Intracranial Artery Atherosclerosis and Lumen Dilation in Cerebral Small-Vessel Diseases: A High-resolution MRI Study

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Keywords

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SUMMARY

Background and Aims: Using high-resolution magnetic resonance imaging (HR-MRI), we aimed to investigate the abnormalities of intracranial artery in relation to cerebral small-vessel diseases (SVD)-related ischemic stroke and white matter lesions (WMLs). **Methods:** Routine cranial MRI and HR-MRI were performed on consecutive patients with a SVD-related acute deep brain infarct (DBI) in the territory of middle cerebral artery (MCA), patients with SVD-related WMLs, and age-matched controls. The presence and distribution of MCA plaque and the area of MCA lumen and wall were comparatively analyzed among the groups. **Results:** A total of 2340 image slices of 260 vessels in 130 subjects (57 with an acute DBI, 28 with WMLs, and 45 control subjects) were analyzed. In the patients with a DBI, eccentric plaques were identified in 26 vessels ipsilateral and 24 vessels contralateral to the ischemic lesions. Superior-wall plaques of MCA were observed more frequently ipsilateral than contralateral to the infarcts (69.2% vs. 37.5%, $P = 0.025$). Compared to the controls, larger outer-wall boundary area ($P \leq 0.017$) and wall area ($P < 0.001$) were observed in the patients, while larger lumen was only observed in the WMLs group ($P < 0.001$). **Conclusions:** Middle cerebral artery superior-wall plaques are associated with acute DBIs, while MCA lumen dilation is associated with WMLs.

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Introduction

The upstream vessels of cerebral small vessels are intracranial large arteries, through which blood flow is transported. Although structurally and functionally connected, the pathophysiology of intracranial large artery in relation to cerebral small-vessel diseases (SVD) has been less well investigated. It is known from post-mortem studies that intracranial atherosclerosis is commonly coexistent with SVD [1]. A plaque can occasionally obstruct a penetrating artery and cause a deep brain infarct (DBI) [2]. Widening of the internal and external diameters of intracranial arteries (dolichoectasia) may occur [3]. These autopsy findings, however, are lack of *in vivo* supportive evidence and suffer from the possible bias due to the low mortality of SVD and the methodological inconsistencies [1].

Recently, high-resolution magnetic resonance imaging (HR-MRI) has been developed as a useful tool in evaluating intracranial artery lesions [4–7]. It can provide *in vivo* images and measurements of intracranial artery lumen and wall [4,8]. Several studies have suggested that HR-MRI is valuable in detecting intracranial artery lesions in patients with a lacunar infarct [9,10]. Using HR-MRI, in this study, we aimed to investigate the abnormalities of intracranial large arteries in patients with SVD-related DBIs and

with white matter lesions (WMLs) by comparison with healthy controls.

Materials and methods

Study Population

This was a single-center observational study. From January 2009 to September 2012, consecutive patients were recruited if they (1) aged >40 years old; (2) had a single symptomatic infarct (maximum infarct diameter <20 mm on axial T2-weighted images) in the perforator territory of the middle cerebral artery (MCA) [11], or age-related WMLs (periventricular and/or deep WMLs) with the grading scale 2 or 3 described by Fazekas et al. [12]; and (3) had normal MCA lumen ipsilateral to the infarct lesion on cranial magnetic resonance angiography (MRA). All patients received thorough evaluations including carotid duplex, transcranial Doppler, electrocardiogram, and echocardiogram. Patients were excluded if they (1) had $\geq 50\%$ internal carotid artery stenosis, or MCA stenosis (including <50% stenosis with irregular lumen) ipsilateral to the infarct lesions; (2) had evidence of cardioembolism such as atrial fibrillation and recent myocardial infarction within 1 month; (3) had evidence of congenital SVD such as

Fabry disease and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, or congenital leukodystrophy such as adrenoleukodystrophy and globoid cell leukodystrophy, or WMLs with non-SVD cause such as carbon monoxide poisoning; and (4) had poor image quality due to motion artifact. For comparative analysis, the patients with unspecific complaints (dizziness, occasional headache, and insomnia) and without cerebrovascular diseases or other definitely diagnosed brain diseases were recruited from out clinics as controls. The hospital ethics committee approved this study, and all patients signed a written consent.

