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MRI findings of small subcortical "lacunar-like" infarction resulting from large vessel disease

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Abstract Small subcortical infarctions resulting from large-vessel disease are often observed. It is important to distinguish these from pure lacunar infarction resulting from small-vessel disease because the investigations and examinations differ. We investigated the differences on brain magnetic resonance imaging (MRI) between small subcortical "lacunar-like" infarcts resulting from large-vessel disease and pure lacunar infarcts. Thirteen subjects with small lacunar-like infarcts (size < 2 cm), resulting from large-vessel disease, and 30 subjects with lacunar infarcts (< 2 cm), without large-vessel disease were studied. We measured infarction size using a 1.5-T MRI device and evaluated silent subcortical hyperintensity lesions using the modified Scheltens' score. Large-vessel lesion was confirmed by conventional angiography, duplex carotid scan, and magnetic resonance angiography. There was no difference in the mean age of the two groups. Cerebrovascular risk factors and atherosclerotic complications were also comparable for the two groups. Progressive stroke was more common in the lacunar-like infarction group than in the lacunar infarction group ($P = 0.004$). Scores for periventricular hyperintensity, white matter hyperintensity, basal ganglia hyperintensity, and total subcortical hyperintensity scores were significantly higher in the lacunar infarction group than in the lacunar-like infarction group. The difference in basal ganglia hyperintensity scores was remarkable ($P = 0.001$). The enlargement of the perivascular space was also significantly greater in the lacunar infarction group than in the lacunar-like infarction group. These findings seem to reflect differences in the pathogenesis of infarction between the two groups. Silent subcortical hyperintensity lesions and enlargement of perivascular space are useful for between distinguishing small lacunar-like infarct resulting from large-vessel disease and pure lacunar infarction. This may have significant implications for the management of patients with lacunar-sized infarctions. It suggests that the pathogenesis of lacunar-sized infarction is variable.

Key words Small subcortical infarction · Large-vessel disease · Magnetic resonance imaging · Silent white-matter hyperintensity · Lacunar infarction

Introduction

We have often observed small subcortical infarction resulting from large-vessel disease that is indistinguishable from lacunar infarction in the territory of the lenticulostriate arteries. Such small subcortical infarction resulting from large-vessel disease has the same size and symptoms as lacunar infarction. Therefore, it is difficult to distinguish small subcortical infarction from lacunar infarction. We call the small subcortical lesions resulting from large-vessel disease "lacunar-like" infarction. In Japan lacunar infarction is more common than the atherothrombotic type [1], and it is therefore important to distinguish lacunar-like infarction from pure lacunar infarction. Several previous studies have reported investigated the clinical features of subcortical and lacunar infarction [2–11]. Computed tomography and magnetic resonance imaging (MRI) findings in these conditions have also been reported [9, 10, 12, 13]. However, no studies have reported the differences in MRI findings between subcortical lacunar-like infarcts and lacunar infarcts. We noted accompanying silent lesions in the subcortical white matter and basal ganglia, and compared MRI findings in subcortical lacunar-like infarcts resulting from large-vessel disease with those of pure lacunar infarcts.

Subjects and methods

We evaluated 171 consecutive patients admitted to Shimane Medical University Hospital with acute cerebral infarct between 1994 and 1997. These included 53 classified as atherothrombotic infarcts, 74 as lacunar infarcts, 37 as cardioembolic infarcts, and 7 were unclassified. Among the 53 with atherothrombotic infarcts 23 had cortical infarcts, 22 subcortical infarcts, and 8 infarcts at the infratentorial area. As examples of lacunar-like infarction resulting from large-vessel disease, we selected 13 patients with atherothrombotic subcortical infarcts smaller than 2 cm in diameter (7 men, 6 women; mean age 70.0 ± 10.2 years; Fig. 1). We selected 2 cm diameter as the cutoff point because the size of the infarct is generally larger in acute MRI than at autopsy. All of these patients had an atherothrombotic subcortical infarction in the territory of the lenticulostriate arteries, caused by stenosis or occlusion of the middle cerebral or internal carotid artery on the affected side. No patient had consciousness disturbance or cortical symptoms. Patients with a lacunar infarcts without large-vessel disease formed the lacunar infarction group (Fig. 2). A lacunar infarct was defined as one smaller than 2 cm in diameter [2, 3] and believed to be caused by small-vessel disease, localized to the basal ganglia and subcortical white matter. There were 30 patients (23 men, 7 women; mean age 69.4 ± 11.2, n.s. by Mann-Whitney *U* test) in the lacunar infarct group. We excluded patients who had recurrent stroke, cardioembolic infarction, risk factors for cardioembolic infarction, or infarction in the infratentorial area.

