Distribution of Atherosclerosis and Risk Factors in Atherothrombotic Occlusion

Masahiro Yasaka, MD; Takenori Yamaguchi, MD; and Motoaki Shichiri, MD

Background and Purpose: The present study was performed to determine the relation between distribution of atherosclerosis and risk factors in Japanese patients with atherothrombotic occlusion.

Methods: We studied 154 patients with atherothrombotic occlusion of the extracranial internal carotid artery (n=75, ICA group), the horizontal portion of the middle cerebral artery (n=47, MCA group), and the basilar artery (n=32, BA group), all of which were confirmed by cerebral angiography. We investigated the distribution of atherosclerosis of the three sites and compared the risk factors for atherosclerosis between the three groups. We used 113 subjects without stroke as the control group.

Results: A strong correlation was present between atherosclerosis of the extracranial internal carotid artery and that of the basilar artery. However, only a weak correlation existed between atherosclerosis of the middle cerebral artery and that of the other vessels. Although the prevalence of smoking and hypertension was higher and high density lipoprotein cholesterol levels were lower in the three groups than in the control subjects, no significant differences were found in age, sex, prevalence of smoking and hypertension, serum levels of triglycerides, and high density lipoprotein cholesterol among the three groups. The prevalence of coronary heart disease and diabetes mellitus and the serum levels of hemoglobin A1c, total cholesterol, and low density lipoprotein cholesterol were higher in the ICA and BA groups than in the MCA group. The prevalence of electrocardiographic evidence of left ventricular hypertrophy was higher in the MCA group than in the other groups.

Conclusions: In addition to smoking, hypertension, and low concentration of high density lipoprotein cholesterol, diabetes mellitus and hypercholesterolemia seem to be associated with atherosclerosis of the extracranial internal carotid artery and the basilar artery, and advanced hypertension may play a role in the development of middle cerebral artery occlusion. (Stroke 1993;24:206–211)

KEY WORDS • angiography • carotid artery diseases • cerebrovascular disorders • risk factors

Angiographic and pathological investigations have indicated racial differences in atherothrombotic occlusive diseases of both the anterior and posterior cerebral circulation.1-9 Specifically, extracranial atherosclerosis is more common in whites, whereas intracranial atherosclerosis is more frequent in blacks and Orientals.

Epidemiological studies have shown that not only genetic factors but also environmental factors are associated with the distribution of atherosclerosis. The Ni-Hon-San study showed that the level of blood pressure did not differ between Japanese men living in Japan and Hawaii, but the incidence of stroke was higher in Japan than in Hawaii, which was inversely associated with dietary animal protein and fat.10,11 The study also reported that serum levels of cholesterol, glucose, uric acid, and triglycerides were lower in Japan than in Hawaii.12 This suggests that appropriate dietary animal protein and fat may exert an inhibitory effect on the incidence of stroke.

High serum levels of cholesterol, however, are related not only to coronary heart disease but also to extracranial carotid artery occlusive disease.13,14 Recently, extracranial carotid occlusive disease has been increasing in Japan in association with dietary changes brought on by the introduction of Western-style foods.

In the present study, to elucidate the relation between the distribution of atherosclerosis and risk factors for atherosclerosis in the Japanese population, we investigated stroke patients with atherothrombotic occlusion of the extracranial internal carotid artery (ICA), the horizontal portion of the middle cerebral artery (MCA), and the basilar artery (BA). We first angiographically examined the distribution of atherosclerosis of the extracranial ICA, MCA trunk, and the BA; we then investigated the relation between risk factors and the distribution of atherosclerosis.

Subjects and Methods

Between January 1, 1985, and June 31, 1991, 2,609 Japanese patients in whom cerebrovascular disease (CVD) was suspected were admitted to the Cerebrovascular Division of the Department of Medicine of the National Cardiovascular Center. According to the clinical findings (including brain computed tomography,
TABLE 1. Distribution of Atherosclerosis According to Group

<table>
<thead>
<tr>
<th></th>
<th>Extracranial ICA</th>
<th>MCA trunk</th>
<th>BA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;25%</td>
<td>25–75%</td>
<td>≥75%</td>
</tr>
<tr>
<td>ICA group</td>
<td>36</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>(56.2)</td>
<td>(25.0)</td>
<td>(18.8)</td>
<td></td>
</tr>
<tr>
<td>MCA group</td>
<td>32</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>(86.5)</td>
<td>(13.5)</td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td>BA group</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>(44.5)</td>
<td>(33.3)</td>
<td>(22.2)</td>
<td></td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery. Numbers in parentheses are percentages.

