Risk Factors of Carotid Stenosis in First-Ever Ischemic Stroke in Taiwan: A Hospital-based Study

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Abstract-

Objective: The aim of this study is to identify the risk factors of extracranial carotid atherosclerosis in patients with first-ever ischemic stroke.

Material and methods: A total of 541 consecutive first-ever ischemic stroke patients were enrolled in the present study. We examined clinical and laboratory factors that were potentially relevant to extracranial carotid artery atherosclerosis. The degree of carotid stenosis was diagnosed based on B-mode ultrasonography.

Results: The sample contained 325 men and 216 women. Among these patients, 80% had a < 50% carotid stenosis and 20% had a ≥ 50% carotid stenosis. Multiple logistic regression analysis revealed that age (odds ratio = 2.15, 95% CI = 1.06~1.11, P < 0.001) and smoking (odds ratio = 1.52, 95% CI = 1.17~3.54, P = 0.012) were significantly associated with ≥ 50% carotid stenosis.

Conclusions: In the present study, age and smoking are found to be the independent risk factors for carotid atherosclerosis. The identification of these risk factors may improve our knowledge in the primary prevention of ischemic stroke in Taiwan.

Key Words: Risk factors, Carotid atherosclerosis, First-ever stroke

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INTRODUCTION

In Taiwan, cerebrovascular diseases (CVD) have been the second leading cause of death over the past two decades[1]. Atherosclerosis has been regarded as an important etiologic factor of ischemic CVD[2-5]. Recent studies have shown that severe carotid atherosclerotic stenosis is associated with an increased risk of ischemic stroke[6-9].

Risk factors of carotid atherosclerosis have been evaluated in previous studies[4,10-16]; and age, gender, hypertension, diabetes, smoking and hyperlipidemia

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were correlated with extracranial carotid atherosclerosis[4,13-15]. However, the results appeared inconclusive in some studies, and few studies have investigated the risk factors of carotid atherosclerosis in patients with first-ever ischemic stroke. In this study, we attempted to define modifiable cerebrovascular risk factors that were associated with the severity of carotid atherosclerosis. Identification of these risk factors may provide new insights into the potential mechanisms promoting extracranial artery atherosclerosis and will be helpful in the prevention of carotid artery disease.

MATERIALS AND METHODS

We retrospectively reviewed the records of all stroke patients hospitalized to the 2nd Department of Neurology in our hospital from June 2002 to May 2003. For those patients with first-ever ischemic stroke admitted within ten days after te onset of stroke were included. This study excluded patients with a previous history of stroke (> 10 days), transient ischemic attack, venous infarction and those with ischemic strokes caused by trauma, cardiac surgery, and vasospasm after subarachnoid hemorrhage. All patients received a chest x-ray, electrocardiography (ECG), complete blood count (hemoglobin, hematocrit, platelet, leukocyte), and blood glucose, electrolytes, triglyceride, and total cholesterol tests. Brain computed tomography with or without magnetic resonance imaging was performed in all patients to define the territories of infarction and to exclude cerebral hemorrhage.

The medical history and risk factors of stroke in each patient were obtained from the chart record, and if there was any uncertainty, further inquiry was made by telephone retrospectively. Hypertension was defined as (1) the patient was previously diagnosed with hypertension by a clinician or (2) systolic blood pressure was ≥ 140 mmHg and/or diastolic blood pressure was ≥ 90 mmHg on 2 different occasions measured at least 2 weeks after the acute stage depending on the severity of stroke. Patients were considered diabetic if they were being treated with oral hypoglycemic agents or insulin, and/or two fasting plasma glucose levels ≥ 126 mg per dL (7.0 mmol per L)[17]. Current smokers were those who smoked ≥ 10 cigarettes per day for more than 6 months before the stroke. Alcohol consumption was defined as the patient regularly drank alcohol ≥ 30 grams per day or ≥ 210 grams per week for more than 6 months before the stroke. Hyperlipidemia was defined when the fasting blood cholesterol level was ≥ 200 mg/dL and/or triglyceride level was ≥ 150 mg/dL at admission.