Magnetic resonance imaging

Brain MRI was performed using a 1.5-T superconducting unit (Signa Advantage, General Electric; Gyroscan ACS-NT, Philips). We obtained T2-weighted images (TR: 3800–2000 ms, TE: 140–100 ms), T1-weighted images (TR: 400–350 ms, TE: 14–12 ms), and proton density weighted images (TR: 3800–3500 ms, TE: 26–20 ms). Transaxial images of the brain were obtained in 6-mm slices with no gap between slices. Two-dimensional Fourier transformation of the images and 256 × 256 data acquisition matrix were used. We evaluated infarctions in the axial views of the T2-, T1-, and proton density weighted images. The images were stored in a personal computer (Macintosh 7600/120) using an image scanner. We determined the high signal intensity area responsible for neurological symptoms and measured the maximum diameter of the lesion on the T2-weighted image using NIH Image (version 1.56).

We evaluated silent subcortical lesions quantitatively on the T2-weighted images, including periventricular hyperintensity (PVH), white matter hyperintensity (WMH), basal ganglia hyperintensity (BGH), and infratentorial hyperintensity (ITH) lesions using the modified method reported by Scheltens et al. (Table 1) [14]. The total score was calculated by adding these scores. It was difficult to

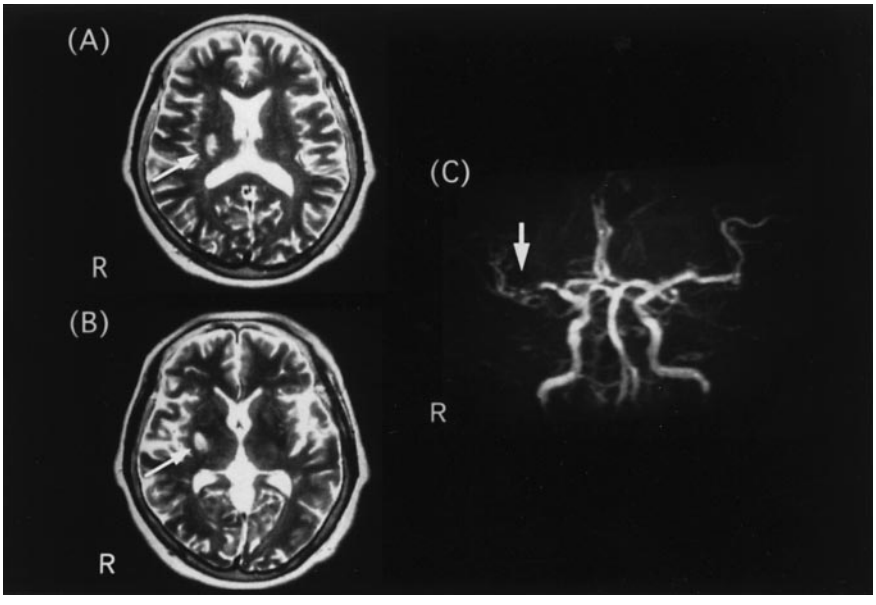

Fig. 1 A–C Case 8. Typical case of small lacunar-like infarction resulting from MCA stenosis. **A**, **B** Hyperintensity lesion from right basal ganglia to corona radiata (*arrow*) was observed on T2-weighted image. There were few accompanying subcortical lesions. **C** Stenosis of the right MCA at M1 portion was observed on magnetic resonance angiography. It showed partial disappearance of flow signal (*arrow*)

