Lesion Patterns and Stroke Mechanisms in Concurrent Atherosclerosis of Intracranial and Extracranial Vessels

Bik Ling Man, MD; Yat Pang Fu, MD; Yin Yan Chan, MD; Wynnie Lam, MD; Andrew Chi Fai Hui, MD; Wai Hong Leung, MD; Vincent Mok, MD; Ka Sing Wong, MD

Background and Purpose—Concurrent atherosclerosis of the intracranial and extracranial cerebrovascular system is common in Asians. The typical lesion patterns and the mechanisms of stroke in patients with concurrent stenoses are unclear. This study aimed to determine these stroke features of such patients in Hong Kong.

Methods—We conducted a cross-sectional cohort study in a university hospital from January 2002 to December 2003. Consecutive Chinese patients with acute ischemic stroke underwent CT brain, MRI brain (with MR angiography and diffusion-weighted imaging sequences), and carotid duplex.

Results—In total, 251 patients were included in the analysis. Of these, 109 (43%) had concurrent stenoses. Patients who had concurrent stenoses, as compared with those without concurrent stenoses, had more symptomatic stenoses (84% versus 58%; OR, 4.0; 95% CI, 2.1 to 7.3; \( P < 0.001 \)), more concomitant perforating artery infarct, pial infarct, and borderzone infarct (14% versus 4%; OR, 3.6; 95% CI, 1.4 to 9.7; \( P = 0.007 \)), more multiple diffusion-weighted imaging lesions (55% versus 37%; OR, 2.1; 95% CI, 1.3 to 3.4; \( P = 0.005 \)), and more infarcts in the territory of the leptomeningeal branches of middle cerebral artery (26% versus 13%; OR, 2.2; 95% CI, 1.2 to 4.3; \( P = 0.01 \)). In multivariate regression analysis, smoking; prior stroke; the presence of concomitant pial infarct, pial infarct, and borderzone infarcts; multiple diffusion-weighted imaging lesions; and symptomatic stenoses were significantly associated with concurrent stenoses. Among patients with concurrent stenoses, those who had tandem lesions, as compared with those who had nontandem lesions, had more perforating artery infarct and borderzone infarcts (27% versus 8%; OR, 4.3; 95% CI, 0.9 to 19.8; \( P = 0.04 \)); more concomitant pial infarct, pial infarct, and borderzone infarcts (18% versus 0%; \( P = 0.02 \)), and more multiple diffusion-weighted imaging lesions (65% versus 23%; OR, 6.2; 95% CI, 2.2 to 17.2; \( P < 0.001 \)). Infarcts in the territory of middle cerebral artery leptomeningeal branches and symptomatic stenoses were more common in patients with tandem lesions.

Conclusions—Concomitant perforating artery infarct, pial infarct, and borderzone infarcts; multiple diffusion-weighted imaging lesions, and infarcts in the leptomeningeal branches of the middle cerebral artery were more common in patients with concurrent stenoses, especially those with tandem lesions. This study suggested that the combination of hemodynamic compromise attributable to concurrent stenoses and artery-to-artery embolization is a common stroke mechanism in these patients. (Stroke. 2009;40:3211-3215.)

Key Words: concurrent stenoses ■ lesion pattern ■ stroke

Concurrent atherosclerosis of the intracranial and extracranial cerebrovascular system is common in Asians\(^1\)\(^-\)\(^5\) and is associated with poor outcomes.\(^6\) The stroke mechanisms and the lesion patterns of patients with concurrent stenoses are unclear. Diffusion-weighted imaging (DWI) is the most sensitive diagnostic modality in detecting acute ischemic lesions.\(^7\)\(^,\)\(^8\) DWI has been used in several studies to explore the pathomechanism of ischemic stroke in patients with atherosclerotic middle cerebral artery (MCA) disease.\(^7\)\(^,\)\(^9\)\(^-\)\(^12\) However, data on concurrent lesions are scanty. This study aimed to use DWI to investigate the ischemic lesion patterns and stroke mechanisms in patients with concurrent stenoses.

