Concomitants of Atherosclerotic Carotid Artery Stenosis

GARY W. DUNCAN, M.D., ROBERT S. LEES, M.D., ROBERT G. OJEMANN, M.D., AND SIDNEY S. DAVID, M.S.

SUMMARY To identify metabolic and other concomitants of a single important type of atherosclerotic cerebrovascular disease, 75 patients with angiographically and surgically proven internal carotid stenosis were compared with age and sex matched control subjects with respect to plasma cholesterol, triglycerides and glucose. They were also compared for blood pressure, cigarette smoking, evidence of ischemic heart disease, peripheral vascular disease and for a family history of these diseases.

Patients with carotid stenosis had higher systolic and diastolic blood pressures and higher plasma cholesterol and triglyceride concentrations than the control groups. They had, as well, a far greater likelihood of being cigarette smokers and a greater likelihood of having diabetes mellitus and previous evidence of coronary and peripheral vascular disease. Patients with carotid stenosis were far more likely to have 2 or more of these common concomitants of atherosclerosis than were the control subjects.

The data suggest that the precursors of carotid stenosis are similar to those of coronary atherosclerosis and raise the hope that modification of these factors may decrease the incidence of this highly prevalent form of cerebrovascular disease.

REFERENCES


From the Arteriosclerosis Center, Massachusetts Institute of Technology, Cambridge, MA and the Departments of Medicine, Neurology and Neurosurgery, Massachusetts General Hospital, Boston, MA.

Dr. Duncan's present address is: Department of Neurology, Veterans Administration Hospital, Nashville, TN.

Reprint requests to: Dr. Lees, 40 Ames St., Cambridge, MA 02142.
site might have its own predisposing factors. The use of cerebral arteriography has allowed for more accurate diagnosis of the various causes of stroke. We report here an analysis of several potential risk factors in patients with atherosclerotic stenosis of the internal carotid artery.

Methods

The charts of all patients with atherosclerotic stenosis of an internal carotid artery who had undergone carotid endarterectomy from November 1968 to April 1975 by one of the authors (R.G.O.) were reviewed. Patients with recent cerebral infarction were excluded, because it might have influenced many of the variables we were studying, including blood pressure, plasma lipids and the electrocardiogram. Of those remaining, all who had determinations of both fasting plasma cholesterol and triglycerides were subjected to further analysis. All had arteriographically proven stenosis of an internal carotid artery, and an atherosclerotic etiology was verified at surgery and pathological examination. The patients’ charts were reviewed for the following variables: age, sex, personal history of hypertension, myocardial infarction, angina pectoris, diabetes mellitus, previous stroke, claudication and smoking, family history of cerebral and cardiac atherosclerosis, blood pressure, evidence of ischemic heart disease (IHD) by electrocardiogram, and values for cholesterol, triglycerides, and glucose.

IHD by electrocardiogram was defined, for the purposes of this study, by the presence of one or more of the following: probable or definite old myocardial infarction, hemiblock, left bundle branch block, intraventricular conduction defect, complete heart block, or ischemic ST and T changes.

Two separate control groups were used. In each, patients were individually and randomly matched for age and sex. The first control group consisted of patients who entered the hospital for aortic and/or mitral valve replacement surgery. These patients were selected because they routinely underwent the laboratory studies listed above. Because the ECG findings and blood pressure of these patients were influenced by their valvular heart disease, these two parameters were also studied in a second age and sex matched control group of patients undergoing iridectomy for cataract. The latter group could not be used for the other variables studied, since these data were not uniformly obtained for cataract patients. Blood samples obtained following a 12 hour fast within the first 3 days of hospitalization were used for determination of cholesterol, triglycerides and glucose. Blood pressure measurements and ECGs were performed prior to surgery.

The data from the study group and the two control groups were analyzed with an IBM 360/75 computer, to determine the prevalence of each of the above concomitants and for multivariate analysis. The x² test was used for analysis of the discrete variables and the paired “t” test for the continuous variables.