Imaging Protocol

Routine cranial MRI (T1-, T2-weighted, fluid-attenuated inversion recovery, and diffusion-weighted imaging), MRA, and HR-MRI were performed on each subject. In patients with a DBI, the imaging evaluation was completed within 4 weeks from stroke onset. All patients were imaged using a 3T MR scanner (GE signa VH/i, General Electric, Milwaukee, WI, USA) and a standard 8-channel head coil. Three-dimensional time-of-flight MRA localizer was used to make sure the cross-section HR-MRI images were perpendicular to M1 segment of MCA [5]. For each artery, average nine slices of HR-MRI images were obtained. The details of the imaging parameters of MRA were described previously [5,8]. The parameters for HR-MRI (FSE-T2WI) were as follows: TR/TE = 3000/50 ms; FOV, 13 cm × 13 cm; matrix size, 256 × 256; slice thickness, 2 mm; slice gap, 0.5 mm; four signal averages; echo train length (ETL) 22. The parameters for routine cranial axial T2 WI were as follows: TR/TE = 3800/88.9, FOV, 24 cm × 24 cm; matrix size, 320 × 224; slice thickness, 6 mm; slice gap, 1 mm; and ETL 23.

Image Analysis

All the HR-MRI image slices of bilateral MCAs in the subjects were analyzed for the artery wall abnormalities. Plaques were identified if there was markedly eccentric wall thickening, whereas the thinnest part was estimated to be less than 50% of the thickest point by visual

inspection (Figure 1) [5,7,8,13]. All cross-sections with plaque were classified based on their plaque orientation being centered on the superior, inferior, dorsal, or ventral side of the vessel [13]. Each cross-section was grouped into one of the four quadrants. In cases in which the plaque was distributed between two quadrants, the quadrant with the maximal plaque thickness was chosen [13]. The lumen area and outer-wall boundaries of MCA were manually measured as described previously [8]. The wall area was calculated as the difference between lumen area and outer-wall boundary area [8].

Image analysis was performed on a workstation (GE, ADW4.2). All images were reviewed by two experienced readers (Xu and Li) who were blinded to clinical details. The differences between two observers were solved by consensus. The measurements of quantitative data were conducted by one experienced neuroradiologist (Li) twice at 1-month interval. The average value was calculated and applied.

Statistics

Quantitative data were described with mean ± standard deviation and qualitative data by percentile. Several rates or proportions were compared using a chi-square test. Comparison of two means in control and SVD subgroups was performed using one-way ANOVA; SPSS 17.0 (SPSS Inc., Chicago, IL, USA) was used as the statistical analysis software.

Results

One hundred and thirty subjects were enrolled, including 57 patients with an acute DBI, 28 patients with WMLs, and 45 control subjects. The time from stroke onset to MRI examination in the patients with a DBI was 12 ± 11 days. The demographic and stroke risk factors for the subjects are summarized in Table 1. Hypertension was the most common risk factors in both patients with a DBI (73%) and WMLs (69%). The difference of vascular risk factors did not reach significance between the two SVD groups.

In 114 vessels of 57 patients with a DBI, four with a stenosis contralateral to the DBIs were excluded from analysis. In the

Figure 1 A patient had an infarct in the right periventricular region on diffusion-weighted images (arrow, **A**). Magnetic resonance angiography showed no stenosis (**B**). On high-resolution T2-weighted imaging of right middle cerebral artery (arrow, **C**), no plaque was seen. For comparison, in another patient with a similar infarct (arrow, **D**) and normal magnetic resonance angiography findings (**E**), a superior-wall plaque was observed (arrow, **F**).

