

CHINESE MEDICAL SCIENCES JOURNAL

ORIGINAL ARTICLE

Relationship between Carotid Atherosclerosis and Cerebral Infarction

Guang-wen Li, Guan-yi Zheng*, Jin-guo Li, and Xu-dong Sun

Department of Geriatrics, Union Hospital, Fujian Medical University,
Fuzhou 350001, China

Key words: carotid atherosclerosis; cerebral infarction; intima-media thickness; color Doppler ultrasonography

Objective To study the relationship between carotid atherosclerosis and cerebral infarction (CI).

Methods Between November 2008 and March 2009, 147 CI patients (CI group) and 48 patients with non-cerebrovascular diseases (control group) were enrolled from inpatients of Neurology Department of our hospital. The diagnostic criterion of thickened carotid intima was set as $1.0 \text{ mm} \leq \text{intima-media thickness (IMT)} < 1.5 \text{ mm}$ and that of carotid plaque was as $\text{IMT} \geq 1.5 \text{ mm}$. Carotid atherosclerosis was divided into three levels: normal intima, thickened intima, and plaque formation. The color Doppler ultrasonography data of carotid arteries in all patients were analyzed and the severity of carotid atherosclerosis was compared between the two groups.

Results In the CI group, 36 (24.5%) patients had normal carotid intima, 22 (15.0%) had thickened carotid intima, and 89 (60.5%) had carotid plaque. In the control group, 22 (45.8%) patients had normal carotid intima, 4 (8.3%) had thickened carotid intima, and 22 (45.8%) had carotid plaque. The severity of carotid atherosclerosis in the CI group was higher than that in the control group ($P=0.022$). There was significant difference in the constitution of carotid plaque between the two groups ($P=0.001$); the CI group mainly had the soft plaque (55/89, 61.8%), whereas the control group mainly had the hard plaque (17/22, 77.3%). The first three common locations of carotid plaque in both groups were carotid bifurcation (CI group: 73.7%; control group: 64.1%), common carotid artery (CI group: 20.4%; control group: 25.6%), and internal carotid artery (CI group: 5.9%; control group: 10.3%). The location of carotid plaque between the two groups was not significantly different ($P=0.438$). There was no difference in the carotid inner diameter or resistance index between the two groups ($P>0.05$).

Conclusions Carotid atherosclerosis is to some extent able to reveal the atherosclerotic condition of cerebral arteries and act as an important predictor for the risk of CI. The color Doppler ultrasonography of carotid arteries can provide a convenient way for the prevention and treatment of CI.

Chin Med Sci J 2010; 25(1):32-37.

CEREBROVASCULAR diseases seriously threaten human health. Following malignant tumors, stroke is the second leading cause of death in Chinese population and one of the most important risk factors for disability.¹ Carotid atherosclerosis (CAS) is one of the major risk factors for cerebrovascular diseases, especially ischemic cerebrovascular diseases. The characteristics of carotid plaque are closely related to the type of ischemic cerebrovascular diseases.^{2,3} The Asymptomatic Carotid Atherosclerosis Study (ACAS) showed that carotid endarterectomy reduced the aggregate risk over 5 years for ipsilateral ischemic stroke by 53% compared with medical therapy (aspirin) (11.0% vs. 5.1%) in patients with asymptomatic carotid stenosis of 60% or greater reduction in diameter.⁴ Therefore, to determine whether ischemic stroke patients suffer from CAS is of important clinical significance. For patients with ischemic stroke, carotid ultrasonography can measure the degree of carotid stenosis, intima-media thickness (IMT), and plaques, providing the basis for evaluating the prognosis of cerebral infarction (CI) and effect of drug treatment.⁵

The present study compared the severity of CAS, characteristics and location of plaques, and inner diameter of carotid arteries between CI patients and patients with non-cerebrovascular diseases based on the results of carotid color Doppler ultrasonography, with the aim of revealing the relationship between CAS and CI.

