Combined Extracranial and Intracranial Atherosclerosis in Korean Patients

Soo Joo Lee, MD; Soo-Jin Cho, MD; Heui-Soo Moon, MD; Young-Min Shon, MD; Kwang Ho Lee, MD; Dong-Ik Kim, MD; Byung-Boong Lee, MD; Hong Sik Byun, MD; Seol-Heui Han, MD; Chin-Sang Chung, MD

Objectives: To evaluate the frequency of intracranial atherosclerosis among patients with steno-occlusive extracranial carotid artery disease and to determine if there are factors related to the combined intracranial atherosclerosis.

Design: Cross-sectional study.

Setting: A tertiary referral hospital.

Patients: We studied 142 consecutive patients who had atherosclerotic steno-occlusive lesions (defined as ≥30% narrowing of the luminal diameter or occlusion) of an extracranial carotid artery confirmed by conventional angiography. We excluded patients who had potential carotidogenic sources of embolism. Potential vascular risk factors for each patient were obtained from medical records.

Main Outcome Measure: We determined the location and severity of atherosclerotic lesions by conventional angiography. We compared the vascular risk factors between patients with steno-occlusive extracranial carotid artery disease alone and patients with combined intracranial atherosclerosis and extracranial carotid artery disease.

Results: Intracranial steno-occlusive lesions (≥30% stenosis or occlusion) were found in 80 patients (56.3%). Of 121 patients with significant (>50% stenosis or occlusion) extracranial carotid artery disease, 58 (47.9%) also had significant lesions of intracranial arteries. Univariate and multivariate analyses showed that diabetes mellitus was the only significant factor associated with combined intracranial atherosclerosis in patients with extracranial carotid artery disease.

Conclusions: Intracranial atherosclerosis is common in Korean patients with steno-occlusive extracranial carotid artery disease. Diabetes mellitus is associated with intracranial atherosclerosis in patients who had steno-occlusive extracranial carotid artery disease.

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Previous angiographic and pathologic studies showed racial differences in the location of cerebrovascular occlusive disease. In white subjects the extracranial carotid arteries are more affected than the intracranial arteries, while the intracranial arteries are more affected in Asian, Hispanic, and African American subjects. Some epidemiological studies have shown that not only genetic factors but also environmental factors were associated with the distribution of atherosclerosis. A recent change of lifestyle in association with dietary changes brought on by the introduction of western-style foods is believed to have caused an increased incidence of extracranial carotid artery disease and ischemic heart disease in populations in which extracranial disease was formerly uncommon. Besides race/ethnicity, the role of other risk factors that can be related to the distribution of atherosclerosis has been controversial. Most previous studies included different race populations and sought a difference between races or between populations with intracranial lesions and those with extracranial lesions. To our knowledge, data have been sparse about risk factors for combined extracranial and intracranial atherosclerosis. We reviewed the angiographic findings of 142 consecutive patients with steno-occlusive extracranial carotid artery disease and compared potential vascular risk factors between patients who had steno-occlusive extracranial carotid artery disease alone with patients who had combined intracranial atherosclerosis and extracranial carotid artery disease. We sought specific factors related to the combined intracranial atherosclerosis in pa-
METHODS

We studied 142 consecutive patients who had atherosclerotic steno-occlusive lesions of an extracranial carotid artery on conventional angiography at Samsung Medical Center, Seoul, South Korea, between October 1, 1994, and February 28, 2001. We collected the data of patients who had 30% or greater narrowing of luminal diameter or occlusion in an extracranial carotid artery (common carotid artery or internal carotid artery) using the North American Symptomatic Carotid Endarterectomy Trial method.5 We excluded patients who had potential cardiogenic sources of embolism. All patients suspected of having an embolic source underwent electrocardiography, thoracic echocardiography, and/or transesophageal echocardiography.