Results

Seventy-five patients who had atherosclerotic stenosis of at least one internal carotid artery had plasma lipid measurements made at the time of hospital admission. Seventy patients had transient ischemic attacks, either transient cerebral hemisphere ischemia or transient monocular blindness, and 5 patients were asymptomatic. None had recent cerebral infarction. There were 56 (75%) males and 19 (25%) females. All were Caucasian. The age range was 42 to 77 years (mean 60 years); the mean age for males and females was 62 and 57 years respectively. In each instance surgical and pathological examination verified that the vascular lesion was atherosclerotic.

Of control group A, which consisted of 75 patients matched for age and sex, who were admitted to the hospital for valvular heart surgery, 39 underwent mitral valve replacement and 36 aortic valve replacement; 6 patients had surgical replacement of both valves. Of control group B, which also consisted of 75 patients matched for age and sex, all underwent elective iridectomy.

Each carotid stenosis patient was compared with his (or her) randomly selected age and sex matched control. We found a significantly higher prevalence (table 1a) of a history of smoking, myocardial infarction, angina pectoris, diabetes mellitus and claudication in the carotid stenosis group when compared with the cardiac surgery control group (group A). When the males were considered separately a history of diabetes mellitus was no longer significant. The prevalence of IHD by electrocardiogram and family history of coronary or cerebral vascular disease was not significantly different in the two groups.

The paired “t” test was used to compare the values for systolic and diastolic blood pressure, cholesterol, triglycerides and fasting blood sugar between the carotid stenosis group and control group A (table 1b). Systolic and

| Table 1a Discrete Concomitants of Carotid Stenosis in Patients and Paired Control Subjects |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                | Carotid Positive (Total) | Control A Positive (Total) | Control B Positive (Total) |
| Smoking                         | 67 (73)                  | 45 (74)*                    | 51 (55)                        |
| Diabetes Mellitus               | 10 (75)                  | 2 (74)*                     | 9 (56)                         |
| Claudication                    | 14 (69)                  | 3 (74)*                     | 8 (51)                        |
| Family History of Vascular Disease | 39 (63)              | 36 (65)*                    | 29 (46)                        |
| Ischemic Heart Disease          | 15 (72)                  | 14 (74)*                    | 13 (53)                        |
| Myocardial Infarction           | 18 (71)                  | 2 (71)*                     | 16 (53)                        |
| Angina Pectoris                 | 11 (71)                  | 5 (71)*                     | 7 (53)                         |
**Table 1b**  Continuous Concomitants of Carotid Stenosis in Patients and Paired Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Carotid Stenosis</th>
<th>Control A</th>
<th>Control B</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>168 ± 25</td>
<td>133 ± 23*</td>
<td>140 ± 22*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>88 ± 13</td>
<td>75 ± 12*</td>
<td>80 ± 11*</td>
</tr>
<tr>
<td>Cholesterol (mg/100 ml)</td>
<td>221 ± 50</td>
<td>193 ± 44*</td>
<td>167 ± 61*</td>
</tr>
<tr>
<td>Triglyceride (mg/100 ml)</td>
<td>167 ± 81</td>
<td>129 ± 65*</td>
<td>151 ± 82*</td>
</tr>
<tr>
<td>Fasting Blood Glucose</td>
<td>85 ± 19</td>
<td>88 ± 31*</td>
<td>85 ± 21*</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Blood Glucose</td>
<td>85 ± 19</td>
<td>88 ± 31*</td>
<td>85 ± 21*</td>
</tr>
</tbody>
</table>

Diastolic blood pressures and cholesterol were all significantly higher in the carotid stenosis patients, when considering the entire group, or the males and females separately. Triglycerides were statistically higher in the entire group and in female carotid stenosis patients. For triglycerides the p value for the male subgroup as a whole was between 0.1 and 0.2; however, if a single outlying male with fasting triglycerides of 786 mg/dl and his paired carotid stenosis patient are omitted, p becomes less than .05 for the males. Fasting blood sugar values were not statistically different in the two groups (p = 0.7).

The presence of significant valvular heart disease is known to alter the blood pressure and ECG, so that Group A patients were not proper controls for these variables. Accordingly, an additional comparison of these parameters was made between the carotid stenosis group and patients entering the hospital to undergo iridectomy in whom the other risk factors were not usually measured (table 1b). The systolic blood pressure was significantly higher in the entire carotid stenosis group and in both the male and female subgroups. The diastolic blood pressure was statistically higher in the carotid stenosis patients in the entire group and in the male subgroup. The prevalence of IHD was not significantly different in the two groups.