PATIENTS AND METHODS

Patients

Between November 2008 and March 2009, 147 CI patients (CI group) and 48 patients with non-cerebrovascular diseases (control group) were enrolled from inpatients of Neurology Department of Union Hospital affiliated to Fujian Medical University. The CI group included 34 patients with atherosclerotic CI and 113 patients with lacunar infarction. The diagnostic criteria for CI were in accordance with the revised diagnostic criteria of 1995 Fourth National Conference for Cerebrovascular Diseases.⁶ All cases were confirmed by cranial magnetic resonance imaging (MRI) or computed tomography (CT) scan. The exclusive criteria were: (1) patients with cerebral hemorrhage; (2) patients with cardiogenic cerebral embolism (such as atrial fibrillation and rheumatic heart disease); (3) patients with cerebral arteritis-induced CI.

Color Doppler ultrasonography

Color Doppler ultrasonic diagnostic equipment (Vivid 7, GE, USA) was applied in this study. The measurement was

carried out when the condition of the CI patients was steady, roughly one week after onset of the disease. Each patient was asked to lie in the supine position in a dark room. A pillow was put under the shoulder of the patient, with his/her head extending back and towards the contralateral side. The linear array transducer with frequency of 5-10 MHz was adopted. First, the probe was placed at the cervical root, scanning along the lateral margin of sternocleidomastoid longitudinally to show the proximal, middle, and distal segments of common carotid artery (CCA), carotid bifurcation (BIF), the beginning of internal carotid artery (ICA), and the external carotid artery (ECA). Then the probe was rotated by 90° to scan along the cross section of carotid arteries. Two-dimensional ultrasound was used to observe the structure of arterial wall, morphology and location of plaques, measure the size of plaques, and determine the natures of these plaques (soft or hard). The inner diameter of CCA was measured at the site 2.0 cm proximal to the BIF, the inner diameter of ICA was measured at the site 1.0 cm distal to the BIF, and the IMT was measured at the posterior wall of CCA proximal to the bulb. The Doppler spectrum was used to measure peak velocity (maximum velocity, V_{max}) and end-diastolic velocity (EDV, V_{min}). Mean velocity (V_{mean}) and resistance index (RI) were calculated with the following formulas: $V_{mean} = \text{integration of flow velocity} / \text{cardiac cycle time}$; $RI = (V_{max} - V_{min}) / V_{mean}$.⁷

CAS severity evaluation

The IMT and carotid plaque were applied as CAS severity index. IMT is the distance between the intima-lumen interface and the media-adventitia interface, which displays as the "dual-line sign" in the two-dimensional longitudinal ultrasound image of the carotid wall, that is, two parallel hyperechogenic lines separated by a hypoechoic line.⁸ The diagnostic criterion of thickened carotid intima was set as $1.0 \text{ mm} \leq \text{IMT} < 1.5 \text{ mm}$; and the diagnostic criterion of carotid plaque was: a focal structure that encroaches into the arterial lumen for at least 0.5 mm or 50% of the surrounding IMT value or demonstrates a thickness $\geq 1.5 \text{ mm}$ at any segment of the carotid.⁹ According to the characteristics of ultrasound echo, the carotid plaques were divided into hard plaques (displayed as hyperecho or with acoustic shadowing) and soft plaques (displayed as isoecho or hypoecho).¹⁰

Statistical analysis

The SPSS 16.0 statistical software was applied for statistical analysis. The univariate numerical data with orderly response variable was tested by Wilcoxon rank sum test; and the constitution of two independent samples was tested by fourfold table χ^2 test and $2 \times C$ table χ^2 test. The

measurement data were expressed as mean $\pm$ SD, and two-sample *t* test was applied when two independent samples' variances were homogenous. A value of $P<0.05$ indicated significant difference.

RESULTS

Baseline characteristics

The CI group involved 83 males and 64 females, with an average age of 66.96 (range, 37-91) years. The control group involved 26 males and 22 females, with an average age of 64.27 (range, 40-83) years. There was no difference in gender or age between the two groups (both $P>0.05$). The prevalence of hypertension was higher in the CI group than the control group ($P=0.012$). The prevalence of diabetes was not significantly different between the two groups ($P>0.05$) (Table 1).

