Original Contribution

Geographic and Sex Difference in the Distribution of Intracranial Atherosclerosis in China

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Background and Purpose—Geographic variation and sex difference in the distribution of intracranial atherosclerosis (ICAS) have not been fully discussed before in Chinese patients with cerebral ischemia. We performed this study with the aim to investigate geographic and sex difference in the distribution of ICAS in China.

Methods—In this prospective multicenter study, we evaluated 2864 consecutive patients who experienced an acute cerebral ischemia within 7 days of symptom onset in 22 hospitals in China. All the inclusive patients underwent 3-dimensional time-of-flight MR angiography and duplex color Doppler ultrasound or contrast-enhanced MR angiography to document the presence of intracranial or extracranial stenosis. Intracranial large-artery atherosclerosis was defined as ≥50% diameter reduction on MR angiography.

Results—The proportion of patients with ICAS was significantly higher in north China than in south China (50.22% versus 41.88%; P<0.0001). Patients in the north were likely to consume more alcohol and smoke more cigarettes and had significantly higher proportion of diabetes mellitus, family history of stroke, history of cerebral ischemia, heart disease, and higher body mass index. In patients aged >63 years, the percentage of ICAS in women was notably higher than in men (51.51% versus 45.40%; P=0.028). In elderly patients, women had higher proportion of diabetes mellitus, hypertension, hyperlipidemia, and heart disease than men.

Conclusions—There exists geographic and sex difference in the distribution of symptomatic ICAS in China. Public health measures should strengthen improving social determinants of health and risk factor prevention/control in high-risk populations for decreasing stroke risk. (Stroke. 2013;44:00-00.)

Key Words: geographic ■ ischemic ■ intracranial stenosis ■ sex differences ■ stroke

Geographic variation in stroke incidence, mortality, and prevalence has been observed in some regions. In United States, higher stroke mortality has long been commonly found among residents of the southeastern states (the stroke belt region). Differences in socioeconomic status, risk factors, and prevalence of common chronic diseases may explain the regional differences. In China, the Sino International collaborative World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project supported the geographic variation in stroke incidence, mortality, and prevalence has been observed in some regions. In United States, higher stroke mortality has long been commonly found among residents of the southeastern states (the stroke belt region). Differences in socioeconomic status, risk factors, and prevalence of common chronic diseases may explain the regional differences. In China, the Sino International collaborative World Health Organization Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) project supported the north–south gradient, with the highest stroke incidence in Heilongjiang province and the lowest incidences in Anhui and Fujian provinces. Large-artery atherosclerosis is a very common subtype of ischemic stroke. Intracranial atherosclerosis (ICAS) is the most common vascular lesions in China. However, until now, geographic difference in the distribution of ICAS in China, even in the world, has not been reported.

In recent years, sex-specific data on stroke incidence, prevalence, subtypes, severity, and case fatality have become available from different parts of the world. Stroke is more common among men, but women are more severely ill. Data regarding ICAS are quite meager and remain controversial. Several studies have shown female predominance in ICAS, whereas others have reported that men are more likely to have ICAS than women. A clinical study in Chinese subjects, mainly in asymptomatic subjects, also reported a male predominance in ICAS. An autopsy study showed that the sex difference in ICAS was influenced by age. From the fourth to sixth decades of life, the percentage of women with no cerebral atherosclerosis was higher than men, but at >65 years of age the frequency of atherosclerotic lesions was the same in 2 sexes.

Above all, geographic variation and sex difference in the distribution of ICAS have not been fully discussed before. So, we performed this study with the aim to investigate geographic and sex difference in the distribution of ICAS in China.

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Methods

Study Design and Patient Eligibility

The Chinese Intracranial Atherosclerosis Study is a prospective, multicenter, cohort, hospital-based study. Twenty-two general hospitals covering a wide geographic area in China participated. (The hospital list is shown in the Appendix.) The study was approved by the institutional review board of the participating hospitals. In addition, all participants provided written informed consent for study participation.

Data were prospectively collected from consecutive patients with cerebral ischemia, including ischemic stroke and transient ischemic attack, using a standardized case report form. Inclusion criteria included onset of symptom within 7 days and age between 18 and 80 years. We excluded patients who were clinically unstable or required close monitoring or were moribund, were disabled before admission (modified Rankin scale >2), were physically or subjectively unable to comply with MR examination, or had severe comorbidity. We excluded patients with cardioembolic risk (including atrial fibrillation, valvular heart disease, postcardiac valve replacement, and so on) to avoid the inclusion of vascular occlusion because of cardioembolism.