Methods

Patients

This was a cross-sectional study conducted at the Prince of Wales Hospital in Hong Kong. The study was approved by local ethics committee. We recruited consecutive patients admitted with acute cerebral ischemia, including transient ischemic attack and cerebral...
infarct, within 7 days of symptom onset from January 2002 to December 2003. We excluded patients <18 years old, those who had atrial fibrillation, intracranial hemorrhage, vascular malformations, active cancer, myocardial infarction, liver and renal failure, prothrombotic tendencies such as underlying active lupus disease, antiphospholipid syndrome, factor C/S deficiency, and those who were pregnant. Those who were unfit for MRI study because of unstable medical conditions and claustrophobia were excluded.

All patients underwent CT and MRI of the brain with DWI to define the patterns of acute infarcts and vascular imaging including MR angiography of the brain and carotid duplex to look for vascular stenoses. Baseline data, including age, sex, medical history, and physical examination, were collected on admission. Vascular risk factors were determined, in particular any history of smoking, hypertension, diabetes mellitus, ischemic heart disease, and previous transient ischemic attack, or stroke. Blood biochemistry, full blood count, electrocardiogram, and chest x-ray were checked routinely.

**MRI, DWI, and MR Angiography**

All patients were scanned within 1 week of symptom onset with a Siemens Sonata (Erlanger, Germany) with a head coil. The 3-dimensional time-of-flight images were acquired with a repetition time of 40 ms, time to echo of 7.15 ms, flip angle of 25°, 20-cm field of view, 192×512 acquisition matrices, and one signal average for a total imaging time of 5 minutes 35 seconds. Acute infarcts on DWI were diagnosed when these lesions were shown to be hyperintense on the DWI integrated for the 3 diffusion sensitivity directions and hypointense on the apparent diffusion coefficient map. For images showing motion artifact in one diffusion sensitivity direction, infarct or subacute infarct was diagnosed only if the lesion showed all of the following features: (1) it had a much higher signal than on the image map with b=0; (2) it was not caused by normal anisotropy of diffusion or artifact; and (3) it was seen on the DWIs in both of the remaining orthogonal diffusion sensitivity directions. DWI lesion patterns were analyzed by an investigator (W.L.) who was blinded to clinical data. The topography of ischemic lesions was determined using published templates. The vascular territories were divided into perforator, pial, and borderzone regions. Perforating artery infarct (PAI) included striatocapsular infarct or perforating vessel infarct of the cerebral arteries. Pial infarct (PI) was defined as an infarct occurring in the vascular territories supplied by the main leptomeningeal branches of the cerebral arteries. Borderzone (BZ) infarcts were defined as anterior or posterior cortical BZ or internal BZ. Multiple DWI lesions referred to multiple noncontiguous hyperintense lesions occurring in the vascular territories described. DWI lesions were allocated to one of the following 10 patterns (Figure): single lesion—(1) small PAI (diameter <2 cm); (2) large PAI (diameter >2 cm); (3) PI; (4) large territorial infarct; (5) BZ infarct; and multiple lesions—(6) PAI and PI; (7) PAI, PI, and BZ; (8) PAI and BZ; (9) PI and PI; (10) and PI and BZ. The MR angiography films were read by experienced neuroradiologists (W.L.) who was blinded to the results of the clinical examination. Extracranial stenosis was graded according to the following criteria: Grade 1, normal or mild stenosis (0% to 29% diameter stenosis); Grade 2, moderate stenosis (30% to 69% diameter stenosis); and Grade 3, severe stenosis (70% to 100% diameter stenosis). The percentage of stenosis of MCA and other intracranial vessels was measured by visual inspection.