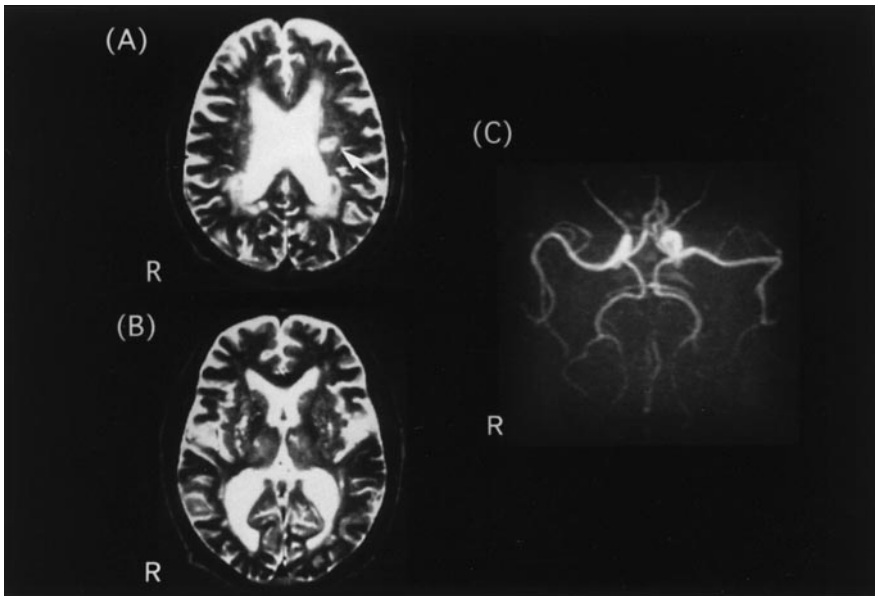

Fig. 2 A–C The case of pure lacunar infarction. **A**, **B** Lacunar infarction at left corona radiata (*arrow*) was observed on T2-weighted image. It showed many accompanying silent subcortical lesions such as PVH and spotty hyperintensity lesions in basal ganglia and deep white matter. **C** Magnetic resonance angiography was normal

Table 1 Rating of high-signal lesions on brain MRI (modified from Scheltens et al. [14])

Periventricular hyperintensity (0–30, bilateral)[a]
Frontal: 0–5
Occipital: 0– 5
Lateral ventricles: 0–5
White-matter hyperintensity (0–48, bilateral)[b]
Frontal: 0–6
Parietal: 0–6
Occipital: 0–6
Temporal: 0–6
Basal ganglia hyperintensity (0–60, bilateral)[b]
Caudate nucleus: 0–6
Putamen: 0–6
Globus pallidum: 0–6
Thalamus: 0–6
Internal capsule: 0–6
Infratentorial hyperintensity (0–24)[b]
Cerebellum: 0–6
Middle brain: 0–6
Pons: 0–6
Medulla oblongata: 0–6

[a] 0, absent; 1, ≤ 5 mm; 2, > 5 mm and ≤ 10 mm; 3, > 10 mm and ≤ 15 mm; 4, > 15 mm and ≤ 20 mm; 5, > 20 mm

[b] 0, absent; 1, ≤ 3 mm, $n < 5$; 2, ≤ 3 mm, $n > 6$; 3, > 3 mm and ≤ 10 mm, $n < 5$; 4, > 3 mm and ≤ 10 mm, $n > 6$; 5, > 10 mm, $n > 1$; 6, confluent lesion

distinguish enlargement of the perivascular space from lacunar infarction using this scoring system, and we therefore devised our own method for scoring enlargement of perivascular space. We defined enlargement of the perivascular space as maximum diameter smaller than 3 mm, spotty high signal intensity on the T2-weighted image, and the same intensity as cerebrospinal fluid on the proton density weighted image [15]. Enlargement of the perivascular space was classified into four grades based on the appearance at the level of the basal ganglia: grade 0, no lesions; grade 1, one to five lesions; grade 2, six to ten lesions; grade 3, more than ten lesions.

