Increase in Extracranial Atherosclerotic Carotid Lesions in Patients With Brain Ischemia in Japan
An Angiographic Study
Tetsuhiko Nagao, MD; Seizo Sadoshima, MD; Setsuro Ibayashi, MD; Yo Takeya, MD; Masatoshi Fujishima, MD

Background and Purpose Atherosclerotic lesions in the cerebral arteries are distributed heterogeneously among different races. Intracranial carotid lesions are reported to be more common than extracranial carotid lesions among Japanese people, which is in sharp contrast to the pattern of cerebral atherosclerosis in whites. However, several Japanese clinicians have the impression, which has yet to be clinically proven, that extracranial carotid diseases are recently increasing in number.

Methods One hundred twenty-one patients who developed ischemic stroke and underwent angiography were examined in the study. Seventy were admitted to our clinic from 1963 to 1965 (early group); the remaining 51 patients were seen from 1989 to 1993 (recent group). Angiographic findings and vascular risk factors were compared between the two groups.

Results Severe atherosclerotic lesions of the extracranial internal carotid arteries increased significantly during the ensuing 24 years between the end of the first period until the beginning of the second period (from 1965 to 1989), whereas lesions in the intracranial carotid system were similar between the two groups. Severe atherosclerosis in the extracranial internal carotid artery was more frequent in patients with diabetes mellitus, which proved to be the only risk factor that showed a temporal increase.

Conclusions The proportion of severe atherosclerosis in Japanese patients with brain ischemia has been increasing in the extracranial internal carotid artery, while that in the intracranial carotid system remains unchanged. Such a temporal change may be the result, at least in part, of an increase in the prevalence of diabetes mellitus. (Stroke. 1994;25:766-770.)

Key Words • atherosclerosis • diabetes mellitus • hypertension • racial differences

Atherosclerotic cerebrovascular lesions responsible for ischemic stroke are distributed heterogeneously among the different races. In Japanese stroke patients, atherosclerosis is more often found in the intracranial than in the extracranial cerebral arteries compared with white patients. However, it has been pointed out that extracranial carotid lesions are increasing in number and are increasingly more common among Japanese stroke patients in recent years. Such a tendency may be a consequence of the westernization of lifestyles in Japan, which is most markedly reflected in the daily diet. Despite the seeming increase in extracranial carotid lesions, little data are available regarding temporal changes at the site of cerebrovascular atherosclerosis in Japanese stroke patients during the past 20 to 30 years. The present study was thus designed to examine whether the distribution of cerebrovascular lesions has indeed been changing in patients with ischemic stroke in Japan. We retrospectively compared angiographic findings and vascular risk factors in both an earlier group and a more recent group of patients with brain ischemia.

Subjects and Methods
Two groups of patients admitted to Kyushu University Hospital for brain infarction, amaurosis fugax, or transient ischemic attack (TIA) were included in the study. One group consisted of patients who experienced an acute onset of transient or prolonged focal neurological deficits and underwent conventional angiography (early group, n=70) during the period 1963 to 1965. The other group included patients who developed similar symptoms and underwent conventional and/or digital subtraction angiography during the period May 1989 to March 1993 (recent group, n=51). The diagnosis for stroke subtypes was made based on clinical pictures, cerebrospinal fluid findings (for all subjects in the early group), and computed tomography and/or magnetic resonance imaging findings (for all subjects in the recent group). Patients with either a brain hemorrhage (determined by a lumbar puncture or brain computed tomogram) or a possible cardioembolic source (atrial fibrillation, rheumatic heart disease, cardiomyopathy, and recent myocardial infarction) were excluded from the study.

The angiographic findings were reviewed by two neurologists who are mainly engaged in the treatment of stroke patients (T.N. and Y.T.). The procedure was not blinded. Arterial lesions on angiography were expressed as percent stenosis of the diameters according to the method described.

Received September 1, 1993; final revision received December 16, 1993; accepted January 6, 1994.

From the Second Department of Internal Medicine, Faculty of Medicine, Kyushu University (T.N., S.S., S.I., M.F.) and Kyushu Central Hospital of the Mutual Aid Association of Public School Teachers, Department of Internal Medicine (Y.T.), Fukuoka, Japan.

Correspondence to Tetsuhiko Nagao, MD, Second Department of Internal Medicine, Faculty of Medicine, Kyushu University, Maidashi 3-1-1, Fukuoka 812, Japan.
Background of Patients With Brain Ischemia in Japan

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>70</td>
<td>51</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>55/15</td>
<td>31/20</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>57±11</td>
<td>61±10</td>
<td>NS</td>
</tr>
<tr>
<td>Transient ischemic events*</td>
<td>66/4</td>
<td>42/9</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>DM (-/+)</td>
<td>59/11</td>
<td>34/17</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>HT (-/+</td>
<td>27/43</td>
<td>17/34</td>
<td>NS</td>
</tr>
<tr>
<td>IHD (-/+</td>
<td>58/9</td>
<td>44/7</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia (-/+</td>
<td>29/30</td>
<td>31/20</td>
<td>NS</td>
</tr>
</tbody>
</table>

DM indicates diabetes mellitus; HT, hypertension; and IHD, ischemic heart disease.