On admission, baseline data, including age, sex, medical history, and physical examination, were collected. All patients underwent detailed clinical evaluation, including laboratory tests, brain MR scan, 3-dimensional (3D) time-of-flight MR angiography (MRA), duplex color Doppler ultrasound, or contrast-enhanced MRA. Intracranial vessels were judged by 3D time-of-flight MRA, and extracranial carotid vessels were examined by duplex color Doppler ultrasound or contrast-enhanced MRA. According to the Huai River–Qinling Mountains line, we divided the participants into northern part and southern part.

From October 2007 to June 2009, 3580 patients were registered. We excluded 325 patients with risk of cardioembolism. In addition, we excluded 391 patients because of incomplete cerebrovascular workup, such as MR/MRA examination. We analyzed the remaining cohort of 2864 consecutive patients.

Definition of Risk Factors

The clinical information included age, sex, hypertension (defined as a history of hypertension or required regular treatment with antihypertensive agent before admission or diagnosed at discharge), diabetes mellitus (defined as a history of diabetes mellitus or being treated for diabetes mellitus or glycosylated hemoglobin ≥7% or diagnosed at discharge), hyperlipidemia (defined as low-density lipoprotein cholesterol 2.6 mmol/L at the time of admission or a history of treatment). Heart disease (defined as a history of myocardial infarction, angina, or being treated for angina or myocardial infarction), hyperhomocystinemia (defined as homocysteine ≥15 μmol/L), and heavy drinking (defined as alcohol intake ≥50 g/day). The clinical information for each patient was carefully recorded by physicians who had received standardized training.

Baseline Characteristics by Geography and Sex

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>By Geography</th>
<th>P Value</th>
<th>By Sex (Patients &gt;63 y)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (men)</td>
<td>North (n=1627)</td>
<td>South (n=1237)</td>
<td>&lt;0.0001</td>
<td>Women (n=530)</td>
</tr>
<tr>
<td>Age*, y</td>
<td>60.21±11.14</td>
<td>64.14±10.98</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>594 (36.51)</td>
<td>397 (22.09)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1267 (77.87)</td>
<td>971 (78.50)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1255 (77.14)</td>
<td>918 (74.21)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>232 (14.26)</td>
<td>64 (5.17)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>706 (43.39)</td>
<td>343 (27.73)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>105 (6.45)</td>
<td>37 (2.99)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hypermucystinemia</td>
<td>689 (42.35)</td>
<td>61 (4.93)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>History of cerebral ischemia</td>
<td>1214 (74.62)</td>
<td>804 (65.00)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>History of hemorrhagic stroke</td>
<td>33 (2.03)</td>
<td>21 (1.70)</td>
<td>0.5193</td>
<td></td>
</tr>
<tr>
<td>Heart disease</td>
<td>161 (9.90)</td>
<td>67 (5.42)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Peripheral angiopathy</td>
<td>16 (0.98)</td>
<td>5 (0.40)</td>
<td>0.0719</td>
<td></td>
</tr>
<tr>
<td>BMI*, kg/m²</td>
<td>25.14±3.17</td>
<td>23.8±2.98</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>NIHSS†</td>
<td>3 (1–7)</td>
<td>4 (2–6)</td>
<td>0.0095</td>
<td></td>
</tr>
<tr>
<td>SBP at admission*, mm Hg</td>
<td>150.84±23.25</td>
<td>157.65±23.81</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>DBP at admission*, mm Hg</td>
<td>89.66±13.82</td>
<td>88.16±13.16</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PP*, mm Hg</td>
<td>61.18±18.22</td>
<td>69.5±18.83</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>MBP*, mm Hg</td>
<td>110.06±15.29</td>
<td>111.32±15.03</td>
<td>0.0074</td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose*, mmol/L</td>
<td>6.11±2.35</td>
<td>6.44±2.7</td>
<td>0.0010</td>
<td></td>
</tr>
<tr>
<td>SCR*, mg/L</td>
<td>2.6 (0.9–7.2)</td>
<td>2.63 (1–6.33)</td>
<td>0.3195</td>
<td></td>
</tr>
<tr>
<td>Glycohemoglobin*, %</td>
<td>6.48±1.73</td>
<td>6.59±1.87</td>
<td>0.2429</td>
<td></td>
</tr>
<tr>
<td>TG*, mmol/L</td>
<td>1.81±1.33</td>
<td>1.88±1.19</td>
<td>0.1410</td>
<td></td>
</tr>
<tr>
<td>TC*, mmol/L</td>
<td>4.61±1.14</td>
<td>4.86±1.25</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>HDL*, mmol/L</td>
<td>1.15±0.3</td>
<td>1.19±0.37</td>
<td>0.0022</td>
<td></td>
</tr>
<tr>
<td>LDL*, mmol/L</td>
<td>2.85±0.95</td>
<td>2.97±0.98</td>
<td>0.0019</td>
<td></td>
</tr>
</tbody>
</table>