Table 1 Demographic data and imaging characteristics of the patients

	DBIs		Total (n = 57)	WMLs (n = 28)
	With plaque (n = 26)	Without plaque (n = 31)		
Male	21 (81%)	23 (74%)	44 (77%)	20 (71%)*
Age (years)	58 ± 19	61 ± 23	60 ± 18	63 ± 5*
Hypertension	14 (65%)	18 (78%)	32 (73%)	19 (69%)*
Smoking	14 (54%)	15 (48%)	29 (51%)	13 (46%)*
Diabetes	5 (19%)	7 (23%)	12 (21%)	7 (25%)*
Hyperlipidemia	10 (38%)	9 (29%)	19 (33%)	9 (32%)*

DBIs, deep brain infarcts; WMLs, white matter lesions. To comparing DBI and WMLs subjects, significant levels were given (*P*), **P* suggests nonsignificant difference. The values are means ± SD or numbers with percentages.

Table 2 Plaque distribution in the patients with DBIs and middle cerebral artery atherosclerosis

Distribution	Ipsilateral to DBIs (vessels, n = 26)	Contralateral to DBIs (vessels, n = 24)	<i>P</i>
Superior wall	18 (69.2%)	9 (37.5%)	0.025
Inferior wall	10 (38.5%)	11 (46%)	0.598
Ventral wall	8 (30.8%)	15 (62.5%)	0.025
Dorsal Wall	2 (8%)	2 (8.3%)	0.933
Multiple involvement	10 (38.5%)	11 (45.8%)	0.598

DBIs, deep brain infarcts.

remaining 990 image slices of 110 vessels, eccentric plaques were identified in 26 (45.6%) vessels ipsilateral (Figure 1) and 24 (45.3%) vessels contralateral to the DBIs. Table 2 summarized the plaque distribution of these vessels (details in Tables S1 and S2). Superior-wall plaque of MCA was more frequently observed ipsilateral than contralateral to the DBI lesions (69.2% vs. 37.5%, *P* = 0.025), while ventral-wall plaque was more commonly contralateral than ipsilateral to the DBIs (62.5% vs. 30.8%, *P* = 0.025). In addition, a plaque was observed in four vessels of patients with WMLs but was absent in control subjects.

Table 3 Measurements of middle cerebral arteries in subject groups

Area (mm ²)	DBIs with plaques (n = 26)		DBIs without plaques (n = 31)	WMLs (n = 52)	Controls (n = 90)
	Plaque segment	Reference			
Lumen area	6.2 ± 2.5	7.9 ± 1.0	7.8 ± 1.5	8.7 ± 0.5	7.6 ± 1.0
<i>P</i> (vs. control)	<0.001	0.362	0.487	0.001	
OWB area	16.2 ± 2.5	14.9 ± 2.5	14.1 ± 1.5	15.3 ± 1.5	12.1 ± 1.0
<i>P</i> (vs. control)	<0.001	0.017	0.005	<0.001	
Wall area	10.3 ± 2.0	7.3 ± 1.0	6.4 ± 1.0	6.8 ± 1	4.8 ± 0.5
<i>P</i> (vs. control)	<0.001	<0.001	<0.001	<0.001	

DBIs, deep brain infarcts; WMLs, white matter lesions without middle cerebral artery plaque; OWB, outer-wall boundary. Reference: the artery segment of normal appearance proximal to the segment with a plaque. If a proximal reference site was not available, the neighboring distal site was used instead.

Table 3 summarized the measurements of MCA wall and lumen in the subject groups. Compared with the controls, the vessels with a plaque ipsilateral to the DBIs had a smaller lumen (*P* < 0.001), while the vessels with WMLs had a larger lumen (*P* < 0.001). All the SVD subgroups had a significantly larger outer-wall boundary area and wall area than the controls.