*Transient ischemic attack, amaurosis fugax.

by Alter et al.* They were then classified into four categories according to severity: grade 0, stenosis <25%; grade 1, stenosis ≥25% and <50%; grade 2, stenosis ≥50% and <75%; and grade 3, stenosis ≥75% and complete occlusion.

The carotid system was divided into the following subdivisions: common carotid, extracranial internal carotid (E-ICA), intracranial internal carotid (I-ICA), middle cerebral (MCA), and anterior cerebral arteries. The most severe lesion was used to determine the grade of stenosis in the corresponding subdivision.

A diagnosis of hypertension was made when blood pressure surpassed 160 (systolic) and/or 95 (diastolic) mm Hg on repeated measurements during hospitalization or when the patient was treated with antihypertensive drugs. In the early group all patients who exhibited glucosuria underwent a 100-g oral glucose tolerance test. Patients were regarded as diabetic when their serum glucose levels were ≥200 mg/dL at 1 hour and ≥150 mg/dL at 2 hours after glucose loading. A diagnosis of diabetes mellitus was based on clinical assessment, serum glucose level, or the 75-g oral glucose tolerance test in the recent group. The diagnostic criteria for diabetes mellitus using the 75-g oral glucose tolerance test were serum glucose level ≥140 mg/dL at a fasting state and/or ≥200 mg/dL at 2 hours after glucose loading. Ischemic heart disease referred to the presence of history of angina pectoris or acute myocardial infarction or electrocardiographic evidence of coronary heart disease (ST depression ≥1 mV [excluding “J-type” depression] and abnormal Q waves). Hypercholesterolemia was defined as a fasting serum total cholesterol level ≥220 mg/dL.

The frequency of stenotic lesions was compared between the early and recent groups by χ² analysis. Fisher’s exact probability test was used when the observed incidence was less than five, at least in one cell. A value of P <.05 was taken to indicate statistical significance.

Results

The age of patients was comparable between the two groups. However, the proportion of male patients was significantly higher in the early group than in the recent group (Table). Transient neurological events (TIA or amaurosis fugax) were more common in the recent group. When four possible risk factors for ischemic stroke (diabetes mellitus, hypertension, ischemic heart disease, and hypercholesterolemia) were compared between the two groups, diabetes mellitus was the only factor that had increased significantly over the period, with a prevalence that was judged to have doubled in the recent group (Table).

The frequency of severe E-ICA lesions was significantly higher in the recent group (Fig 1). Arteries classified as grade 3 (≥75% stenosis and total occlusion) existed five times more frequently in the recent group than in the early group (10 and 2 arteries, respectively). E-ICA lesions were present almost exclusively at the carotid bifurcation. A complete occlusion was present in 8 E-ICAs from the recent group and 1 E-ICA from the early group. No other temporal change was noted in the other carotid systems (Fig 1). Only 1 examined I-ICA was classified as grade 3 in both groups.

The increasing trend of E-ICA lesions in the recent group remained significant even after patients with transient ischemic events (TIA, amaurosis fugax) were excluded from the analysis (Fig 2). There was no difference in the frequency of arterial lesions between men and women when patients from both groups were combined (Fig 3).

When extracranial (common carotid, internal carotid) and intracranial (internal carotid, middle cerebral, anterior cerebral) carotid system lesions were compared in the early and recent groups, severe intracranial lesions were more frequently observed in the early group, whereas no such difference could be detected in the recent group (Fig 4).

An analysis was made to assess the contribution of risk factors to the incidence of E-ICA lesions. All

FIG 1. Bar graphs show temporal changes in the frequency of atherosclerotic lesions in the intracranial and extracranial internal carotid artery (ICA). The proportion of arteries was expressed as the percentage in each grade of stenosis. Statistical difference was evaluated by χ² (contingency table) analysis.
patients from both the early and recent groups were combined and analyzed. The incidence of E-ICA stenotic lesions was significantly higher in patients with diabetes mellitus or ischemic heart disease than in those without (Fig 5). In contrast, the presence of hypertension or hypercholesterolemia had no detectable influence on the incidence and severity of E-ICA lesions (Fig 5).

We compared the number of patients with stenotic lesions (≥25%) in both the E-ICA and I-ICA systems in the early and recent groups (Fig 6). Although the proportion of such patients was higher in the recent group, the difference did not reach statistical significance (P=.121).

