Etiology of intracranial stenosis in young patients: a high-resolution magnetic resonance imaging study

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Background: Using high-resolution magnetic resonance imaging (HRMRI), we sought to investigate the underlying etiology of intracranial stenosis in young patients.

Methods: We retrospectively studied 122 Chinese young adult patients (from 18 to 45 years old, mean age 36.2 ± 7.5 years) with unilateral middle cerebral artery (MCA) stenosis based on a prospectively established HRMRI database. The eccentricity, degree of stenosis, and remodeling types of MCA lesions were analyzed. The MCA lesions were classified as eccentric (presumed atherosclerosis) or concentric stenosis (presumed non-atherosclerosis). The clinical data and vessel wall properties were compared between the patients >35 years old and the patients \leq 35 years old.

Results: Eccentric stenosis was observed in 98 (80.3%) patients and concentric stenosis in 24 (19.7%) patients. The patients with eccentric stenosis were older (37.5 \pm 6.8 vs. 31.4 \pm 8.4 years old, P<0.001) and more likely had atherosclerosis risk factors (56.1% vs. 25.0%, P=0.006). The patients >35 years old had higher prevalence (90.1% vs. 66.7%, P=0.001) of eccentric stenosis and atherosclerosis factors (60.6% vs. 35.3%, P=0.006) than the patients \leq 35 years old. Most of the patients with concentric stenosis were \leq 35 years old (17/24, 70.8%) and were female (16/24, 66.7%). Binary Logistic analysis suggested smoking (OR =3.171; 95% CI, 1.210–8.314) and remodeling ratio (OR =1.625; 95% CI, 1.001–2.636) were independent predictive factors for symptomatic stenosis.

Conclusions: Atherosclerosis is the most common cause of intracranial stenosis in Chinese young patients. Non-atherosclerosis disease is an important etiology in young female, especially in the patients aged 35 years old or younger.

Keywords: Intracranial stenosis; high-resolution magnetic resonance imaging (HRMRI); youth stroke; atherosclerosis

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Introduction

Intracranial artery stenosis is highly prevalent in stroke patients of Asian, African, and Hispanic ancestry (1). Atherosclerosis is the widely accepted underlying etiology, especially in old patients. In patients at a young age, however, intracranial stenosis has varied causes, such as dissection, moyamoya disease, fibromuscular dystrophy, and vasculitis (2-4). Current imaging techniques, including digital subtraction angiography, CT angiography, and magnetic resonance angiography (MRA) cannot provide direct proof of the casual etiology, because different pathologies can result in similar patterns of intracranial lumen stenosis. The vascular pathophysiology of intracranial stenosis in young patients has been less well studied.

In the past decade, the technique of high-resolution magnetic resonance imaging (HRMRI) has been developed (5-8). Emerging studies have suggested that HRMRI is reliable for detecting intracranial artery wall lesions, consistent with histology findings (7-11). On HRMRI, eccentric stenosis is suggestive of atherosclerosis while concentric stenosis is suggestive of non-atherosclerotic diseases, although overlap may occasionally exist (3,8,12-14). In this study, using HRMRI, we sought to observe the vessel wall properties of intracranial stenosis in Chinese young patients and investigate the underlying etiology.

Methods

Participants

This is a retrospective study based on a prospectively established HRMRI database, approved by the ethics committee of Peking Union Medical College Hospital (15). Formal written consents were obtained from all the patients.

Consecutive young adult patients (from 18 to 45 years old) with transcranial Doppler (peak velocity >160 cm/s) or MRA suspected middle cerebral artery (MCA) stenosis were recruited (15). Patients were excluded if they had: (I) bilateral MCA stenosis or definite moyamoya disease, i.e., bilateral stenosis and/or occlusion of the intracranial internal carotid artery and its proximal branches, with development of collateral network (moyamoya vessels) (16); (II) extracranial carotid or vertebral artery stenosis; (III) cardiac embolic stroke; (IV) normal MRA and HRMRI findings; (V) poor image quality.