Comparison of CAS severity between two groups

In the CI group, 22 (15.0%) patients had thickened carotid intima and 89 (60.5%) had carotid plaque. In the control group, 4 (8.3%) patients had thickened carotid intima and 22 (45.8%) had carotid plaque. The severity of CAS in the CI group was significantly higher than that in the control group ($P=0.022$) (Table 2).

Comparison of constitution of carotid plaques between two groups

There was significant difference in the constitution of carotid plaque between the two groups ($\chi^2=10.842$, $P=0.001$). The CI group mainly had soft plaques (61.8%), whereas the control group mainly had hard plaques (77.3%) (Table 2).

Comparison of location of carotid plaques between two groups

The first three common locations of carotid plaque in both groups were BIF, CCA, and ICA. The plaques can be single and bilateral. Among 89 cases with carotid plaques in the CI group, 71 cases had plaques existed in one of the above three sites; 15 cases had plaques existed in two of the three sites, and 3 cases had plaques existed in all of the three sites. The total number of plaques in the CI group was 152. Among 22 cases with carotid plaques in the control group, 18 cases had plaques existed in one of the above three sites, and 4 cases had plaques existed in two of the three sites. The total number of plaques in the control group was 39. There was no significant difference in the location of carotid plaques between the two groups ($P=0.438$) (Table 2).

Comparison of inner diameters and resistance indices of carotid arteries between two groups

The inner diameters of CCA and ICA were not significantly different between two groups (all $P>0.05$). Meanwhile, the resistance indices of CCA and ICA were not significantly different between two groups (all $P>0.05$) (Table 3).

Table 1. Comparison of baseline characteristics between CI group and control group

Group	Male, <i>n</i> (%)	Age (yr), mean $\pm$ SD	Hypertension, <i>n</i> (%)	Diabetes, <i>n</i> (%)
Control group (<i>n</i> =48)	26 (43.54%)	64.27 $\pm$ 8.93	23 (47.92%)	10 (20.83%)
CI group (<i>n</i> =147)	83 (56.46%)	66.96 $\pm$ 9.78	100 (68.03%)	37 (25.17%)
<i>t</i> or χ^2	0.077	1.687	6.284	0.372
<i>P</i>	0.781	0.093	0.012	0.542

CI: cerebral infarction.

Table 2. Comparison of CAS severity, constitution of carotid plaques, and location of carotid plaques between CI group and control group

Item	Control group	CI group	<i>Z</i> or χ^2	<i>P</i>
Carotid intima			-2.288	0.022
Normal	22 (45.8%)	36 (24.5%)		
Thickened	4 (8.3%)	22 (15.0%)		
Plaque	22 (45.8%)	89 (60.5%)		
Total	48	147		
Characteristics of plaques			10.842	0.001
Hard	17 (77.3%)	34 (38.2%)		
Soft	5 (22.7%)	55 (61.8%)		
Total	22	89		
Location of carotid plaques			1.652	0.438
BIF	25 (64.1%)	112 (73.7%)		
CCA	10 (25.6%)	31 (20.4%)		
ICA	4 (10.3%)	9 (5.9%)		
Total	39	152		

CAS: carotid atherosclerosis; BIF: carotid bifurcation; CCA: common carotid artery; ICA: internal carotid artery.

Table 3. Comparison of inner diameters and resistance indices of carotid arteries between CI group and control group

Item	Control group	CI group	<i>t</i>	<i>P</i>
Inner diameter (mm)				
LCCA	6.5 ±0.8	6.4 ±0.8	0.886	0.376
LICA	5.2 ±0.7	5.1 ±0.7	0.611	0.542
RCCA	6.5 ±0.8	6.3 ±0.8	2.821	0.185
RICA	5.2 ±0.7	5.0 ±0.7	1.735	0.084
Resistance indices				
LCCA	0.75±0.07	0.77±0.10	0.947	0.345
LICA	0.65±0.07	0.67±0.08	1.632	0.104
RCCA	0.75±0.07	0.77±0.10	1.128	0.261
RICA	0.65±0.09	0.67±0.11	1.025	0.307

LCCA: left common carotid artery; LICA: left internal carotid artery; RCCA: right common carotid artery; RICA: right internal carotid artery.