Discussion

In this study, the MCA wall abnormalities in patients with DBIs and WMLs were investigated by HR-MRI. An MCA plaque ipsilateral to an acute DBI, often involving superior wall, was seen in as high as 45.6% patients. MCA wall thickening and widening of outer-wall boundaries were revealed in both DBIs and WMLs, while MCA lumen dilation was prominent in the patients with WMLs.

In autopsies, large artery atherosclerosis was reported in nearly 50% patients with symptomatic lacunar stroke [1]. As SVD share common risk factors with large artery atherosclerosis, it is not surprising to see the two pathological processes coexistent. The strength of this study was that it provided an opportunity to *in vivo* examine the relationship between MCA plaque distribution and an acute DBI. It is known most of penetrating branches arise from the dorsal-superior surface of MCA [14]. Although Fisher [2] observed that an atheroma in the superior division of the MCA may obstruct a penetrating artery and cause a DBI, it was seldom reported in other postmortem studies [1]. In our study, MCA superior-wall plaques were observed frequently ipsilateral to the symptomatic DBIs. The results raised the concerns whether the role of MCA superior-wall plaque has been underestimated in the pathogenesis of DBIs. In patients with advanced MCA atherosclerosis, superior-wall plaques have been reported to be associated with the penetrating artery infarcts [13]. It should be noted, however, that HR-MRI did not provide the direct evidence that MCA plaque blocking the orifices of crime penetrating arteries. And coexistence of penetrating artery atherosclerosis or lipohyalinosis could not be excluded.

In patients with chronic hypertension, concentric or eccentric hypertrophy of heart muscles and ventricular dilation (often indicating cardiac failure) are gradually induced [15]. Wall thickening and lumen dilation were also observed in aortic, carotid, and femoral atherosclerosis, suggesting a diffuse cardiovascular process [16–18]. In this study, about 70% patients had hypertension.

Interestingly, while wall thickening was observed in both DBIs and WMLs, lumen dilation was only observed in WMLs, suggesting different underlying pathophysiology in SVD subgroups. It is known that there is a long-term cross-talk between large and small vessels which exaggerates arterial damage, following a vicious circle [19]. In the brain, cerebral small arteries and arterioles are the principal points of physiological resistance to blood flow. Evidence from transcranial Doppler studies suggested cerebrovascular resistance is increased in WMLs [20,21] and the WMLs are associated with whole brain low perfusion [22]. We assume “intracranial artery failure” may be induced in patients with WMLs by both systematic atherosclerotic injury and cerebrovascular resistance overload. It explains why WMLs generally prefer to occur in the external border zone in the absence of large artery stenosis. The lumen changes in WMLs may also represent early dolichoectasia, although there has been no consensus on the diagnostic criterion for MCA dolichoectasia [23].

Our hypothesis is of clinical relevance once confirmed by others in the future. It has been known that an important prevention strategy for heart failure is to avoid long-term peripheral vascular overload. Similarly, before the development of WMLs or at the early stage of WMLs, it may be also critical to reduce cerebrovascular resistance and protect intracranial large arteries from a “failure”. Therefore, the drugs with the effects of dilating cerebral vasculature, such as nimodipine, may be a choice for primary prevention of WMLs. Further investigations are warranted.

Limitations

Our study suffered from several limitations. First, the control group was recruited from out clinics. Although these subjects did not have cerebrovascular diseases and other definitely diagnosed brain diseases, they may not represent completely healthy population. Second, intracranial atherosclerosis is highly prevalent in Chinese patients [24]. Ethnic bias may not be excluded although recent autopsy study has suggested intracranial atheroma is not uncommon in white population [25]. Third, patients with asymptomatic DBIs and with mild WMLs (the grading scale 1 described by Fazekas) were not recruited. The findings of this study should not be applied in those groups.

In conclusion, our results suggest that the pathophysiology of intracranial large artery may be different in SVD subtypes. HR-MRI may be helpful for further stratifying SVD.

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Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

The following supplementary material is available for this article:

Table S1. Plaque distributions ipsilateral to DBIs.

Table S2. Plaque distribution contralateral to DBIs.