It is known that there is a sharp rise in the prevalence of traditional risk factors over the age of 35 years and "young stroke" increasingly resembles 'old' stroke (17). To address whether this "sharp risk factors rise" is meaningful for intracranial vessel pathophysiology, we further divided patients into two subgroups: patients >35 years old and patients \leq 35 years old.

MR protocol

From January 2007 to June 2013, all patients underwent conventional T2 weighted imaging, diffusion weighted imaging, three-dimensional time-of-flight MRA and bilateral MCA HRMRI. The details of HRMRI protocol were described elsewhere (15). Briefly, HRMRI was composed of cross-section T2 and T1 weighted imaging, which were perpendicular to M1 segment of MCA, with slice thickness 2 mm and gap 0–0.2 mm. Acquisition resolution was 0.25 mm × 0.25 mm (T2WI) and 0.3 mm × 0.3 mm (T1WI). TR/TE =3,000/40 ms (T2WI), 600/12 ms (T1WI). Gd-DTPA enhancement (0.1 mmol/kg) was performed with T1WI sequence.

After July 2013, the technique of HRMRI was updated in our institution. The patients were imaged using a new 3.0 T scanner (GE Discovery MR750). The new HR-T1WI was obtained using a fast spin echo 3D technique (CUBE T1WI). The parameters were as follow: TR 565 ms, TE 16 ms, FOV 20 cm, matrix 320×256 , ZIP 512, slice thickness 0.8 mm, ZIP 2. The display resolution were 0.4 mm × 0.4 mm × 0.4 mm. One hundred twenty coronal slices cover anterior and posterior circulation were acquired with scan time 5 min.

Image analysis

All MR images were transformed to a workstation for analysis. The eccentricity, degree of stenosis, and remodeling types of MCA lesions were analyzed by two experienced HRMRI reviewers (ML Li and YY Xu) blinded to the clinical data. The differences between two observers were solved by consensus.

Eccentric stenosis were identified if the thinnest part of the wall was estimated to be less than 50% of the thickest point on at least one image slice of T2 weighted images (15). Concentric stenosis was diagnosed if the



Figure 1 Measurements of vessel area and luminal area. Magnetic resonance angiography (A) shows a stenosis at the M1 segment of left MCA (arrowhead). On high-resolution MRI, the vessel wall images (B, arrowhead) at the maximal lumen narrowing site and the reference site (C, arrowhead) are shown. The vessel area and luminal area of the sites can be measured (demonstrated by the magnified images). MCA, middle cerebral artery; MRI, magnetic resonance imaging.

thinnest part of the wall was estimated to be no less than 50% of the thickest point on all image slices or a stenosis without wall thickening (8). We defined the reference sites as the nearest plaque-free segments proximal or distal to the maximal lumen narrowing sites. The degree of stenosis on HRMRI was calculated as follows: (1-luminal area at the maximal lumen narrowing site/reference luminal area) $\times 100\%$ (15,18). The remodeling ratio of MCA stenosis was defined as the ratio of the outer-wall boundary area at the maximal lumen narrowing site to that at the reference site (19). Expansive remodeling was defined for a remodeling ratio of more than 1.05 (19). Constrictive remodeling was defined for a remodeling ratio of less than 0.95 (19) (*Figure 1*).

Statistical analysis

The intraclass correlation coefficient was used to find the intra-observer and inter-observer reproducibility for the measurements of luminal area and vessel wall area. Continuous variables were described as mean \pm standard deviation in normally distributed data. The continuous variables between the two groups were compared by the independent samples *t*-test. Categorical variables were compared by the chi-square test or Fisher exact test. The variables were entered the binary Logistic regression model to study the relationship between predictive variables (atherosclerosis factors, eccentricity and remodeling ratio) and the dependent variable (cerebral infarction). A value of P<0.05 was used to indicate statistical significance.