brain magnetic resonance imaging, duplex carotid ultrasonography, transcranial Doppler sonography, and cerebral angiography), the diagnosis of cerebral hemorrhage was made in 275, cardioembolic stroke in 433, atherothrombotic infarction in 345, lacunar infarction in 857, cerebral infarction of undetermined cause in 172, transient ischemic attack in 183, and other neurological disorders in 344 patients.

Of the 2,609 patients, intra-arterial conventional arteriography or digital subtraction arteriography was performed in 1,079 patients in whom a major vessel occlusive lesion or vascular anomaly, such as arteriovenous malformation or angioma, was suspected in the carotid system in 763 patients and in the vertebrobasilar system in 316. Routine examinations included anteroposterior and lateral projections. Of these patients, 154 patients (117 men and 37 women, with a mean age of 64.7 years, ranging from 38 to 78 years) were found to have atherothrombotic infarction or transient ischemic attack resulting from atherothrombotic occlusion of the extracranial ICA (n=75, ICA group), MCA trunk (n=47, MCA group), or BA (n=32, BA group). We entered these 154 patients into the present study.

No patients had a history of or concomitant arterial embolism of the limbs or other parts of the body, or rheumatic heart disease, atrial fibrillation, acute myocardial infarction, prosthetic cardiac valve, nonischemic cardiomyopathy, infective endocarditis, nonbacterial thrombotic endocarditis, congenital septal defect, or cardiac tumor, which were possible sources of cardioembolic stroke.15

Angiographic examinations were performed via the transfemoral route in 137 patients and via the brachial route in the remaining 17 patients. After discarding missing, inadequate, or unsatisfactory angiographic studies, we were able to obtain good visualization of the right carotid system in 144 patients (93.5%), of the left carotid system in 133 patients (86.4%), and of the basilar system in 132 patients (87.5%). The proximal part of the extracranial vertebral arteries was not routinely examined. We therefore omitted the investigation of vertebral arteries from the current study.

In the ICA and MCA groups, we measured the degree of stenosis of the contralateral ICA origin, the MCA trunk, and the BA according to the method of Alter et al,16 relating the diameter of the narrowed lumen to the lumen proximal to the stenosis. In the BA

FIGURE 1. Bar graph shows degree of stenosis of contralateral extracranial internal carotid artery (ICA), contralateral middle cerebral artery (MCA) trunk, and basilar artery (BA) in ICA group (mean+SEM). *p<0.00001 vs. MCA trunk, p<0.005 vs. BA; **p<0.00001 vs. MCA trunk, p<0.01 vs. BA; +p<0.005 vs. MCA trunk, +p<0.01 vs. MCA trunk by analysis of variance coupled with Scheffe’s multiple comparison test.

FIGURE 2. Bar graph shows degree of stenosis of contralateral extracranial internal carotid artery (ICA), contralateral middle cerebral artery (MCA) trunk, and basilar artery (BA) in MCA group (mean+SEM). *p<0.005 vs. extracranial ICA and BA by analysis of variance coupled with Scheffe’s multiple comparison test.
TABLE 2. Concomitants and Risk Factors in Three Cerebrovascular Disease and Control Groups