BMI indicates body mass index; DBP, diastolic blood pressure; ICAS, intracranial atherosclerosis; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; MBP, mean arterial pressure; NIHSS, National Institutes of Health Stroke Scale; PP, pulse pressure; SBP, systolic blood pressure; SCR, serum C-reactive protein; TC, total lipoprotein cholesterol; and TG, triglyceride.

*Continuous variables with normal distribution expressed as mean±SD.
†Continuous variables with non-normal distribution expressed as interquartile range; other values are expressed as n (%).
of hyperlipidemia or received lipid-lowering treatments or diagnosed at discharge), a history of cerebral ischemia (including a history of ischemic stroke and transient ischemic attack or evidence of old infarct on MRI), a history of hemorrhagic stroke (including intracerebral hemorrhage and subarachnoid hemorrhage), and heart disease (defined as a known history of myocardial infarction, angina pectoris, and congestive heart failure). In addition, current smoker (defined as a patient who had smoked continuously for 6 months ≥1 cigarette a day), heavy drinker (drinking ≥2 U/d on average for men or ≥1 U/d on average for women), and hyperhomocystinemia (serum level of total homocysteine ≥15 μmol/L) were noted.

Image Analysis/Interpretation
All patients underwent conventional MRI on a 3.0 or 1.5T MR scanner, including a sequence of 3D time-of-flight MRA. Other MR sequences, such as T2-/T1-weighted imaging, fluid-attenuated inversion recovery sequences, and diffusion-weighted imaging (DWI), were also performed. All MRI/MRA images were stored in digital format and were read centrally by 2 readers (X.Y. Zou and Y. Soo) who were blinded to the subjects’ clinical information or outcome. Disagreements of >10% degree of stenosis were resolved by a third reader who decided the final value.

Degree of intracranial stenosis on MRA was calculated using the published method for the Warfarin–Aspirin Symptomatic Intracranial Atherosclerosis Disease Study.11 All measurements were made with Wiha DigiMax Digital Calipers 6” (Germany), with a resolution of 0.01 to 0.03 mm for 0 to 100 mm. We assessed the following arterial segments: bilateral intracranial internal carotid artery, anterior cerebral artery A1/A2, middle cerebral artery M1/M2, posterior cerebral artery P1/P2, and basilar artery. For the internal carotid artery, an intracranial location was defined as distal to the ophthalmic artery. According to the severity of stenosis, we classified the patients into 4 groups: <50% or no stenosis, 50% to 69% stenosis, 70% to 99% stenosis, and occlusion groups. We regarded focal flow void found on MRA with distal filling as severe stenosis (70%–99%).11 Absence of distal filling on MRA would be regarded as 100% occlusion. According to the distribution of stenosis, we categorized vessels with >50% stenosis or occlusion as presence of intracranial stenosis, extracranial stenosis, or tandem group (both intracranial and extracranial stenosis). The extracranial part of internal carotid artery was estimated with ultrasonographic examination according to the published diagnostic criteria13 or by contrast-enhanced MRA.

Statistical Analysis
All analyses were performed with SAS software version 9.1 (SAS Institute Inc, Cary, NC). Continuous variables were summarized as median (interquartile range) or mean (SD). Categorical variables, such as sex, vascular risk factors, and location of stenotic arteries, were presented as percentages. Independent samples t test or Wilcoxon test was used for comparison of continuous variables, and χ² test or Fisher exact test was used for comparison of categorical variables. When the incidence of ICAS was compared, we used logistic regression to adjust for age and sex. All tests were 2-sided, with a significance level fixed at 5%.

