Risk Factors for Cervical Atherosclerosis in Patients With Transient Ischemic Attack or Minor Ischemic Stroke

Heikki Palomäki, MD; Markku Kaste, MD; Ralli Raininko, MD; Olli Salonen, MD; Seppo Juvela, MD; Seppo Sarna, PhD

Background and Purpose: Our purpose was to study potential determinants of the presence and the severity of cervical atherosclerosis in patients with transient ischemic attack or minor ischemic stroke. Methods: Two hundred ninety-four patients up to 60 years of age were included in this cross-sectional study. The male to female ratio was 171/123. Atherosclerosis was defined as the presence of any visible atherosclerotic lesion in anteroposterior or left oblique views of cervical arteries in aortic arch angiograms. The severity of atherosclerosis was assessed using three scores, which were computed separately for the total thickness and length of all plaques as well as for the percent stenosis of the vessels.

Results: Atherosclerosis was present in 180 patients (61.2%). In a multiple stepwise logistic regression analysis, age, serum triglycerides, smoking history for more than 20 years, arterial hypertension (defined as systolic or diastolic blood pressure values at least 150 or 100 mm Hg, respectively, or the use of antihypertensive medication), regular light alcohol consumption (inversely), and body mass index (marginal inverse association) were independent determinants of the presence of atherosclerosis; the respective odds ratios were 1.1/1 y, 1.8/1 mmol/L, 3.3, 2.4, 0.3, and 0.9/1 kg/m². In multiple linear regression models, age was associated positively and the ratio of high density lipoprotein to total cholesterol was associated negatively with the severity of atherosclerosis regardless of the scoring method, whereas current smoking and female sex were predictors only of the percent stenosis and the length of the lesions. Arterial hypertension showed a significant association only with the length of the lesions.

Conclusions: Age, cigarette smoking, and arterial hypertension contribute substantially to atherosclerosis in cervical arteries, but this study also confirms the independent associations of lipid or lipoprotein variables with atherosclerotic disease. An independent inverse association of regular light consumption of alcohol with cervical atherosclerosis was also observed. (Stroke 1993;24:970-975)

KEY WORDS • alcohol drinking • atherosclerosis • risk factors

The vast majority of all ischemic cerebrovascular events is due to thromboembolic or atherothrombotic mechanisms. The sources of embolism can be located in the heart or in the aortic arch, but the main sources of thrombosis and embolism are the atherosclerotic lesions in extracranial arteries.1 The role of lipids in coronary atherosclerosis has been thoroughly investigated,2 but much less is known about their contributions in cervical arteries. However, there is increasing evidence also relating blood lipids and lipoproteins to cerebrovascular atherosclerosis.3-11

Generally, risk factors for coronary atherosclerosis appear to increase the risk in other arteries also. In several studies, age has proved to be a risk factor for extracranial atherosclerosis.5-7,9,11-14 Also, male sex,4,6,9,12,14,15 arterial hypertension,5-7,10-12,14-16 diabetes mellitus,12,14,16 and cigarette smoking4-8,10-14,16 have been associated with cerebrovascular atherosclerosis.

Alcohol intoxication or heavy drinking appear to increase the risk of stroke,17 whereas light to moderate drinking has been suggested as having the opposite effect.18,19 Some data also suggest an inverse association between carotid artery atherosclerosis and alcohol use.20

There is experimental evidence linking hypoxemia with atherosclerosis.21 Obstructive sleep apnea syndrome is connected with sleep-related hypoxemic periods and is practically always accompanied with heavy snoring. Snoring and obstructive sleep apnea syndrome appear to increase the risk of ischemic stroke,22 but the relation between snoring history and cerebrovascular atherosclerosis is not known.

The purpose of this study was to evaluate the relation between several patient characteristics and the presence and severity of visible atherosclerosis in all major arteries of the neck in patients with transient ischemic attack (TIA) or minor ischemic stroke.

Subjects and Methods

This cross-sectional study was performed on patients treated in the Department of Neurology, University of Helsinki. All of them had suffered an acute ischemic stroke or TIA and had undergone an aortic arch angi-
ography between January 1984 and December 1986. We excluded patients over 60 years of age as well as those using lipid lowering drugs and those who, on the basis of angiographic studies, revealed arterial diseases unrelated to atherosclerosis. All patients fulfilling inclusion criteria received an invitation to participate in outpatient clinic and laboratory examinations. The response rate was 294 of 423 patients (69.5%).

A detailed medical history was obtained from the patients and from their hospital records. We collected the data on arterial hypertension (previous antihypertensive medication or systolic blood pressure values remaining at least 150 mm Hg or diastolic values remaining at least 100 mm Hg during follow-up) and diabetes mellitus (antidiabetic medication or special diet because of impaired glucose tolerance) known previously.

Smoking history (current smoking, the past years of smoking for current and past smokers, and the amount of cigarettes per day) and drinking habits (the frequency of drinking and the estimated weekly amount of alcohol consumption) were obtained using a standardized questionnaire, as was snoring history (the frequency of snoring and its possible associations with nocturnal respiratory pauses).

All patients were interviewed about possible cerebrovascular diseases in their relatives. A family history of stroke was recorded as positive if a parent or sibling had any confirmed cerebrovascular disorder in their history, excluding TIA. Body mass index in kilograms per square meter was calculated for each patient.