An analysis was made of the prevalence of multiple factors, including presence of a history of smoking, total cholesterol greater than 220, triglycerides greater than 135, systolic blood pressure greater than 140, diastolic blood pressure greater than 90 and a fasting blood sugar greater than 100 (table 2). The carotid stenosis patients consistently had a greater number of the concomitants of disease than the control subjects. Whereas only 20 (27%) of control group A patients had more than 2 concomitants, 52 (69%) of the carotid stenosis patients did. All female carotid stenosis patients had at least 2 of the abnormalities studied.

**Discussion**

We have studied disease concomitants in a single type of cerebral vascular disease—atherosclerotic stenosis of the origin of the internal carotid artery. This lesion is a known precursor of stroke.

A group of patients with radiologically proven disease were compared with 2 age and sex-matched patient groups. The patients in control Group A were used because plasma lipid values were routinely obtained on hospital admission, as they were for the great majority of carotid stenosis patients. Because the blood pressure and electrocardiograms of the Group A patients were known to be affected by their valvular heart disease, a second age and sex-matched group admitted for cataract extraction was compared for these variables. We believe the results to be meaningful because of the lack of known bias in the referral of patients for evaluation of their carotid disease. To our knowledge, patients were not referred because of their sex, or because of the presence or absence of known or suspected disease concomitants or medical complications. The presence of stable coronary artery disease is not considered a contraindication to carotid endarterectomy in our institution. Nevertheless, our conclusions must be considered ten-
tative until such time as they are confirmed by prospective studies.

Our study was retrospective and the factors analyzed were concomitants of carotid disease, since the latter was already present, rather than risk factors. It seems unlikely, however, that the presence of carotid disease had altered these mostly metabolic parameters. Some justification for this conclusion may stem from the fact that many of the correlating concomitants are similar to the known risk factors for coronary artery disease. The ratio of males to females among our patients was 3 to 1. This male predominance more resembles that of myocardial infarction than thrombotic strokes in general. Although the male to female ratio might have been influenced by hospital admitting practices, sex differences in acceptance of invasive procedures or other selective processes, we know of no such bias. Interestingly, the presence of IHD by ECG was similar in the carotid stenosis and control B patients.

Our results show that, in comparison with controls, patients with atherosclerotic carotid stenosis are more likely to have the following single concomitants of disease: hypertension, hypertriglyceridemia, hypercholesterolemia and history of smoking. The finding of a higher prevalence of hypertension and cigarette habit in carotid stenosis patients is in agreement with other studies. Hypertension appears in all these studies to be the single most important risk factor for stroke; the correlation in our study was higher with the systolic pressure than with the diastolic, in agreement with the Framingham study of "atherosclerotic brain infarction." To date, treatment of hypertension is the only proven effective preventive therapy. The effectiveness of cessation of cigarette smoking has not been established.

Abnormal serum lipids are frequently associated with coronary artery disease, but have not been consistently found in patients with thrombotic strokes. However, in two other studies, which identified patients with and without arteriographic evidence of cerebral atherosclerosis, abnormal serum lipids were significantly associated with the atherosclerotic lesions.

While the carotid stenosis patients more frequently gave a history of being diabetic than did control subjects, the fasting blood glucose values were similar in the two groups. More thorough studies of carbohydrate metabolism were not performed. Sufficient number of patients with determinations of individual serum lipoproteins and of serum uric acid were not available to make any comment on the significance of these variables.

Patients with carotid stenosis had a greater number of the risk factors than did controls and these factors may be synergistic in their contribution to atherogenesis. This phenomenon was particularly evident in women; no female with carotid stenosis had less than 2 of the factors studied.