**Carotid Duplex**

For the Duplex ultrasound examination of the extracranial carotid arteries, we used a Philips SD800 ultrasound machine and a 7.5-MHz transducer. Extracranial stenosis was graded as mild (<30%), moderate (30% to 69%), and severe (70% to 99%). The diagnostic criteria for 70% stenosis of the internal carotid artery required a peak systolic velocity ratio of 2.4. These diagnostic criteria in the neurovascular laboratory were based on laboratory references, which had a quality assurance program with supplementary angiographic studies.

Concurrent stenoses were defined as presence of any degree of stenoses in both extracranial and intracranial vessels, including stenoses in both extracranial and intracranial vessels, including concurrent stenoses were defined as presence of any degree of stenoses in both extracranial and intracranial vessels, including...
PAI was less frequent (35%). Patients who had concurrent stenoses, as compared with those without concurrent stenoses, had more concomitant PAI, PI, and BZ infarcts (14% versus 4%; OR, 3.6; 95% CI, 1.4 to 9.7; $P=0.007$) and more multiple DWI lesions (53% versus 37%; OR, 2.1; 95% CI, 1.2 to 3.4; $P=0.005$). In contrast, single small PAI was more common in patients with nonconcurrent stenoses (51% versus 35%; OR, 1.9; 95% CI, 1.2 to 3.2; $P=0.01$; Figure; Table 2).

### Vascular Territory of Stroke

Infarcts in the territory of the MCA leptomeningeal branches were more common in patients with concurrent stenoses (26% versus 13%; OR, 2.2; 95% CI, 1.2 to 4.3; $P=0.01$), but MCA perforating branch infarcts were more common in patients with nonconcurrent stenoses (47% versus 35%; OR, 1.7; 95% CI, 1.0 to 2.8; $P=0.05$; Table 3).

After adjustment of age and sex, univariate linear regression analysis showed that smoking ($R^2=0.302, P<0.0001$); prior stroke ($R^2=0.046, P=0.01$); the presence of concomitant PAI, PI, and BZ infarcts ($R^2=0.044, P=0.01$); multiple DWI lesions ($R^2=0.044, P=0.01$); and symptomatic stenoses ($R^2=0.12, P<0.0001$) were associated with concurrent stenoses. In multivariate regression analysis, all these factors were significantly associated with concurrent stenoses.

### Tandem Versus Nontandem Lesions

Among 109 patients with concurrent stenoses, 83 (76%) had tandem lesions. Symptomatic stenoses occurred more frequently in patients with tandem lesions than those with nontandem lesions (89% versus 69%; OR, 3.7; 95% CI, 1.2 to 10.8; $P=0.02$). Most patients (64%) with tandem lesions had multiple concomitant infarcts and almost half of them (49%) had BZ infarcts in any combination. Infarcts in the territory of MCA leptomeningeal branches were more common in patients with tandem lesions than those with nontandem lesions (33% versus 4%; OR, 12.1; 95% CI, 1.6 to 93.7; $P=0.003$). In contrast, single small PAI was the most common infarct pattern in patients with nontandem lesions (73% versus 23%; $P=0.005$).
Severity of Tandem Lesions
Among 83 patients with tandem lesions, 34% had nonsignificant (<70%) intracranial and extracranial stenoses, 48% had a significant (>70%) stenosis in one vessel, and 18% had significant stenoses in both vessels. Patients who had significant stenoses of both vessels as compared with those who had no significant stenosis; had more concomitant PAI, PI, and BZ infarcts (47% versus 7%; OR, 11.4; 95% CI, 2.0 to 66.1; \( P = 0.002 \)) and more multiple DWI lesions (93% versus 50%; OR, 14.0; 95% CI, 1.6 to 121.4; \( P = 0.004 \)). Single small PAI was more common in patients who had no significant stenosis than those who had significant stenoses of both tandem lesions (36% versus 0%, \( P = 0.01 \)).