Potential vascular risk factors in each patient were obtained from medical records. Hypertension was defined as a systolic blood pressure of 140 mm Hg or higher and a diastolic blood pressure of 90 mm Hg or higher based on repeated measurements or a patient's self-report of a history of hypertension and antihypertensive drug use. Diabetes mellitus was diagnosed if the patient had a history of insulin or oral hypoglycemic agent use, or if the fasting blood glucose level was above 140 mg/dL (>7.8 mmol/L). The history of hyperlipidemia was defined as the patient's having a previous diagnosis and receiving a cholesterol-lowering drug. Coronary artery disease referred to a history of angina pectoris, myocardial infarction, or use of cardiac medications or interventions. We also collected information about the history of limb claudication suggesting peripheral vascular disease and a history of current or past smoking. Total serum cholesterol level on admission to the hospital was also obtained.

Atherosclerotic stenotic lesions on conventional angiography were subdivided into extracranial and intracranial categories. The origin of the vertebral artery could not be accurately evaluated because the number of patients who had an angiogram that included the origins of the vertebral artery was small. If an artery was not visible, we did not count it. The stenosis of the extracranial carotid artery was measured using the North American Symptomatic Carotid Endarterectomy Trial method.5 Intracranial stenoses were estimated according to the methods described in the Warfarin-Aspirin Symptomatic Intracranial Disease Study.10 For this study, the presence of an atherosclerotic lesion in extracranial carotid arteries or intracranial cerebral arteries was defined as 30% or more narrowing of the luminal diameter or occlusion. A significant stenotic lesion was defined as 50% or more narrowing in vessel diameter or occlusion.

Characteristics of patients with and without combined intracranial lesions were compared by use of a $\chi^2$ test. The numbers of expected frequencies in each cell of the contingency table were more than 5. Group means were compared by the 2-tailed $t$ test. Normality of each variable was observed on the Kolmogorov-Smirnov test. A logistic regression model was used to assess the independent factor related to the combined intracranial atherosclerosis and to estimate odds ratio and the 95% confidence interval. To adjust for the effects of other factors, age (≥65 years) and total serum cholesterol level (cutoff level, 240 mg/dL [6.2 mmol/L]) were fitted as independent dichotomous variables. We used a logistic regression model including all 9 potential predictor variables (old age; sex; the presence of hypertension, diabetes mellitus, and/or coronary artery disease; a history of hyperlipidemia, smoking tobacco, and/or limb claudication; and a high total serum cholesterol level). The presence or absence of the combined intracranial atherosclerotic lesion was regarded as a dependent variable. The Hosmer-Lemeshow goodness-of-fit $\chi^2$ test was used to assess the model fit. $P<.05$ was considered statistically significant. All statistical analyses were performed with the use of a commercially available software (SPSS-PC, Version 10.0; SPSS Inc, Chicago, Ill).

RESULTS

Of the 142 patients, 124 (87.3%) were men and 18 (12.7%) were women (mean age [SD], 65.5 [7.4] years; age range, 43-81 years). Ninety-three patients (65.3%) had symptoms (transient ischemic attack or stroke) related to the extracranial carotid stenotic lesions and/or tandem intracranial stenotic lesions. The other 49 patients (34.5%) had no appropriate symptoms related to the arterial lesions.

ANGIOGRAPHIC FINDINGS

We reviewed 282 extracranial carotid arteries on angiography. Two extracranial carotid arteries could not be evaluated because of selection failure during the angiographic procedures. The total number of atherosclerotic lesions (≥30% stenosis or occlusion) in the extracranial carotid arteries was 192. Forty-seven patients (33.1%) had steno-occlusive lesions in bilateral extracranial carotid arteries. Fifty percent or more of the 139 steno-occlusive lesions were seen in 121 patients.

Intracranial steno-occlusive lesions (≥30% narrowing of the luminal diameter or occlusion) were found in 80 patients (56.3%). The intracranial atherosclerotic lesions were most frequently found in the intracranial internal carotid arteries (20.9%). Twenty-eight patients (23.1%) had vascular lesions in the intracranial cerebral arteries of anterior circulation (intracranial internal carotid artery, middle cerebral artery, or anterior cerebral artery), 21 in the intracranial arteries of posterior circulation (intradural vertebral artery, basilar artery, or posterior cerebral artery), and the other 31 in both anterior and posterior circulatory arteries. Of the 121 patients who had significant extracranial carotid artery steno-occlusions, 58 (47.9%) also had significant intracranial lesions (≥50% stenosis or occlusion).