There are many reasons why the factors studied might predispose to atherosclerosis. Hypertension may directly damage the arterial endothelium, particularly at arterial bifurcations, where wall shear is high. The role of hypercholesterolemia and hyperglyceridemia is not completely clear; the lipid-bearing lipoproteins may enter arterial walls through intact or damaged vascular endothelium and cause or complicate atherosclerotic plaques. In addition, blood platelets of hypercholesterolemic patients are more sensitive than normal to certain naturally occurring stimuli to platelet aggregation.

The evidence that treatment of these identified concomitants of carotid artery stenosis will prevent stroke is not complete; however, it seems to be a logical conclusion. A Veterans Administration study has shown that stroke incidence is reduced with treatment of hypertension; an important extension of this study was the demonstration that even partial reduction of blood pressure was better than no treatment at all when subsequent myocardial infarctions, congestive heart failure, and stroke were considered.

References

1. Freis ED: Veterans Administration Cooperative Study Group on antihypertensive agents. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 219 mmHg. JAMA 202:1028-1034, 1967
2. Freis ED: Veterans Administration Cooperative Study group on antihypertensive agents. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mmHg. JAMA 213:1143-1152, 1970
Concomitants of Carotid Stenosis/Duncan et al.

Unilateral Internal Carotid Arterial Occlusion: Special Considerations

Charles A. Andersen, M.D., LTC M.C. U.S.A.,
Norman M. Rich, M.D., F.A.C.S., Col M.C. U.S.A.,
George J. Collins, Jr., M.D., LTC M.C. U.S.A.,
Paul T. McDonald, M.D., LtC M.C. U.S.A.,
and Stephen C. Boone, M.D., LTC M.C. U.S.A.

Summary

Cases of patients with unilateral internal carotid arterial occlusion and contralateral internal carotid arterial stenosis are reviewed. Forty-two percent presented with a fixed neurological deficit. The deficit was referable to the side of occlusion in 92% and to the side of stenosis in 8%. Eleven percent had a neurological complication following carotid endarterectomy on the side of the stenotic lesion. The neurological complication was referable to the side of stenosis in 67% and to the side of occlusion in 33%. Patients have been followed for an average of 19 months and have not developed any additional TIA's or strokes in the followup period. There may be a role for an extracranial-intracranial bypass (ECIC) on the occluded side prior to an endarterectomy on the stenotic side if a poor collateral situation exists. An ECIC should be done in patients who remain symptomatic following carotid endarterectomy on the stenotic side. These data do not support doing ECIC in asymptomatic patients with unilateral carotid arterial occlusion.

Methods

Between January 1974 and December 1976, 189 carotid endarterectomies were performed on 154 patients at Walter Reed Army Medical Center. Twenty-eight of the 154 patients (18%) presented with a unilateral internal carotid arterial occlusion and a contralateral significant (greater than 50% as demonstrated arteriographically) internal carotid arterial stenosis. An analysis of these 28 cases forms the basis of this report. There were 24 males and 4 females ranging in age from 26 to 73 years with an average age of 56 years. Twelve of the 28 patients (43%) had a fixed neurological deficit at the time of initial evaluation. In 11 of the 12 patients (92%), the deficit was referable to the side of the occlusion; however, in one patient, it was referable to the side of the stenosis.

The indications for surgery in these 28 patients were transient ischemic attacks (TIA's) in 15 (54%); fixed neurological deficit with TIA's in 6 (21%); fixed neurological deficit without TIA's in 6, (21%); and as prophylaxis prior to major surgery in 1, (4%). An analysis of the 21 patients having TIA's showed the TIA's to be referable to the side of the occlusion in 6 patients, (29%), referable to the side of stenosis in 9 patients, (43%), and non-localizing or bilateral in 6 patients (29%).

All 28 patients had a carotid endarterectomy performed on the side of the stenotic lesion. In none of the patients was an attempt made to open the occluded internal carotid artery. No patients were operated on during the acute phase of a stroke. Following a stroke, patients were stabilized for at least six weeks or until the static portion of the brain scan returned to normal before an operation was performed. Also, no arteriograms were performed during the acute phase of a stroke.

Concomitants of atherosclerotic carotid artery stenosis.
G W Duncan, R S Lees, R G Ojemann and S S David

Stroke. 1977;8:665-669
doi: 10.1161/01.STR.8.6.665
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1977 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/8/6/665

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/