<table>
<thead>
<tr>
<th></th>
<th>Age (years)</th>
<th>Smoking</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Ischemic heart disease</th>
<th>High voltage on ECG</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>59</td>
<td>65.8±1.2</td>
<td>52 (88.1%)</td>
<td>42 (71.2%)</td>
<td>31 (52.5%)</td>
<td>20 (33.9%)</td>
</tr>
<tr>
<td>Women</td>
<td>16</td>
<td>65.5±1.8</td>
<td>7 (43.8%)</td>
<td>13 (81.3%)</td>
<td>5 (31.3%)</td>
<td>3 (18.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>75</td>
<td>65.7±1.0</td>
<td>59 (78.7%)</td>
<td>55 (73.3%)</td>
<td>36 (48.0%)</td>
<td>23 (30.7%)</td>
</tr>
<tr>
<td>MCA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>35</td>
<td>62.7±2.1</td>
<td>26 (74.3%)</td>
<td>29 (82.9%)</td>
<td>5 (14.3%)</td>
<td>3 (8.6%)</td>
</tr>
<tr>
<td>Women</td>
<td>12</td>
<td>68.2±3.2</td>
<td>10 (83.3%)</td>
<td>10 (83.3%)</td>
<td>3 (25.0%)</td>
<td>4 (33.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>64.1±1.8</td>
<td>36 (76.6%)</td>
<td>39 (83.0%)</td>
<td>8 (17.0%)</td>
<td>7 (14.9%)</td>
</tr>
<tr>
<td>BA group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>23</td>
<td>61.2±2.3</td>
<td>20 (87.0%)</td>
<td>19 (82.6%)</td>
<td>9 (39.1%)</td>
<td>9 (39.1%)</td>
</tr>
<tr>
<td>Women</td>
<td>9</td>
<td>68.8±1.5</td>
<td>6 (66.7%)</td>
<td>7 (77.8%)</td>
<td>3 (33.3%)</td>
<td>2 (22.2%)</td>
</tr>
<tr>
<td>Total</td>
<td>32</td>
<td>63.3±1.8</td>
<td>24 (75.0%)</td>
<td>26 (81.3%)</td>
<td>12 (37.5%)</td>
<td>11 (34.4%)</td>
</tr>
<tr>
<td>Control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>75</td>
<td>60.9±0.9</td>
<td>37 (49.3%)</td>
<td>22 (29.3%)</td>
<td>4 (5.3%)</td>
<td>1 (1.3%)</td>
</tr>
<tr>
<td>Women</td>
<td>38</td>
<td>62.4±1.1</td>
<td>9 (23.7%)</td>
<td>10 (26.3%)</td>
<td>4 (10.5%)</td>
<td>1 (2.6%)</td>
</tr>
<tr>
<td>Total</td>
<td>113</td>
<td>61.4±0.8</td>
<td>46 (40.7%)</td>
<td>32 (28.3%)</td>
<td>8 (7.1%)</td>
<td>2 (1.8%)</td>
</tr>
</tbody>
</table>

ICA, internal carotid artery; MCA, middle cerebral artery; BA, basilar artery; [C], vs. control group; [M], vs. MCA group; [I], vs. ICA group; [B], vs. BA group.

The χ² test was used for prevalence of smoking, hypertension, diabetes mellitus, ischemic heart disease, and high voltage on electrocardiogram (ECG). Analysis of variance with Sheffe’s multiple comparison test was used for levels of hemoglobin (Hb) A1c, total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol.

For HbA1c, there are two missing values in an ICA group man and an MCA group man; for HDL and LDL cholesterol, there are two missing values in ICA group men.

*p<0.001, †p<0.01, ‡p<0.05.

We compared the degree of stenosis of the extracranial ICA, MCA trunk, and BA in the ICA and MCA groups, and that of the extracranial ICA and MCA trunk in the BA group. In accordance with these data, we analyzed whether any relation existed in the distribution of atherosclerosis.

The following data were carefully collected for each patient from the medical records: 1) age; 2) sex; 3) history of smoking; 4) history of hypertension (defined as past use of antihypertensive agents or blood pressure recordings before stroke onset with systolic ≥160 mm Hg or diastolic ≥95 mm Hg); 5) history of diabetes mellitus (use of insulin or oral hypoglycemic agents, fasting blood glucose ≥140 mg/dl, or random blood glucose ≥200 mg/dl); 6) history of ischemic heart disease (myocardial infarction and/or angina pectoris); 7) left ventricular hypertrophy on electrocardiogram (ECG) (high voltage=SV1+RV5 ≥3.5 mV); 8) serum level of hemoglobin A1c (HbA1c); 9) fasting serum level of total cholesterol; 10) triglycerides; 11) high density lipoprotein (HDL) cholesterol; and 12) low density lipoprotein (LDL) cholesterol (determined using the formula LDL cholesterol=total cholesterol−HDL cholesterol−triglycerides/5).