Results
Of the patients included in these analyses, the mean age at admission for index stroke was 61.9±11.2 years (19–80 years); 1944 (67.9%) were men, and 1627 (56.8%) were from northern part of China. In patients aged ≤63 years, 1118 (74.1%) were men, and in patients aged >63 years, 826 (60.9%) were men.

Patients with ICAS were significantly higher in northern part than in the southern part (50.22% versus 41.88%; odds ratio, 1.400; 95% confidence interval, 1.260–1.708). The difference in baseline characteristics by geography and sex is shown in Table 1. Patients in southern China were older than the patients in northern China, with higher proportion of men (37.59% versus 27.97%; P<0.0001). Patients in the north were more likely to consume alcohol and cigarettes and had significantly higher proportion of diabetes mellitus, family history of stroke, history of cerebral ischemia, heart disease, and higher body mass index. On admission, southern patients had higher National Institutes of Health Stroke Scale, systolic blood pressure, pulse pressure, mean arterial pressure, fasting blood glucose, total lipoprotein cholesterol, and high-density and low-density lipoprotein cholesterol levels. In addition, northern patients were likely to have cerebral atherosclerotic lesions, especially in extracranial, and both intracranial and extracranial lesions. Northern patients had significantly higher percentage of multiple intracranial atherosclerosis (23.91% versus 15.68%; P<0.0001) and occlusive lesion (30.12% versus 20.45%) than the southern patients.

In total, the distribution of ICAS between men and women had no significant difference (46.09% versus 47.72%; P=0.4151), nor did the patients aged ≤63 years. For patients aged >63 years, the percentage of ICAS in women was notably higher than in men (51.51% versus 45.40%; P=0.028). Regarding the distribution of extracranial atherosclerosis, men had significantly higher percentage than women (15.90% versus 10.00%; P<0.0001). The percentage of ICAS and extracranial atherosclerosis in different age stages between men and women is shown in the Figure. In elderly patients, women had higher proportion of diabetes mellitus, hypertension, hyperlipidemia, and heart disease than men. Men were more likely to consume alcohol and smoke cigarettes and had significantly higher proportion of hyperhomocystinemia and history of cerebral ischemia than women. On admission, women had higher systolic blood pressure, pulse pressure, mean arterial pressure, fasting blood glucose, glycohemoglobin, triglyceride, total lipoprotein.
cholesterol, and high-density and low-density lipoprotein cholesterol levels. In addition, female patients were likely to have intracranial atherosclerotic lesions (43.96 versus 34.14%), yet male patients were likely to have extracranial and both intracranial and extracranial lesions. Multiple intracranial atherosclerotic lesions were more common in women (24.72% versus 20.10%; \( P = 0.0447 \)).

**Discussion**

**Geographic Difference in ICAS**

Our data indicate that distribution of ICAS has geographic variation in China, with higher rates in the north and lower rates in the south. Furthermore, northern patients are more likely to have both intracranial and extracranial atherosclerotic lesions, multiple intracranial atherosclerosis, and occlusive lesion than the southern patients. Northern patients have more risk factors of atherosclerosis, such as diabetes mellitus, hyperlipidemia, family history of stroke, smoking, heavy drinking, hyperhomocystinemia, and overweight, which help to explain the difference (Table 2).

People in the north and south have different lifestyle, food habits, and environment. People in the north are more likely to smoke cigarettes, drink alcohol, and consume fatty foods and salt. This may increase the risk of having hypertension, diabetes mellitus, hyperlipidemia, obesity, and so on. Previous studies in China have documented regional variations in the prevalence of hypertension, diabetes mellitus, hyperlipidemia, and obesity. Genetic polymorphism is another influential factor for these differences. Hu et al. found that positive correlation existed between the e4 allele frequency distribution and a northern latitude (\( r = 0.586; \ P = 0.008 \)) in China. Many studies have shown that ICAS is associated with lipid disorder, hypercholesterolemia, tobacco use, and diabetes mellitus. Diabetes mellitus, as well as a history of ischemic heart disease, was found to be more significantly prevalent in patients with combined extracranial internal carotid artery and intracranial stenosis. The results of our study improve the understanding of the various factors that affect patients with cerebral ischemia in different regions of China. Primary prevention (such as improved lifestyle and control risk factors) should be strengthened to reduce the incidence of ICAS in the northern area.