Results

From Jan. 2009 to Aug. 2015, two hundred and forty-eight young patients with MCA stenosis were recruited. One hundred cases with moyamoya disease, 15 with bilateral MCA stenosis, 3 with cardiac embolic stroke, 12 with extra-cranial artery stenosis and 9 with poor image quality were excluded. The data of 122 patients with unilateral MCA stenosis were finally analyzed (Table 1). Of them, 68 patients were diagnosed with ischemic stroke, confirmed by diffusion weighted and/or T2 weighted imaging. Seven patients had systemic immune diseases. The remaining patients had non-specific symptoms such as headache and dizziness, etc., but no lesion was found on T2 weighted and diffusion weighted images. No patients with dissection or reversible cerebral vasoconstriction syndrome were clinically diagnosed. The intra-observer and interobserver reproducibility of measurements of the luminal area were 0.882 (95% CI, 0.689-0.974) and 0.929 (95% CI, 0.667-0.983). The intra-observer and inter-observer reproducibility of measurements of the wall area were 0.848 (95% CI, 0.595-0.954) and 0.974 (95% CI, 0.950-0.990).

The demographic data and wall morphologic

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Table 1 Demographic data and MRI findings

Clinical and MRI features	Eccentric stenosis (n=98)	Concentric stenosis (n=24)	Р
Age (year)	37.5±6.8	31.1±8.4	<0.001
35 years or younger (%)	34 (34.7)	17 (70.8)	0.001
Female (%)	26 (26.5)	16 (66.7)	<0.001
Atherosclerosis factors (%)	55 (56.1)	6 (25.0)	0.006
Hypertension	31 (31.6)	2 (8.3)	0.021
Hyperlipidemia	24 (24.5)	4 (16.7)	0.388
Diabetes	7 (7.1)	0 (0.0)	0.343
Smoking	33 (33.7)	1 (4.2)	0.004
Immune disease (%)	4 (4.1)	3 (12.5)	0.136
Infarctions (%)	56 (57.1)	12 (50.0)	0.528
Multi-stenosis* (%)	20 (20.4)	8 (33.3)	0.185
Severe stenosis (>70%) (%)	36 (33.3)	14 (70.3)	<0.001
Enhancement examination (%)	19	8	
Enhancement	13 (68.4)	8 (100.0)	0.072
Non-enhancement	6 (31.6)	0 (0.0)	0.136
At the reference site (mm ²)			
Vessel area	11.51±2.85	9.06±2.08	<0.001
Luminal area	6.86±1.82	5.21±1.54	<0.001
At the maximal lumen narrowing site (mm ²)			
Vessel area	10.39±4.13	4.85±1.66	<0.001
Luminal area	2.75±1.94	1.49±1.33	0.005
Degree of stenosis (%)	61.1±23.6	72.8±23.7	0.03
Remodeling ratio	0.90±0.28	0.55±0.19	<0.001
Expansive remodeling (%)	36 (36.7)	0 (0.0)	<0.001
Constrictive remodeling (%)	46 (46.9)	23 (95.8)	<0.001

*, two or more vessel stenosis. MRI, magnetic resonance imaging.

characteristics were summarized in *Table 1*. Eccentric stenosis was observed in 98 (80.3%) patients and concentric stenosis in 24 (19.7%) patients. The patients with eccentric stenosis were older (P<0.001), and more likely had atherosclerosis risk factors (P=0.016). The patients with concentric were more likely to be female (P<0.001) and 35 years old or younger (P=0.001). All concentric stenosis (100%) showed constrictive artery remodeling, while eccentric stenosis had heterogeneous remodeling types (P<0.001). In 27 patients with available enhanced images, six patients with eccentric stenosis had enhancement (13/19,

68.4%), as compared with concentric stenosis (8/8, 100%; P=0.072) (*Figure 2*).

In subgroup analysis, there were 51 patients \leq 35 years old and 71 patients >35 years old. Compared with the patients \leq 35 years old, those aged 35 years old or older had much higher prevalence of atherosclerosis factors (P=0.006), and eccentric stenosis (P=0.001, *Table 2*). Most of patients with concentric stenosis were \leq 35 years old (17/24, 70.8%) and were female (16/24, 66.7%).