We analyzed the relation between these data and the angiographically evaluated distribution of atherosclerosis. Data collection was complete except for six values: two missing HbA1c values in a group ICA man and a group MCA man, two HDL cholesterol values in a group ICA man, and two LDL cholesterol values in a group ICA man. These six values were omitted in the statistical comparisons of HbA1c, HDL cholesterol, and LDL cholesterol levels.

We routinely performed duplex carotid ultrasonography and transcranial Doppler sonography in patients.

**FIGURE 3.** Bar graph shows degree of stenosis of extracranial internal carotid artery (ICA) and middle cerebral artery (MCA) trunk in basilar artery group (mean±SEM).

*p=0.0028, †p=0.033, ‡p=0.027 vs. MCA trunk by unpaired t test.
with suspected CVD as a screening procedure. Of the 344 patients who were finally diagnosed as having neurological disorders other than CVD, we obtained satisfactory and normal B-mode imaging of the bilateral carotid arteries and Doppler sonograms of the common carotid arteries, MCA, ophthalmic artery, and BA in 132 cases. We discarded 19 cases aged <38 years or >79 years to match the ages of the 154 patients with atherothrombotic occlusion. We used 113 subjects (75 men and 38 women, aged 61.4±0.8 years) as a control for statistical comparison. They were composed of patients with epilepsy, cerebral angioma, brain tumor, headache, syncope, peripheral vertigo, or cervical spondylosis.

Continuous data were expressed as mean±SEM. The χ² test was used for analysis of discrete variables. We used the unpaired t test or analysis of variance, coupled with Scheffe’s multiple comparison test, for analysis of continuous variables.

**Results**

In the ICA group, severe or moderate occlusive lesions of the contralateral extracranial ICA were noted in 28 patients (43.8%) and of the BA in 10 patients (18.6%). There were no patients with severe lesions of the contralateral MCA trunk and only two patients (3.2%) with moderate lesions (Table 1). The degree of stenosis of the contralateral extracranial ICA (41.5±3.8%) was significantly greater than that of the contralateral MCA trunk (13.1±1.8%) and that of the BA (27.2±2.3%) (Figure 1). In addition, the degree of stenosis of the BA was also significantly greater than that of the MCA trunk.

In the MCA group, severe or moderate occlusive lesions of the contralateral MCA horizontal portion were demonstrated in 12 patients (31.6%). Severe lesions of the extracranial ICA or BA were not seen, and there were only a few patients with moderate lesions of the extracranial ICA or BA (Table 1). The degree of stenosis of the contralateral MCA horizontal portion (31.6±4.0%) was significantly greater than that of the contralateral extracranial ICA (21.1±2.5%) and that of the BA (20.6±1.6%) (Figure 2).

In the BA group, severe or moderate occlusive lesions of the extracranial ICA were detected in 15 patients (55.5%), whereas very few patients had moderate stenotic lesions of the MCA trunk (Table 1). The degree of stenosis of the ICA origin (38.8±5.7%) in this group was significantly greater than that of the MCA trunk (20.0±2.0%) (Figure 3).

There were no sexual differences in the distribution of atherosclerosis between the ICA, MCA, and BA groups (Figures 1–3).

Risk factors and concomitants with respect to each group are summarized in Table 2.

The prevalence of smoking, hypertension, ischemic heart disease, and high voltage on ECG was higher and serum levels of HDL cholesterol were lower in the three CVD groups than in the control group. The prevalence of diabetes mellitus and serum levels of HbA1c, total cholesterol, and LDL cholesterol were significantly higher in the ICA and BA groups than in the control group but were not higher in the MCA group. No significant difference was found in the triglyceride level between the three groups and the control group.

In the ICA, MCA, and BA groups, there were no differences in age, prevalence of smoking, hypertension, and serum levels of triglycerides and HDL cholesterol. However, ischemic heart disease and diabetes mellitus were more frequently found in the ICA and BA groups than in the MCA group. The serum levels of HbA1c in the ICA and BA groups were higher (significant in the ICA group men and in the total) than those in the MCA group. The incidence of high voltage on ECG was higher in the MCA group than in the other groups. The total cholesterol and LDL cholesterol concentrations in the ICA and BA groups were higher than those in the MCA group.