DISCUSSION

CI, mainly caused by cerebral atherosclerosis, is common in the elderly. Therefore, more and more attention should be paid to the diagnosis and treatment of atherosclerotic CI. However, the condition of cerebral atherosclerosis is hard to obtain due to the location of the cerebral arteries. Thus, it is important to find an indicator of the condition of cerebral atherosclerosis. This study showed that the CAS severity of the CI group was significantly higher than the control group, suggesting that as part of systemic atherosclerosis, CAS could be an indicator that reflects the condition of cerebral atherosclerosis. Nagai et al¹¹ reported that the sensitivity and specificity of carotid plaque predicting the cardio- and cerebrovascular diseases was 84% and 79%, respectively. Therefore, the diagnosis of CAS in clinic is attracting more and more attention.

Atherosclerosis is the important pathological basis of cardio- and cerebrovascular diseases, and it takes a few decades from atherosclerosis genesis to cardio- and cerebrovascular diseases occurrence. In fact, the pathological changes may begin from adolescence or even childhood, but the clinical symptoms only manifest in the elderly. The present study also showed that different degrees of CAS existed in both the CI group and the control group.

About 70%-85% of blood in cerebral circulation is supplied by carotid arteries. The CAS can also lead to CI directly because the carotid artery is one of the upstream of the cerebral arteries. However, it was reported that only about 10% of all CI directly result from CAS.¹² CAS results in CI through the following mechanisms: (1) the atherosclerotic plaque enlarges and obstructs the carotid directly; (2) the embolus coming from the ulceration or rupture of plaque results in embolization of the distal arteries;⁸ (3) the thrombus formed by the coagulation factors and platelet activation on the rough surface of the plaques

blocks the carotid.¹³

The study found that the CI group mainly had the soft plaques (61.8%), whereas the control group mainly had the hard plaques (77.3%). There was significant difference between the two groups in the constitution of carotid plaque ($P=0.001$). It is generally believed that arterial stenosis of <50% reduction in diameter will not cause significant hemodynamic abnormality. In recent years, some study found that significantly narrow lumen resulting from carotid plaque is not common. Zhang et al¹⁴ reported that carotid stenosis of >50% reduction in diameter with hemodynamic significance existed in only 13.5% of CI patients, while the prevalence of carotid plaque was 81.2%. Therefore, CI was correlated not only with carotid lumen stenosis, but also with the characteristic of carotid plaque more closely.¹⁵ The hypoechoic soft plaque, containing more lipids with loose texture, is vulnerable to the hemodynamic effects and is likely to rupture, shed, hemorrhage, and form the thrombus, therefore is the main cause of CI. Whereas the hyperechoic hard plaque, constituted mainly by fibrous tissue, has more stability due to the surface calcification and it is not prone to broke or drop, therefore having less relation to CI.¹⁶

The present study found that the first three common locations of carotid plaque in the CI group and the control group were BIF (73.68%; 64.10%), CCA (20.39%, 25.64%), and ICA (5.92%; 10.26%), with no difference between the two groups. It was consistent with Hayashi et al's report¹⁷ that carotid plaque was mostly seen at BIF, followed by the CCA trunk and the original segment of ICA. This might be related to hemodynamics. The fundamental research has confirmed that when blood flows into the anatomical expansion areas, such as carotid BIF, or when the surface is not smooth, turbulence would form. Because of the pressure increase in the center of the turbulence, the erythrocyte is prone to be injured, releasing out procoagulant substances such as adenosine diphosphate (ADP) to promote platelet aggregation and coagulation, forming

micro-thrombosis which organizes as plaque eventually. In addition, the high-frequency oscillation of turbulent flow slows the blood velocity, increases the local shear stress, injures the endothelial cells, and gradually develops into atherosclerotic plaque.