A binary Logistic regression model was constructed to study the relationship between cerebral infarction and other

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Figure 2 Imaging of eccentric and concentric stenosis. In a patient with an infarction in the right hemisphere (A, arrowhead), right MCA stenosis (B, arrowhead) was observed. A plaque involving the anterior vessel wall (C, arrowhead) with slight enhancement was seen (D, arrowhead) on high-resolution MRI. In an asymptomatic patient (E–H) with right MCA stenosis (F, arrowhead), a concentric wall lesion (G, arrowhead) with ring-like enhancement (H, arrowhead) was seen. MCA, middle cerebral artery.

variables including atherosclerosis factors, eccentricity and remodeling ratio (details of univariate analysis are listed in *Table 3* in supporting information). Binary Logistic analysis suggested smoking (OR =3.171; 95% CI, 1.210–8.314; P=0.019) and remodeling ratio (OR =1.625; 95% CI, 1.001–2.636; P=0.049) were independent predictive factors for symptomatic stenosis (*Table 4*).

Discussion

Evidence from the comparative studies between HRMRI and histology has supported that intracranial eccentric wall lesions represent the pathology of atherosclerosis (7,9-11). In this study, a high percentage (80.3%) of Chinese young patients with unilateral MCA stenosis had such eccentric wall lesions on HRMRI. Unsurprisingly, these patients were older and more likely to have atherosclerotic risk factors than those with concentric stenosis. Further analysis suggested that even in those ≤ 35 years old, eccentric stenosis was observed in as high as 2/3 of the patients. Taken together, our study suggests that atherosclerosis is the most common cause of intracranial stenosis in Chinese young patients, similar to the old (20,21). On the other hand, the patients aged 36 to 45 years old had more traditional vascular risk factors and eccentric stenosis than those \leq 35 years old, supporting that the rising incidence of traditional vascular risk factors have effects on intracranial artery pathophysiology (17,21,22).

Although intracranial concentric wall lesions can be seen in patients with atherosclerosis, they were more frequently reported infective or non-infective vasculitis, and other vasculopathy (3,8,23,24). In this study, 19.7% patients had concentric wall lesions. Most of them were female, younger than 35 years old, and without atherosclerosis risk factors. High proportion of wall enhancement was observed, suggesting active inflammation and high intrawall microvessel density (25). All the concentric stenosis showed unique constrictive remodeling, in comparison with the heterogeneous remodeling types in eccentric stenosis. Overall, the patients with concentric stenosis had different imaging and clinical features from those with eccentric wall lesions, i.e., presumed atherosclerosis. However, because the diagnostic tests including spinal tap tests and brain biopsies were not routinely performed, the stratified etiologies of

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Table 2 Comparison	between pa	tients ≤35	and 36-45	years old
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Clinical and MRI features	≤35 years (n=51)	36–45 years (n=71)	Р
Female (%)	23 (45.1)	22 (31.0)	0.111
Atherosclerosis factors (%)	18 (35.3)	43 (60.6)	0.006
Hypertension	7 (13.7)	26 (36.6)	0.005
Hyperlipidemia	8 (15.7)	20 (28.2)	0.106
Diabetes	1 (2.0)	6 (8.5)	0.237
Smoking	11 (21.6)	23 (32.4)	0.188
Immune disease (%)	4 (7.8)	3 (4.2)	0.450
Infarctions (%)	28 (54.9)	40 (56.3)	0.875
Eccentric stenosis (%)	34 (66.7)	64 (90.1)	0.001
Concentric stenosis (%)	17 (33.3)	7 (9.9)	0.001
Multi-stenosis* (%)	11 (21.6)	17 (23.9)	0.758
Severe stenosis (>70%) (%)	19 (37.3)	31 (43.7)	0.478
Degree of stenosis (%)	65.7±18.3	61.7±27.3	0.609
Remodeling ratio	0.78±0.29	0.86±0.30	0.310
Expansive remodeling (%)	12 (23.5)	24 (33.8)	0.220
Constrictive remodeling (%)	33 (64.7)	36 (50.7)	0.124

*, two or more vessel stenosis. MRI, magnetic resonance imaging.