The Sequoia (Acuson C256, U.S.A.) ultrasonography, combining a high resolution real-time 7.5 MHz B-mode imaging system for morphologic investigation and a pulsed-wave Doppler spectrum analyzer for carotid flow detection, was used in this study. Direct visualization on B-mode and Doppler flow analysis of the common, internal and external carotid arteries were carried out with longitudinal (anterioposterior, posterioanterior, lateral) and transverse views. The B-mode diagnostic criteria for carotid artery stenosis was based on a previous report from our laboratory[18] and the maximum percentage stenosis was computed by measuring the residual lumen diameter (A) and the original diameter (B) at the site of maximal stenosis and dividing the difference by the original diameter (B-A/B(100%) with or without Doppler flow change. Significant stenosis was defined as (50% diameter stenosis[19]. A total of 591 consecutive first-ever ischemic stroke patients (20 to 96 years old, 64.7% of a total of 914 ischemic stroke patients) were investigated. Of the 50 patients without ultrasound examination, 24 died during the acute stage of their strokes, 7 suffered cardioembolic stroke, 3 were severely dependent in their daily activity, and 16 had unknown reasons. The rest 541 patients received ultrasound (extracranial 4-vessel and transcranial) examinations. Among these 541 patients, 516 (95.4%) had vascular examination within 2 weeks after the onset of stroke.

SPSS 10.0 software was used for statistical analysis. Continuous variables were expressed as mean±SD, and discrete variables were expressed as percentages. Comparisons between patients with and without significant stenosis were performed with two-tailed Student's t-test for continuous variables and with chi-square test (or Fisher's exact test whenever appropriate) for discrete variables. Stepwise multiple logistic regression analysis was performed to assess the association between significant carotid stenosis and risk factors adjusting for potential confounders. A Pvalue < 0.05 was regarded as statistically significant.

RESULTS

Among the 541 patients receiving ultrasound examinations (mean age: 64.96±12.64 years), there were 325 men (60.1%) and 216 women (39.9%). The prevalence of risk factors in age-specific and sex-specific groups is demonstrated in Table 1. The prevalence of hypertension was higher in the older-age group (≥ 65 years) compared with the younger-age group (75.8% vs. 60.6%, χ^2 test, P < 0.001). The prevalence of smoking was significantly higher in male than in female (56.3% vs. 4.2%, χ^2 test, P < 0.001). The findings of ultrasound examinations in the 541 patients are presented in Table 2.

The patients were divided into 2 groups according to the severity of carotid artery stenosis. There were 433 patients (80.0%) with ≥ 50% carotid artery stenosis and 108 patients (20.0%) with ≥ 50% carotid artery stenosis. The clinical characteristics of patients with < 50% and ≥ 50% carotid stenosis are shown in Table 3. Subjects with ≥ 50% carotid stenosis were significantly older (71.6±9.0 years) than patients with < 50% carotid stenosis (63.3±12.9 years) (two-sample t test, P < 0.001). Men were more likely to have ≥ 50% carotid stenosis than to have < 50% carotid stenosis (73.1 % vs. 56.8%, χ^2 test, P = 0.003). Smoking was more frequently seen in patients with ≥ 50% carotid stenosis than those with < 50% carotid stenosis (51.9% vs. 31.4%, χ^2 test, P < 0.001). No significant differences in the distribution of hypertension, diabetes, alcohol consumption, hypercholesterolemia and hypertriglyceridemia were found between these two groups of carotid stenosis.

However, multivariate logistic regression analyses showed that age and current smoking were significantly associated with ≥ 50% carotid stenosis (age in each 10 years, OR = 2.15, 95% CI= 1.69~2.74, P < 0.001; current smoking, OR= 1.52, 95% CI = 1.30~1.89, P = 0.018) (Table 3).

Table 1. *Characteristics of 541 patients with first-ever ischemic stroke*

Total (n = 541)	Age < 65 years (n = 231)	Age ≥ 65 years (n = 310)	P value	Men (n = 325)	Women (n = 216)	P value
Age, (mean±SD)	53.0 ± 9.0	73.8 ± 5.8	< 0.001†	64.3 ± 12.3	65.9 ± 13.1	0.14
Male, %	64.5	56.8	0.08	-	-	-
Smoking, %	39.8	32.7	0.08	56.3	4.2	< 0.001†
Hypertension, %	60.6	75.8	< 0.001†	66.5	73.6	0.10
Diabetes, %	31.6	38.4	0.12	31.1	42.1	0.01*
Cholesterol ≥ 200mg/dL, %	46.1	34.1	0.01*	36.5	43.3	0.14
Triglyceride ≥ 150 mg/dL, %	45.9	36.4	0.03*	34.6	49.3	0.001†

The statistics was done by χ^2 test. *P < 0.05; †P<0.01.