**Sex Difference in ICAS**

For the entire sample, there was no difference in the distribution of ICAS between men and women. But in patients aged
>63 years, the difference was significant. Multiple intracranial atherosclerotic lesions were also very common in women aged >63 years. Men were likely to have extracranial atherosclerosis, which has been proved in other population.26 These results are similar to those of Flora et al.,10 who found that the frequency of cerebral atherosclerosis increases more rapidly in women after the sixth decade. In our study, elderly women have more diabetes mellitus, hypertension, hyperlipidemia, and history of heart disease, which can help explain the difference. Our results were not unexpected. Among premenopausal and early perimenopausal women, hormones, particularly low sex hormone–binding globulin and high free androgen index, are related to elevated cardiovascular risk factors (higher insulin, glucose, hemostatic and inflammatory markers, and adverse lipids).27 Sex difference was also found on prevalence of diabetes mellitus. The China National Diabetes and Metabolic Disorders Study showed that female patients aged >60 years had higher prevalence of diabetes mellitus than men.28

### Strengths and Limitations

These are the first data about geographic and sex difference of ICAS in Chinese patients with cerebral ischemia. The results are from a multicenter, large-sample, consecutive cohort study that uses MRA as the screening tool for ICAS. It decreases the diagnostic error for ICAS. As to the limitations, this study was hospital based, and the participating hospitals were all upper first-class hospitals, and some degree of sampling bias existed. It is difficult to distinguish occlusion caused by embolism of uncertain source from atherothrombotic occlusion on MRA.

### Conclusions

There exists geographic and sex difference in the distribution of symptomatic ICAS in China. The proportion of ICAS is higher in the north, and northern patients are more likely to have multiple intracranial atherosclerosis and occlusive lesion than the southern patients. Female patients aged >63 years have higher percentage of ICAS, whereas men were likely to have extracranial atherosclerosis. Difference in risk factors helps to explain the variation in ICAS prevalence. To decrease the risk of stroke, the government should support early implementation of cerebrovascular examination in high-risk populations; public health measures should strengthen improving social determinants of health and risk factor prevention/control in those with high risk of ICAS.

### Appendix

Beijing Tongren Hospital of Capital Medical University, Beijing (Xiaojun Zhang); Shanghai Jiaotong University Affiliated Sixth People’s Hospital, Shanghai (Xiaojiang Sun); Shanghai Pudong New Area People’s Hospital, Shanghai (Qingke Bai); Tianjin Huahua Hospital, Tianjin (Lan Yu); Shanxi Provincial People’s Hospital, Xi’an, Shanxi (Minxia Guo); The First Affiliated Hospital of Xiamen University, Xiamen, Fujian (Qilin Ma); Xiangya Hospital Central-South University, Changsha, Hunan (Bo Xiao and Le Zhang); Chengdu No.3 People’s Hospital, Chengdu, Sichuan (Zhong Zhang); The First Affiliated Hospital of Jiujiang University, Guangzhou, Guangdong (Anding Xu); Guangzhou City Peoples First Hospital, Guangzhou, Guangdong (Xiaoping Pan); Guangdong Hospital of Traditional Chinese Medicine, Guangzhou, Guangdong (Yefeng Cai); Handan Central Hospital, Handan, Hebei (Juntao Li); Handan First People’s Hospital, Handan, Hebei (Yiping Wu and Jie Lin); Qingdao Municipal Hospital, Qingdao, Shandong (Chengming Xing); The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan (Yuming Xu); The First Affiliated Hospital of Zhejiang University, Hangzhou, Zhejiang (Benyan Luo); The First Affiliated Hospital of Wenzhou Medical College (the first provincial Wenzhou Hospital of Zhejiang), Wenzhou, Zhejiang (Rongyuan Zheng and Zhao Han); Affiliated Kailuan Hospital, North China Coal Medical College, Tangshan, Hebei (Xiaodong Yuan); The First Affiliated Hospital of Beifang Medical College, Zhangjiakou, Hebei (Wanlin Cui and Yuan Zou); Shijiazhuang Center Hospital, Shijiazhuang, Hebei (Heli Yan).

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### Disclosures

None.

### References

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