DIFFERENCE IN THE VASCULAR RISK FACTORS BETWEEN PATIENTS WITH AND WITHOUT COMBINED INTRACRANIAL ATHEROSCLEROTIC LESIONS

On univariate analysis, diabetes mellitus was more frequently found in 32 of 80 patients with combined intracranial atherosclerotic lesions than in 12 of 62 patients without intracranial atherosclerotic lesions (40.0% vs 19.4%; $P = .02$; odds ratio, 2.7; 95% confidence interval, 1.2-5.8) (Table 1). The other demographic data and risk factors did not show a statistically significant difference between the 2 groups. In the 121 patients with significant extracranial carotid steno-occlusive lesions (≥50% stenosis or occlusion), diabetes mellitus showed a difference between patients with significant intracranial atherosclerotic lesions and those without intracranial atherosclerotic lesions (39.7% vs 20.6%; $P = .04$; odds ratio,
Data about combined atherosclerosis of extracranial and intracranial arteries have been sparse. Lui et al reported that, in Taiwan Chinese, 19 (42.2%) of 45 patients with steno-occlusive extracranial carotid artery disease had combined intracranial lesions on magnetic resonance angiography. Feldmann et al reported that 39% of Chinese patients and 34.2% of white patients had stenoses in both extracranial and intracranial locations. Intracranial atherosclerotic disease has been estimated to occur in 20% to 50% of the patients with extracranial carotid stenosis depending on the definition of intracranial atherosclerotic disease. Intracranial atherosclerotic disease was observed in about half of the patients who had extracranial carotid artery disease in our study.

Although race plays an important role in determining the sites at which disease is predominant, we speculate that factors other than race determine whether a patient develops occlusive cerebrovascular disease. All of our patients were from a single racial population (Korean) and racial differences did not influence our results. Our results showed that diabetes mellitus was the significant factor associated with combined intracranial atherosclerosis in patients with steno-occlusive extracranial carotid artery disease.

Nishimaru et al reported that coronary artery disease was more common in American patients, but the frequency of diabetes mellitus was greater in Japanese patients. Sacco et al found that no difference was noted between races in the proportion of patients with extracranial atherosclerotic stroke, while intracranial atherosclerosis was seen more frequently in African American and Hispanic subjects than in white subjects. The greater prevalence of diabetes mellitus in African American and Hispanic subjects accounted for the increased frequency of intracranial atherosclerotic stroke. The 2001 study by Sacco et al also reported the race/ethnicity disparities in the influence of stroke risk factors. These data indicating that diabetes mellitus is more frequent in Asian subjects than white subjects can partially explain the racial difference of atherosclerotic location.

Solberg et al reported that atherosclerotic lesions appeared in intracranial arteries about 1 decade later in life than they did in the carotid artery, but our study findings did not show any age difference between the 2 study groups. We speculate that the evolving pattern of extracranial and intracranial atherosclerosis in Asian patients may be different from that in white patients.

Previous studies reported a consistent finding that there was male preponderance in extracranial carotid artery disease (59%-83% male preponderance), although selection criteria varied in the individual series. In our study, the proportion of males was compatible with other studies but seemed much higher than the others. However, data regarding intracranial occlusive disease were meager when contrasted with the data available for extracranial disease. Our results showed that the proportion of women was not different between patients with combined intracranial atherosclerosis and those who had steno-occlusive extracranial carotid artery disease alone. Thus, we did not find the effect of sexual preponderance for combined intracranial atherosclerosis among patients with extracranial carotid artery disease, but the number of women in our study was very small.