Table 2. *Carotid ultrasound findings in 541 patients with first-ever ischemic stroke*

Stenosis / No. (%)	L CCA	L ICA	L ECA	L VA	R CCA	R ICA	R ECA	R VA
0%	308 (56.9)	401 (74.1)	523 (96.7)	539 (99.4)	305 (56.4)	421 (77.8)	514 (95)	540 (99.8)
1-49%	183 (33.8)	88 (18.3)	16 (3.0)	1 (0.2)	201 (37.2)	89 (16.5)	22 (4.1)	1 (0.2)
50-99%	48 (8.9)	46 (8.5)	2 (0.4)	1 (0.2)	34 (6.3)	27 (5.0)	5 (0.9)	0 (0.0)
100%	2 (0.4)	6 (1.1)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.7)	0 (0.0)	0 (0.0)

CCA: common carotid artery; ICA: internal carotid artery; ECA: external carotid artery; VA: vertebral artery; R: right; L: left.

Table 3. The clinical characteristics of patients and multiple logistic regression analysis of the risk factors for carotid atherosclerosis

	Carotid stenosis		Multivariate model	
	< 50% (n = 433, 80%)	≥ 50% (n = 108, 20%)	OR (95% CI)	P value
Age (yr/10, mean ± SD)	6.3±1.3	7.2±0.9	2.15 (1.69-2.74)	< 0.001†
Male, %	56.8	73.1	0.55 (0.30-0.99)	0.06
Hypertension, %	69.3	69.4	1.17 (0.70-1.94)	0.55
Diabetes, %	36.7	30.6	1.28 (0.77-2.11)	0.34
Smoking, %	31.4	51.9	1.52 (1.30-1.89)	0.018*
Alcohol, %	9.9	14.8	0.91 (0.45-1.83)	0.79
Cholesterol ≥ 200 mg/dL, %	38.7	41.1	0.77 (0.47-1.26)	0.30
Triglyceride ≥ 150 mg/dL, %	41.9	34.6	0.95 (0.56-1.62)	0.85

OR: odds ratio; CI: confidence interval. *P < 0.05; †P < 0.01. In multiple logistic regression, the confounding risk factors include age, gender, hypertension, diabetes, smoking, alcohol, atrial fibrillation, hypercholesterolemia, and hypertriglyceridemia.

DISCUSSION

Previous reports in Taiwan demonstrated that 13% of the patients with ischemic stroke[12] and 8% of patients with first-ever ischemic stroke[20] had ≥ 50% carotid stenosis. Our study showed that ≥ 50% carotid stenosis was present in 20% of patients with first-ever ischemic stroke. As our study focused on the survey for risk factors in carotid atherosclerosis, we diagnosed carotid stenosis mainly based on B-mode image, and the Doppler flow criteria were not included. The diagnostic accuracy of B-mode is related to the quality of image, the content of plaque and the severity of carotid stenosis. As the carotid stenosis increases, the accuracy of B-mode may be decreased[21]. Doppler flow study can provide hemodynamic assessment of blood flow and can help to detect severe stenosis or occlusion[22]. The previous two studies used combined B-mode imaging and Doppler flow criteria. As their diagnostic criteria were more stringent, which resulted in lower sensitivity and higher specificity[23], their results showed a lower frequency of ≥ 50% carotid stenosis than ours.

In our study, after age 20, every 10-year increase in age would double the risk of from having < 50% carotid stenosis to becoming ≥ 50% carotid stenosis. Age shows the strongest correlation with ≥ 50% carotid stenosis in the present study and also in previous hospital-based and community-based studies[4,12,14,15]. Age may affect the pathogenesis of atherosclerosis by inducing physiological vascular changes and by increasing the exposure to traditional risk factors[15,24,25].