Three observers evaluated the MRI findings. One observer evaluated all the images, and the other two evaluated 25 images independently to investigate the reliability of the interpretation of the radiological findings. These observers were unaware of the purpose of this study and had no clinical information on the patients.

Vascular lesions

Lesions of the extracranial carotid artery were evaluated with conventional angiography and/or carotid duplex sonography using a 7.5-MHz probe (Ultramark 9, ATL; SSD-2000, Aloka). Eight subjects in the large-vessel group underwent angiography. We defined mild stenosis as less than 30% stenosis at the origin of the internal carotid artery, moderate as 30–75% stenosis, and severe as more than 75% stenosis. Using the example of the European Carotid Surgery Trial, we determined the ratio of the diameter of the internal lumen to the whole vessel on angiography and carotid duplex sonography [16].

The intracranial arteries were evaluated by 3D-time-of-flight MR angiography. MR angiography was performed to all cases. We defined mild stenosis as partial narrowing of the caliber of the artery, severe stenosis as partial disappearance of the flow signal and occlusion as complete interruption of the flow signal [17, 18].

Clinical findings

The presence of the following risk factors for cerebrovascular disease was assessed: age, sex, history of transient ischemic attack, hypertension, diabetes mellitus, hypercholesterolemia (history or total cholesterol ≥ 220 mg/dl), current smoking and alcohol consumption. On admission, all patients received a physical examination and complete neurological examination. Laboratory analysis included a whole blood cell count and blood coagulation and biochemistry studies. A history of complications of atherosclerosis, such as arteriosclerosis obliterans and coronary heart disease, was also assessed on admission. The onset of the stroke was divided into two types: acute and progressive stroke. Case with progression of neurological deficit over 24 h were defined as progressive stroke.

Table 2 Clinical and radiological findings of the lacunar-like infarction group (*ICA* internal carotid artery, *MCA* middle cerebral artery, *HP* hemiparesis, *HS* hemisensory deficit, *CR* corona radiata, *IC* internal capsule, *CN* caudate nucleus, *CS* centrum semiovale; angiography or carotid sonography: *occl* occlusion, *S+* mild stenosis, *S++* moderate stenosis, *S+++* severe stenosis; magnetic resonance angiography: *occl* occlusion, *S++* stenosis, *S+++* severe stenosis; * confirmed by angiography)

Patient no.	Sex	Age (years)	Side	Onset	Symptoms	Site of lesion	Lesion size (mm)	ICA	MCA
1	M	80	L	Acute	HP	CR	1.90	Normal	S++
2	M	76	L	Progressive	HP, HS	IC	0.73	Normal	S++
3	M	56	R	Acute	HP	CN, CR	1.60	S++*	Occl*
4	F	84	R	Progressive	HP, HS	IC, CR	1.09	Normal	S++
5	M	58	R	Progressive	HP	CR	1.60	S+++*	Normal
6	M	70	R	Progressive	HS	IC	1.33	Occl*	Normal
7	F	68	R	Acute	HP, HS	CR, CS	1.16	S+++*	Normal
8	F	70	R	Progressive	HP, HS	IC, CR	1.56	Normal	S+++*
9	F	57	R	Acute	HP	Putamen, CR	1.82	Normal	S+++*
10	M	82	R	Acute	HP	Putamen, CR	0.94	Normal	S+++
11	M	78	R	Progressive	HP, HS	CR, CS	1.75	Normal	S+++
12	F	58	R	Progressive	HP, HS	CR, CS	1.78	Normal	S+++
13	F	62	L	Progressive	HP, HS	Putamen, CR, CS	1.33	Normal	S++

Table 3 requency of cerebrovascular risk factors and differences in clinical features in two subgroups of the lacunar-like infarction group and lacunar infarction group