Table 3 Comparison	between symptomatic and	l asymptomatic MCA stenosis
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Clinical and MRI features	Symptomatic MCA stenosis (n=68)	Asymptomatic MCA stenosis (n=54)	Р
Age (year)	36.18±8.13	36.33±6.72	0.909
Female (%)	22 (32.4)	23 (42.6)	0.244
Atherosclerosis factors (%)	38 (55.9)	23 (42.6)	0.145
Hypertension	22 (32.4)	11 (20.4)	0.139
Hyperlipidemia	16 (23.5)	12 (22.2)	0.865
Diabetes	6 (8.8)	1 (1.9)	0.100
Smoking	26 (38.2)	8 (14.8)	0.004
Immune disease (%)	7 (10.3)	0	0.017
Eccentric stenosis (%)	56 (82.4)	42 (77.8)	0.528
Concentric stenosis (%)	12 (17.6)	12 (22.2)	0.528
Multi-stenosis* (%)	16 (23.5)	12 (22.2)	0.865
Severe stenosis (>70%) (%)	25 (36.8)	25 (46.3)	0.288
Degree of stenosis (%)	61.0±25.6	66.4±21.6	0.536
Remodeling ratio	0.90±0.28	0.75±0.29	0.035
Expansive remodeling (%)	25 (36.8)	11 (20.4)	0.049
Constrictive remodeling (%)	31 (45.6)	38 (70.4)	0.006

*, two or more vessel stenosis. MRI, magnetic resonance imaging; MCA, middle cerebral artery.

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 Table 4 Logistic regression analysis to identify the determinants of cerebral infarction

Variables	OR (95% CI)	Р
Hypertension	1.173 (0.460–2.992)	0.738
Diabetes	3.489 (0.384–31.717)	0.267
Smoking	3.171 (1.210–8.314)	0.019
Remodeling ratio	1.625 (1.001–2.636)	0.049
Eccentricity	0.588 (0.212–1.625)	0.306

concentric stenosis were undefined.

Our results are potentially clinically important. It has been known that the prognosis of young stroke is not as favorable as previously thought, with respect either to mortality, or cardiovascular disease, or to psychosocial consequences (17). Early etiology diagnosis and pathophysiology evaluation of intracranial stenosis are meaningful. For example, aggressive risk factors control, anti-thrombosis treatments and life style modification may be beneficial for premature intracranial atherosclerosis. HRMRI is helpful for giving a clue for further diagnostic procedures and establishing the treatment strategy.

There have been several studies on intracranial stenosis in young patients. In a multinational cohort study in Europe, intracranial atherosclerotic stenosis and occlusions (11.8%) were more prevalent than extracranial carotid artery disease (8.9%) in patients ≤ 55 years old with ischemic stroke and transient ischemic attacks (26). In another single-center cohort study in South Korea, using HRMRI, intracranial atherosclerosis was diagnosed in 27.4% patients aged ≤55 years old with unilateral MCA stenosis and with no or minimal (≤ 1) atherosclerotic risk factors (24). Comparatively, the strength of current study was that the patient recruitment was based on the presence of intracranial artery stenosis, regardless of clinical background (atherosclerosis risk factors and ischemic events). This inclusion criterion and the application of HRMRI made it possible to give an analysis to the underlying etiology of the vessel lesion patterns.

Unfortunately, current study suffered from several limitations. First, this was a single-center retrospective study in Chinese, a population with high prevalence of intracranial atherosclerosis. The ethnic bias couldn't be excluded. Second, the follow-up imaging was not regularly performed. Some rare conditions including unilateral moyamoya disease may have been underestimated (27).

Conclusions

The current HRMRI study provides strong evidence that atherosclerosis is the most common cause of intracranial stenosis in Chinese young patients. Non-atherosclerosis disease is an important etiology in young female, especially in the patients aged 35 years old or younger.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This is a retrospective study based on a prospectively established HRMRI database, approved by the ethics committee of Peking Union Medical College Hospital (No. JS-872). Formal written consents were obtained from all the patients.

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