**Discussion**

According to our cooperative study on the racial difference in cerebrovascular disease between Japanese and American populations in the 1960s, E-ICA lesions were found to be less frequent and milder in Japanese stroke patients than in Americans. Stroke victims in Japan were characterized by a higher incidence of intracranial arterial lesions. The present study provided angiographic evidence of the increasing incidence of severe E-ICA lesions in recent stroke patients in Japan. It thus appears that the distribution of carotid atherosclerotic lesions in Japan has been changing toward the American or white pattern.

Although there were more men than women in the early group of this study, this alone does not explain the changing pattern of carotid stenotic lesions in the Japanese. This contention is prompted by the fact that there is no difference in the distribution of E-ICA stenosis between men and women. One possible explanation for the temporal change is that more attention has recently been paid by both physicians and patients to transient ischemic events (TIA and amaurosis fugax) than in earlier days. TIA is often associated with E-ICA lesions, at least in Americans. Thus, the chance to examine patients with extracranial lesions might have increased in the recent group. However, this does not fully explain the temporal changes because the recent increase in E-ICA lesions was still significant even after patients with TIA or amaurosis fugax were excluded from the analysis.

The changing pattern of carotid stenotic lesions in Japanese may be related to a change in their vascular risk factors. Hypertension is the most common risk factor for stroke in both the early and recent groups. Hypertension has a particularly strong relation with intracranial cerebral atherosclerosis. However, there was no temporal change in the frequency of hypertension. In addition, the presence of hypertension was not associated with a higher incidence of E-ICA lesions. In contrast, the proportion of patients with diabetes mellitus increased significantly during the observed period. Furthermore, patients with diabetes mellitus had a significantly higher incidence of E-ICA lesions than those without when all patients were considered together. The latter observation may thus provide evidence against the possibility that different diagnostic criteria used in early and recent patients might have resulted in an overestimation of diabetes mellitus as a risk factor for E-ICA lesions. Diabetes mellitus is known to be a predisposing factor in atherosclerotic brain infarction. An increased prevalence of diabetes mellitus in the Japanese population has also been demonstrated in our recent epidemiologic study. The increase in diabetes is most likely related to the westernization of Japanese lifestyles, particularly in regard to changes in the Japanese daily diet. Patients with ischemic heart disease also had a higher incidence of E-ICA lesions, suggesting that the E-ICA and the coronary artery share a similar mechanism for atherosclerosis. In regard to hypercholesterolemia, a major risk factor for ischemic heart disease, the metabolic disorder did not show any temporal increase in this particular group of patients. Furthermore, patients with hypercholesterolemia did not necessarily suffer from more E-ICA lesions than nonhypercholesterolemic patients. Indeed, hypercholesterolemia has been reported to be less important in the development of stroke than ischemic heart disease. It may be that the coronary artery is more susceptible to hypercholesterolemia,
and markedly higher levels of serum cholesterol are required for the development of E-ICA lesions.

It is noteworthy that the frequency of I-ICA lesions did not change over a quarter of a century in Japanese stroke patients. This may reflect the fact that patients with multiple lesions in both the E-ICA and I-ICA systems have increased in number. However, this is not likely the case because the ratio of such patients was comparable between the early and recent groups (Fig 6), which suggested that patients with major arterial lesions (intracranial and/or extracranial) increased their proportion in the recent group. This may partly reflect the fact that more patients with major arterial lesions were selected in the recent group, probably because of the more rigid criteria for cerebral angiography. I-ICA and MCA were affected more commonly in the past and are still major sites of atherosclerotic lesions in Japanese patients. In contrast, severe E-ICA lesions are increasing in number and now have become as important as intracranial lesions. Whether E-ICA lesions will keep increasing while I-ICA lesions stay unchanged remains an issue of interest that needs to be studied further.

An increased awareness by physicians of the importance of E-ICA lesions could result in a preferential selection of patients with such lesions. However, carotid duplex ultrasonography is not generally used as a routine diagnostic tool in hospitals near Fukuoka. In addition, in recent years we have recommended cerebral angiography for patients suspected of having major cerebral arterial lesions as assessed by duplex ultrasonography, transcranial Doppler, computed tomography, magnetic resonance imaging, and single-photon emission-computed tomography. The combination of these diagnostic techniques is not considered to cause any major selection bias for E-ICA lesions.
However, we still cannot rule out the possibility that a subtle change in the referral pattern at our clinic has taken place over the past 25 years.

The present study revealed an increasing incidence of E-ICA lesions in Japanese patients with ischemic stroke. These results are considered to have important clinical relevance because some symptomatic patients with severe E-ICA stenosis may well benefit from carotid endarterectomy.15,16

Acknowledgment

The authors are grateful to Dr Brian T. Quinn for reading the manuscript.

References

Increase in extracranial atherosclerotic carotid lesions in patients with brain ischemia in Japan. An angiographic study.
T Nagao, S Sadoshima, S Ibayashi, Y Takeya and M Fujishima

Stroke. 1994;25:766-770
doi: 10.1161/01.STR.25.4.766

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/25/4/766

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/