Risk factor or clinical feature	Lacunarlike infarction group (n = 13)		Lacunar infarction group (n = 30		
	n	%	*n*	%	*P**
Hypertension	8	61.5	20	66.6	0.742
Diabetes mellitus	1	7.7	9	30.0	0.236
Hypercholesterolemia	3	23.1	7	23.3	> 0.999
Coronary artery disease	1	7.7	2	6.7	> 0.999
Current smoking	6	46.1	13	43.3	> 0.999
Alcohol consumption	3	23.1	17	56.7	0.054
Sex: males	7	53.8	23	76.7	0.163
Transient ischemic attack	1	7.7	4	13.3	> 0.999
Onset: acute/progressive	5/8	17.2/82.8	24/4	85.7/14.3	0.004
Hemiparesis	10	76.9	23	76.7	> 0.999
Hemisensory deficits	7	53.8	14	46.7	> 0.999

*χ^2 test

Table 4 Differences in MRI findings in two subgroups of the lacunar-like infarction group and lacunar infarction group

	Lacunar-like infarction group (n = 13)	Lacunar infarction group (n = 30)	*P*
Score of silent lesions[a]			
PVH score	4.7 ± 1.4	9.6 ± 1.4	0.035
WMH score	9.2 ± 2.2	15.8 ± 1.8	0.038
BGH score	8.1 ± 1.9	18.4 ± 1.8	0.001
Total score	22.3 ± 5.0	45.8 ± 3.9	0.001
Grade of dilatation of perivascular space[b]			0.001
0°	6	1	
1°	6	9	
2°	1	13	
3°	0	7	

[a] Mann-Whitney *U* test
[b] χ^2 test

Statistical analysis

The nominal variables (risk factors for cerebrovascular disease, atherosclerotic complications, clinical symptoms, onset of stroke, and grades of enlargement of the perivascular space) were analyzed by the χ^2 test. Age and laboratory examinations were analyzed by Student's *t* test. PVH, WMH, BGH, ITH, and total scores were studied using the Mann-Whitney *U* test. The interobserver reliability in scoring silent lesions was assessed using Pearson's correlation coefficient. These statistical analyses were performed by statistical software package StatView version 4.5.

Results

The interobserver reliability was good for all scores in evaluating silent lesions (r = 0.763–0.895, average 0.845). The lesion sites on MRI and the angiographic findings for the lacunar-like infarction group are presented in Table 2. Middle cerebral artery stenosis was more common than extracranial internal carotid artery stenosis. We found two

cases of contralateral stenosis of large vessel, one of middle cerebral artery stenosis, and one of internal carotid artery stenosis. The frequency of cerebrovascular risk factors and clinical symptoms in the two groups is presented in Table 3. There was no difference in age between the two groups ($P = 0.869$). The two groups had comparable cerebrovascular risk factors. Progressive stroke was more frequent in the lacunar-like infarction group (82.8%) than in the lacunar infarction group (14.3%; $P = 0.004$). Otherwise, the clinical symptoms in the two groups did not differ.

The Scheltens' score for PVH, WMH, BGH, and the total score for silent subcortical lesions were significantly higher in the lacunar infarction group than in the lacunar-like infarction group. The difference in BGH scores was remarkable ($P = 0.001$; Table 4). The grade of enlargement of the perivascular space was significantly higher in the lacunar infarct group than in the lacunar-like infarction group (Table 4). Only one patient in the lacunar-like infarct group (7.7%) had more than grade 2 enlargement of the perivascular space but 20 patients in the lacunar infarction group (66.7%).