The present study showed that the inner diameters of CCA and ICA of the CI group were slightly smaller than the control group, but the differences were not statistically significant. It was consistent with Fang et al's study,¹⁸ in which no difference was found in the inner diameters of carotid arteries between the CAS group and the control group. In that study, there were only 3 cases with at least one carotid stenosis $\geq 50\%$; 17 cases with at least one stenosis $\geq 20\%$; most cases showed only carotid plaque formation but no significant stenosis. The carotid stenosis of the CI group in the present study may be similar to that. Turkenburg et al¹⁹ reported that after the first onset of symptoms, 12%-13% of the patients with severe carotid stenosis bore the risk of complete stroke in one day and up to 30%-35% in five days. Handa et al²⁰ held the view that the risk of recurrence of CI in patients with severe carotid stenosis was 21 folds higher than patients without carotid stenosis. The results of multi-center prospective studies showed that carotid endarterectomy at an early stage could significantly reduce the risk of the occurrence and recurrence of CI in patients with serious CAS and stenosis.²¹

Bradshaw et al²² found that about 5%-7% of females and 7%-10% of males have carotid stenosis $> 50\%$ in a population older than 65 years. CAS from intima thickens to plaque formation or even lumen stenosis, and the blood flow velocity increases, accompanied by the remodeling of atherosclerotic arteries. At the early stage of atherosclerosis, the artery expands outwards compensatorily when vessel wall thickens in order to maintain the inner diameter, which is called the "positive remodeling". When the lesion develops, the artery can no longer expand compensatorily and the plaque encroaches into the lumen resulting in lumen stenosis or even occlusion, this is called the "negative remodeling".²³ This was consistent with the conclusion drawn by Glagov et al²⁴ that the expansion of artery was a kind of vascular remodeling adapting to the progress of atherosclerosis, rather than a degenerative change with increasing age. Glagovs et al²⁴ found in the study on the relationship between lumen area and plaque area in coronary atherosclerosis that the lumen area did not decrease in relation to the percentage of stenosis (lesion area/internal elastic lamina area) for values between zero and 40 percent but did diminish markedly and was in close relation to the percentage of stenosis for values above 40

percent.

The results of our study also showed that the resistance indices of CCA and ICA of the CI group were slightly larger than the control group, but the difference was not statistically significant. This was also consistent with the results of the study by Fang et al.¹⁸ According to the formula of resistance index: $RI = (V_{\max} - V_{\min}) / V_{\text{mean}}$, RI was correlated with the blood flow velocity, and the blood flow velocity was correlated with the stenosis degree. The narrower the lumen, the greater the blood flow velocity, but the flow velocity would increase significantly only when the lumen narrowed severely, and resulting in significant RI increase.²⁵ However, in the present study, severe carotid stenosis in the CI group was scarce, and the case number (48) in the control group was small, so it could not reveal difference between the two groups.

There were some limitations in this study that needed to be pointed out. Firstly, the measurement depended on the subjects' consciousness greatly, therefore the measurement data varied greater among different measuring times than an auto-measuring software could have achieved. Secondly, in view of the safety of the CI patients, the measurement was carried out when the condition of the patients was steady, roughly one week after the onset of the disease, therefore the lesion state at the measurement might be different from the state at the onset of the disease.

The imaging techniques of carotid arteries, including digital subtraction angiography (DSA), computed tomography angiography (CTA), and magnetic resonance angiography (MRA), all have limitations. They may be traumatic, expensive, or have contraindications and complications. The carotid color Doppler ultrasound imaging, however, is low-cost, non-invasive, and has significant diagnostic value. It can show the structure of carotid wall clearly, detect the atherosclerotic plaques and thrombi, identify soft plaque and hard plaque, and determine the degree of carotid stenosis accurately, thus it has important clinical significance for understanding the condition of cerebral atherosclerotic lesions and predicting the occurrence and recurrence of CI.

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