Before summarizing our results, the limitation in the present study should be discussed. First, a selection bias is possible. Most patients underwent conventional angiography to determine if patients with extracranial ca-

Table 1. Difference in Vascular Risk Factors in 142 Consecutive Patients With Atherosclerotic Steno-Occlusive Lesions of an Extracranial Carotid Artery

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Absent (n = 62)</th>
<th>Present (n = 80)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>65.4 (7.4)</td>
<td>65.6 (7.4)</td>
<td>.91</td>
</tr>
<tr>
<td>Male sex</td>
<td>55 (88.7)</td>
<td>69 (86.3)</td>
<td>.79</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44 (70.9)</td>
<td>63 (78.6)</td>
<td>.38</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (19.4)</td>
<td>32 (40.0)†</td>
<td>.02†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>18 (29.0)</td>
<td>28 (35.0)</td>
<td>.70</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>21 (33.8)</td>
<td>37 (46.3)</td>
<td>.18</td>
</tr>
<tr>
<td>Smoking tobacco</td>
<td>36 (58.1)</td>
<td>44 (55.0)</td>
<td>.89</td>
</tr>
<tr>
<td>Limb claudication</td>
<td>8 (12.9)</td>
<td>16 (20.0)</td>
<td>.31</td>
</tr>
<tr>
<td>Total serum cholesterol</td>
<td>198.9 (28.3)</td>
<td>206.1 (33.0)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Table 2. Odds Ratio and 95% Confidence Interval on Multivariate Logistic Regression According to the Location of Intracranial Lesion

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Old age, ≥65 y</td>
<td>0.55 (0.26-1.16)</td>
<td>.11</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.69 (0.20-2.36)</td>
<td>.55</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.40 (0.98-5.66)</td>
<td>.06</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3.90 (1.67-9.14)</td>
<td>.&lt;.01†</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1.43 (0.63-3.22)</td>
<td>.39</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>1.88 (0.87-4.06)</td>
<td>.10</td>
</tr>
<tr>
<td>Smoking tobacco</td>
<td>0.80 (0.56-1.30)</td>
<td>.59</td>
</tr>
<tr>
<td>Limb claudication</td>
<td>1.96 (0.68-5.66)</td>
<td>.22</td>
</tr>
<tr>
<td>Hypercholesterolemia (serum cholesterol level &gt;240 mg/dL)</td>
<td>2.33 (0.77-7.09)</td>
<td>.14</td>
</tr>
</tbody>
</table>
rotid artery lesions were candidates for endarterectomy. Before performing conventional angiography, we used magnetic resonance angiography and duplex ultrasonography as screening methods in most patients. There may be a misclassification bias in the selection of these patients because some patients having 30% or more stenosis or occlusion could have been missed by the non-invasive screening tests. Thus, we classified the patients using a different threshold (≥50% stenosis or occlusion) and reanalyzed the data. The difference in numbers between the sexes may be explained by possible selection bias because the proportion of male patients seemed much higher than those used in other studies.

Second, this study would be strengthened if a group of patients with just intracranial disease were included. We did not perform further invasive conventional angiography in patients who had only intracranial stenosis or mild stenosis at the carotid bifurcation on magnetic resonance angiography or ultrasonography. For this reason we excluded the patient group with pure intracranial atherosclerosis. The ideal comparison to make would be among patients with isolated intracranial atherosclerosis, extracranial atherosclerosis only, and both intracranial and extracranial atherosclerosis for looking at factors influencing the development of the distribution of the atherosclerotic lesions. A control group should be also included as a reference.

Third, angiography failed to examine every artery in every patient. Poorly visualized vessels distal to high-grade stenosis or occlusion could not be accurately evaluated. Angiographic films were not always satisfactory to evaluate stenosis when catheters could not be introduced into selected arteries. Although we excluded patients with suggested embolic disease, limitation in angiography and noninvasive cardiac testing (echocardiography and 24-hour Holter monitoring) made it impossible to always exclude this diagnosis. Embolic occlusion with partial recanalization can angiographically resemble stenosis. The fourth limitation of the study was that results did not include quantitative information about each vascular risk factor, for example, the duration and severity of disease or exposure, or the effect of medication because of the retrospective review.

CONCLUSIONS

Intracranial atherosclerosis is common in Korean patients with steno-occlusive extracranial carotid artery disease. Diabetes mellitus may be associated with the development of intracranial atherosclerosis in patients with steno-occlusive extracranial carotid artery disease.

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Corresponding author and reprints: Chin-Sang Chung, MD, Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 30 Irwon-dong, Gangnam-gu, Seoul 133-710, South Korea (e-mail: cschung@smc.samsung.co.kr).

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