**Discussion**

The ICA origin, MCA trunk, and BA, which were investigated in this study, have been shown to be
frequently involved by atherosclerosis. Baker and Iannello\textsuperscript{19} investigated the location and severity of atherosclerosis in 173 consecutive autopsy cases and found that the most common sites of involvement were the ICA origin and the distal BA. The MCA and the proximal and mid portions of the BA were the next most frequently involved.

In patients with extracranial ICA occlusion, occlusive lesions were also commonly seen in the contralateral ICA. Likewise, in patients with MCA trunk occlusion, occlusive lesions on the contralateral side were often found. These findings suggest that ICAs or MCAs on both sides were affected very similarly by hemodynamics and risk factors for atherosclerosis.

In patients with extracranial ICA occlusion, atherosclerotic changes were more often seen in the BA than in the MCA trunk, and in BA occlusion, these changes were more commonly noted in the extracranial ICA than in the MCA trunk. However, ICA and BA lesions were rarely seen in patients with MCA occlusion. These results suggest that there is a stronger relation between the distribution of atherosclerosis in the extracranial ICA and BA than that in the extracranial ICA and MCA trunk or that in the BA and MCA trunk. Atherosclerosis of the extracranial ICA has been reported to be accompanied rarely by an MCA trunk lesion, and this finding has been explained mainly by racial differences.\textsuperscript{1-8} ICA lesions are more common in whites, whereas MCA lesions are more frequent in blacks and Orientals. The same racial differences have also been reported in the posterior circulation.\textsuperscript{9} However, there are few reports on the relation in the distribution of atherosclerosis between the extracranial ICA and BA or that between the MCA trunk and BA.

Regarding the concomitants and risk factors for atherosclerosis, our data indicate that smoking, hypertension, and low levels of HDL cholesterol are basically related to atherosclerosis of the major brain vessels. These factors have already been emphasized as risk factors for atherosclerosis.\textsuperscript{20,21} Moreover, in our study, there were curious differences in risk factors and other concomitants that were associated with the distribution of atherosclerosis. The prevalence of ischemic heart disease and diabetes mellitus and serum levels of HbA1c, total cholesterol, and LDL cholesterol in the ICA and BA groups were higher than those in the MCA group. It has already been indicated that the extracranial ICA atherosclerotic lesions tended to coexist in patients with coronary heart disease and were commonly associated with hypercholesterolemia.\textsuperscript{13,14,21} These reports are consistent with our results. In addition, our results suggest that ischemic heart disease and a high level of serum cholesterol are strongly associated not only with extracranial ICA lesions but also with BA lesions.

Although the Framingham study indicated that diabetes mellitus was an independent risk factor for cerebral infarction,\textsuperscript{22} it has yet to be fully elucidated whether diabetes mellitus affects the distribution of atherosclerosis in cerebral arteries. Bogousslavsky et al\textsuperscript{10} reported that the prevalence of diabetes mellitus was higher in patients with ICA occlusion than in control subjects. Gorelick et al\textsuperscript{9} investigated racial differences in the distribution of posterior circulation occlusive disease and found that distal basilar atherosclerotic lesions and diabetes mellitus were more common in blacks than in whites. Our results also suggest that diabetes mellitus is strongly associated with the extracranial ICA and BA.

On the other hand, although the prevalence of hypertension in the MCA group was not significantly higher than in the ICA and BA groups, high voltage on ECG was more common in the MCA group than in the other two groups. This result suggests that advanced hypertension is associated with atherosclerosis of the MCA trunk. Some reports have already indicated that occlusive lesions of the intracranial cerebral arteries are associated with severe hypertension.\textsuperscript{23,24}

According to the modified Fisher’s classification of occlusive CVD presented by Caplan et al,\textsuperscript{7} extracranial ICA and BA lesions belong to the same group, consisting of lesions of large arteries, which are commonly seen in whites, and they are closely related to serum lipid levels and coronary heart disease. Our results suggest that not only in whites but also in the Japanese population, atherosclerosis of extracranial ICA and BA is strongly associated with serum lipid levels and coronary heart disease.

In conclusion, atherosclerosis of the major cerebral arteries is basically associated with smoking, hypertension, and low serum levels of HDL cholesterol. In addition to these risk factors, diabetes mellitus and high serum levels of total or LDL cholesterol may play a role in the development of ICA and BA atherosclerosis, and advanced hypertension may be related to MCA trunk atherosclerosis.

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**References**

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