Discussion
Concurrent atherosclerosis of intracranial and extracranial vessels is common in Asian.\(^2\,^{14-17}\) It is associated with higher mortality and risks of recurrent cerebrovascular events.\(^3\,\,6\) The underlying mechanisms are thought to be burden of atherosclerosis and hemodynamic compromise attributable to concurrent stenoses of intracranial and extracranial arteries.\(^3\,\,5\) However, the exact mechanism remains unclear. DWI has been used for exploration of stroke mechanisms in previous studies of internal carotid artery, MCA stenosis, and BZ infarcts.\(^7\,\,10\,\,12\,\,18\) Our study was the first MRI study using DWI to define stroke mechanisms in concurrent stenoses. Concerning the risk factor profiles, patients with concurrent stenoses were older and more likely hypertensive. There were nonsignificant trends for patients with concurrent stenoses to have other vascular risk factors, including diabetes, hyperlipidemia, smoking, and more prior stroke. Our data agreed with previous studies, which suggest a possible role for diabetes mellitus, metabolic syndrome, and other cardiovascular risk factors in the development of larger artery disease.\(^3\,\,4\,\,9\,\,20\)

Concomitant PAI, PI, and BZ infarcts were more common in patients with concurrent stenoses, whereas a single small PAI was more common in patients with nonconcurrent stenosis. This can be accounted by the difference in the vascular territory involved because patients with concurrent stenoses had more infarcts in the leptomeningeal branches of MCA, whereas patients without concurrent stenosis had more infarcts in the perforating branches of the MCA. A previous study suggested that internal BZ infarcts are caused mainly by hemodynamic compromise.\(^8\) We found that pure BZ infarct was rare (only 0.8% of the cohort). Most BZ infarcts were accompanied by multiple concomitant infarcts. Most of the patients with concurrent stenoses, especially those who had severe tandem lesions, got concomitant PAI, PI, and BZ infarcts.
infarcts. The multiple DWI lesions may be markers of embolism. Our findings suggested that the combination of hemodynamic compromise attributable to concurrent stenoses and artery-to-artery embolization is a common stroke mechanism in concurrent stenoses. The results of an autopsy series revealed that embolic materials were observed frequently within SZ areas that contained infarcts.11,22 Caplan and Hennerici had postulated that the combination of embolism and hypoperfusion can lead to impaired clearance of emboli and produce infarcts in SZ where perfusion is most impaired, especially in patients with severe internal carotid stenosis.23 A previous study also suggested that patients with high-grade stenosis or occlusion of MCA have a higher risk of artery-to-artery embolization than those with milder stenosis.10 There was an experimentally proven case of BZ infarct induced by microemboli.24 Another study had shown that the number of microembolic signals on transcranial Doppler predicted the number of acute infarcts on DWI.12 All that the number of microembolic signals on transcranial Doppler is a common stroke mechanism in patients with concurrent stenoses.

Strengths and Limitations

The strength of this study included that, first, MRI and MR angiography, which are safe and noninvasive imaging, were used to evaluate stroke mechanism and vascular etiology. Second, a relatively large number of patients were recruited. Limitations of this study included, first, the samples were hospital-based and might not be representative of all patients with concurrent stenoses. Second, differentiating multiple PIs from multiple SZ infarcts can sometimes be difficult. Third, conventional cerebral angiogram, which is the “gold standard” to confirm the diagnosis of occlusive disease, was not used. However, it would be impossible to conduct a large study with catheter conventional angiography because of the cost and risks associated with this procedure.

Conclusion

Infarcts in the leptomeningeal branches of MCA; concomitant PAI, PI, and SZ infarcts as well as multiple DWI lesions were significantly associated with concurrent stenoses. This study suggested that the combination of hemodynamic compromise attributable to concurrent stenoses and artery-to-artery embolization is a common stroke mechanism in patients with concurrent stenoses. A more precise elucidation of the pathophysiologic mechanisms leading to concurrent stenoses helps to plan future clinical trials for prevention and treatment of this disorder.

Disclosure

None.

References

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