Discussion

Lacunar infarction is typically a small subcortical infarction. Fisher [2] and Fisher and Curry [3] report that lacunar infarction results from arteriosclerosis of small penetrating arteries caused by lipohyalinosis and angionecrosis (see also [19]). Important risk factors for lacunar infarction include hypertension and aging [2, 3, 8, 19–21]. The size of lacunar infarction ranges from very small (3–4 mm) to large (1.5–2.0 cm) and presents with specific symptoms referred to as the lacunar syndrome [2, 3]. Lacunar infarcts tends to be evaluated only by size, not by pathogenesis. Millikan and Futrell [22] have described the shortcomings of the lacunar hypothesis and the variable pathogenesis of lacunar infarction [22]. Waterstone et al. [11] reported small deep subcortical infarctions associated with occlusive internal carotid artery disease; they suggested that most small deep infarctions result from small-vessel disease, but that some of these infarctions are due to a hemodynamic mechanism [11]. We have also observed small lacunar-like subcortical infarcts resulting from large-vessel disease. Based on lesion size on brain MRI and computed tomography only, these lacunar-like infarcts are indistinguishable from pure lacunar infarctions resulting from small-vessel disease.

We attempted to clarify the differences in MRI findings and clinical findings between subcortical lacunar-like infarcts resulting from large-vessel disease and pure lacunar infarcts. We noted accompanying silent lesions in the subcortical white matter and basal ganglia because we believe that these MRI findings reflect differences in the pathogenesis of infarction between the lacunar-like and lacunar infarct groups. The scores for hyperintensity lesions were significantly higher in the lacunar infarction group than in the lacunar-like infarction group. The grade of enlargement of the perivascular space was also greater in the lacunar infarction group. Significant PVH and white matter high-intensity lesions on T2-weighted MRI were also thought to be related to ischemia resulting from arteriosclerosis of small penetrating arteries [23–27]. The enlargement of the perivascular space is also closely related to arteriosclerosis of small penetrating arteries, aging, and hypertension [28]. We have previously reported that silent brain lesions on MRI are strongly related to hypertensive small-vessel vasculopathy [29]. Therefore our findings suggest that silent subcortical lesions are associated with arteriosclerosis of small arteries and reflect differences in the pathogenesis of subcortical infarction. Japanese in Japan have small intracerebral artery disease more commonly than those of Japanese ancestry in Hawaii [30, 31]. Inzitari et al. [32] reported that intracranial arterial lesions are more frequent than extracranial arterial lesions in Oriental populations. It is possible that differences in frequency of intracranial atherosclerosis and silent white matter high-intensity lesions are related to racial differences in cerebrovascular disease. The frequency of hypertension was slightly but not significantly higher in the lacunar infarction group than in the large-vessel group in our series. Millikan and Futrell [22] also reported that hypertension is not a specific risk factor for lacunar infarction. We consider hypertension also to be a significant risk factor for large-vessel disease.

Waterstone et al. [11] have also reported the patients with small deep infarcts associated with occlusive internal carotid artery disease often show cortical symptoms. We examined the differences between lacunar-like infarcts resulting from large-vessel disease and lacunar infarcts in this study. Although there were three patients with cortical symptoms associated with small deep infarction, we excluded these in this study.

Our findings clearly show that small lacunar-like infarctions can result from large-vessel disease. It is therefore necessary to be more careful in evaluating and managing the vascular lesions of patients with small lacunar-like infarctions with few accompanying silent subcortical lesions. If we can predict large-vessel lesions in patients with a small lacunar-like subcortical infarction, we could begin antithrombotic therapy before the symptoms progress. It is possible to determine which additional examinations to employ efficiently, for example, magnetic resonance angiography, carotid ultrasonography, and cerebral angiography. We studied MRI findings, but our results may also be applicable to computed tomography.

Conclusion

Associated silent subcortical hyperintensity lesions on brain MRI were significantly more frequent in the lacunar in-

farction group than in the lacunar-like infarction group. This finding seems to reflect differences in the pathogenesis of small lacunar-like infarcts resulting from large-vessel disease and lacunar infarcts resulting from small-vessel disease. Silent subcortical hyperintensity lesions and enlargement of perivascular space are useful for distinguishing between small lacunar-like infraction resulting from large-vessel disease and pure lacunar infarction. This may have significant implications for the management of patients with lacunar-sized infarctions. It suggests that the pathogenesis of lacunar-sized infarction is variable.

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