2)	
White-matter abnormality, <i>n</i> (%)				0.237
None	17 (27)	3 (27)	14 (27)	
Punctate hyperintensity	10 (16)	4 (36)	6 (12)	
Early confluent hyperintensity	31 (50)	4 (36)	27 (53)	
Confluent hyperintensity	4 (6)	0 (0)	4 (8)	
Duplex ultrasonography, <i>n</i> (%)				
Carotid plaques, <i>n</i> (IMC ≥1.5 mm)	28 (45)	3 (27)	25 (49)	0.327
DVT, <i>n</i> (%)	5/30 (17)	4/9 (44)	1/21 (5)	0.033*
Plasma D-dimer levels, μg/mL†	1.1 ± 1.4	1.7 ± 1.4	1.0 ± 1.4	0.007*

Chi-square test and the Mann–Whitney test were used.

* Significant at the *p* < 0.05 level; all other comparisons were not significantly different.

† Mean ± SD.

HDM = hypertension and/or diabetes; DVT = deep venous thrombosis; IMC = intima–media complex; NIHSS = NIH Stroke Scale.

Table 3 Multiple logistic regression analysis of variables predicting the non-HDM group

	Odds ratio	95% CI	<i>p</i> Value
Female gender	1.68	0.24–11.76	0.600
Family history	1.39	0.21–8.56	0.759
Current smoking	0.49	0.06–4.26	0.515
NIHSS score on admission	0.76	0.41–1.42	0.396
Neurological deterioration	0.27	0.04–1.67	0.159
Right-to-left shunt	7.43	1.09–50.81	0.041*
Plasma D-dimer levels	1.50	0.87–2.59	0.147
White-matter abnormality	0.80	0.30–2.08	0.641

* Significant at the *p* < 0.05 level; all other variables were not significantly different.

HDM = hypertension and/or diabetes; NIHSS = NIH Stroke Scale.

small. Thus, given the results of this study, a larger study is warranted. Second, because only patients with RLS were examined for the presence of DVT, one cannot compare the frequency of DVT between the non-HDM and HDM groups.

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Tularemia with brain abscesses

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After eating wild rabbits, a 51-year-old woman presented with fever, headache, blurry vision, and declined consciousness. Uveitis and pulmonary infiltrates were present, CSF examination revealed leukocytes of 450/mm³, and cultures grew *Francisella tularensis*. Streptomycin and doxycycline were started. CT was normal, but cranial MRI showed three lesions with restricted diffusion (figure). Outcome at one year was poor.

The diagnosis of tularemia rests on specific inquiry into exposure with the bacillus, use of specific culture media, and serologic testing.¹ Due to its extreme virulence and ease of aerosol dissemination, there has been renewed interest in tularemia as a potential bioweapon.²

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Figure. Fluid-attenuated inversion recovery weighted MRI (axial view [A and C]) showing meningeal enhancement, enlarged ventricles, and hyperintense lesions in right temporal lobe and right posterior occipital lobe; T1-weighted images (B and D) after gadolinium showed ring-enhancing lesions.

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