We did not find any association between gender and carotid atherosclerosis. The Cardiovascular Health Study[19] showed that among the elderly (≥ 65 years), women have less carotid atherosclerosis than men. The Atherosclerosis Risk in Communities (ARIC) Study[25] revealed that the carotid wall intima-media thickness is greater in men than in women aged 45 to 64 years. Caplan et al.[26] demonstrated that female may be more susceptible to intracranial arterial occlusive disease than extracranial carotid disease.

Multiple logistic regression analysis shows that smoking is a significant predictor of ≥ 50% carotid stenosis. Many studies have shown that smoking is a significant risk factor for carotid atherosclerosis[3,10,14,15,27-30]. Active and passive smoking are also associated with increased carotid wall thickness[31]. We found that the habit of smoking is greatly different between men and women in the present study (Table 1). The prevalence of smoking was 56.3% in male patients but only 4.2% in female patients. The high prevalence of smoking in men may also contribute to the high risk of carotid atherosclerosis.

Hypertension is a well-known risk factor for stroke. Our data did not show any association between hypertension and carotid atherosclerosis. Fisher[32,33] originally suggested that the smaller penetrating intracranial vessels are often damaged by hypertension. However, previous reports showed that hypertension as a risk factor of carotid stenosis was inconsistent. In previous hospital-based studies, Handa et al.[4] revealed no relation between hypertension and carotid stenosis in Japanese. In previous population-based Italian studies, Fabris et al.[14] had the same conclusion. However, Su et al.[10], in their study on 3602 community population in Taiwan, showed that hypertension strongly predicted carotid stenosis. The Framingham Heart Study[27] demonstrated that high systolic blood pressure was associated with a risk of carotid stenosis. A potential source of bias may be related to the study design, since anti-hypertensive agents were not taken into account and the blood pressure before medications were not recorded. The dichotomy in hypertension in our current study may make the results become not associated due to data reduction bias.

Diabetes is an independent risk of atherosclerosis and atherothrombotic brain infarction[34,35]. Several studies found a significant correlation between carotid atherosclerosis and diabetes[4,12,15,16], but other studies failed to confirm the result[10,12-14,27]. The present study did not reveal any significant association between diabetes and carotid stenosis. Further studies are needed to identify the relation between the diabetic control and the severity of carotid stenosis.

Although some studies have suggested an association between cholesterol and extracranial carotid atherosclerosis[8,10], there is still controversy about the role of triglyceride and cholesterol in carotid atherosclerosis in large angiographic studies[36-37] and in population-based studies[38-40]. The recent population-based studies showed a conflicting result both for cholesterol and triglyceride in the prediction of carotid intima-media thickness[41-43]. Our study also did not show any association between hyperlipidemia and carotid stenosis. The potential source of bias may be related to the study design, since lipid-lowering therapy is usually not taken into account and the time-point of obtaining blood samples may be different. Transient changes in lipid levels are well known to occur after stroke[44], and important lipoprotein abnormalities may be missed in acute phase. Time-integrated measurement of cholesterol was found to show a higher degree of association with carotid stenosis than that was measured at the time of carotid evaluation[27]. Single evaluation of risk factors in acute stage after stroke may underestimate associations with clinical or subclinical vascular diseases between young patients and elders[45].

In regard to the relation between carotid atherosclerosis and risk factors, evidence from the literature is quite discordant[4,10,13-16,27]. Of all the risk factors investigated, age has by far the strongest independent association with carotid atherosclerosis. Although hypertension, diabetes, alcohol and hyperlipidemia were considered important risk factors for atherosclerosis, we did not find this relationship in our multivariate logistic regression model. However, age-related distribution of risk factors confirmed that hypertension was significantly relevant among older patients with carotid disease and hyperlipidemia among young subjects. Several investigators have reported that the association between hyperlipidemia and clinical atherosclerosis being weaker in the elderly[38-40]. The relation between vascular disease and the time-integrated measurements of lipid level can be expected to be stronger than the association with a single measurement. A potential source of bias was the cross-sectional nature of the population so the application of multiple measurements and time-integrated effect of longitudinal study may further evaluate the association between hyperlipidemia and carotid stenosis.

In conclusion, our study shows that age and smoking are independent risk factors for carotid atherosclerosis in first-ever ischemic stroke. Since age is unmodifiable, our study highlights the importance of smoking cessation, especially in men, for preventing the risk of ischemic stroke.

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