Before blood sampling at about 10 AM, all subjects were advised to have an overnight fast for at least 12 hours. For the assay of cholesterol and triglyceride levels, serum from venous blood and Boehringer kits were used. The major lipoproteins, viz, low density lipoprotein (LDL) and high density lipoprotein (HDL) fractions, were separated by flotation in an ultracentrifuge.

The presence of any visible atherosclerotic lesion (including all irregularities of the internal walls of arteries, atheromatous stenotic plaques, and total occlusions) concerning 11 extracranial arteries (brachiocephalic, subclavian, vertebral, common carotid, and internal and external carotid arteries) in aortic arch angiograms was assessed by two neuroradiologists (R.R. and O.S.), who were blind to the case histories and the risk factors. The measurements began at the aortic arch, and all extracranial parts of the arteries were evaluated. To reach a uniform grading of angiographic atherosclerosis, the first 20 angiograms were simultaneously evaluated by both of the observers. The observers worked closely together at the later stage also, and all initial gradings considered as doubtful by one observer were reviewed by the other, and a consensus grading was reached.

Both the anteroposterior and the left oblique views of the angiograms were evaluated. In nine cases in which left oblique views were not available, right oblique views were used for analyses. In two patients, anteroposterior projections of the angiograms were not available, leaving 292 for further analyses. For the presence of atherosclerosis, all visible atherosclerotic lesions in both projections of the angiograms were taken into account.

The severity of atherosclerosis was evaluated using three indexes: two sum scores concerning the absolute dimensions (thickness and length) of the plaques and one sum score indicating the percent stenosis caused by the plaques. The principles of measuring atherosclerotic plaques are illustrated in the Figure. After measuring the maximal thickness of each plaque, the sum of the relaxing measures was computed separately for two projections. The mean sum of the thickness of all plaques from both projections was used as the first indicator of the severity of atherosclerosis. The maximal length of all separate atherosclerotic lesions was also measured, and the sum of the lengths was computed in both of the projections. The mean of the sums from both projections was used as the second indicator of the severity of atherosclerosis.

For statistical analyses, the following transformations were made: Arterial hypertension, diabetes mellitus, and family history of stroke were dichotomized as yes versus no; snoring, as habitual snoring (always or almost always) versus nonhabitual snoring (including nonsnoring); and current smoking, as smoking at least one cigarette per day versus occasional smoking or nonsmoking. The duration of smoking was studied in three categories: never, up to 20 years, and more than 20 years. To evaluate the effects of different patterns of alcohol consumption on the presence of atherosclerosis, the estimated average weekly consumption was analyzed by 50-g intervals, and the frequency of drinking was dichotomized as regular consumption (from at least once a week to daily drinking) versus occasional consumption (not more than three times per month).
To find out the univariate associations between individual variables and the presence of atherosclerosis, a univariate logistic regression model was used, after which a multiple logistic regression analysis was carried out with potential risk factors as independent variables. A maximum-likelihood stepwise forward elimination procedure was used, and selection of variables to be added was based on the magnitude of their probability values (smaller than 0.1). Multiple linear regression analyses were carried out to establish the possible associations between potential risk factor variables and the severity of atherosclerosis among the subgroup of patients with atherosclerosis.

## Results

Of all 294 patients, 174 (59.2%) had suffered an ischemic stroke, whereas 120 (40.8%) had TIA symptoms only. The male to female ratio was 171/123. The median time interval between the acute-stage angio-

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Atherosclerosis present (N=180)</th>
<th>Atherosclerosis not present (N=114)</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>51.4±7.0</td>
<td>43.1±10.0</td>
<td>1.11/y</td>
<td>1.08-1.16</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.4±3.8</td>
<td>25.5±4.2</td>
<td>1.06/kg/m²</td>
<td>1.00-1.13</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>6.58±1.36</td>
<td>6.08±1.22</td>
<td>1.4/mmol/L</td>
<td>1.1-1.6</td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L)</td>
<td>1.45±0.40</td>
<td>1.57±0.37</td>
<td>0.5/mmol/L</td>
<td>0.3-0.9</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>4.64±1.19</td>
<td>4.19±1.16</td>
<td>1.4/mmol/L</td>
<td>1.1-1.7</td>
</tr>
<tr>
<td>HDL cholesterol/cholesterol</td>
<td>0.23±0.07</td>
<td>0.27±0.08</td>
<td>0.5/1 unit</td>
<td>0.3-0.7</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.86±0.99</td>
<td>1.32±0.68</td>
<td>2.5/mmol/L</td>
<td>1.7-3.6</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval. Univariate logistic regression analyses with categorical variables were used.

*At least once a week to daily consumption.
†Not more than three times per month.

On the basis of evaluation of all major 11 extracranial arteries, atherosclerosis was present in 162 (55.5%) of 292 anteroposterior projections, in 170 (57.8%) of 294 left oblique projections, and in 180 (61.2%) of 294 projections when both projections were taken into account. In patients with present atherosclerosis, the mean sum score from anteroposterior and left oblique projections was 5.16 (median, 3.25; range, 0.25 to 28.8) mm for the plaque thickness, 50.5 (median, 20.1; range, 1.0 to 569.2) mm for the plaque length, and 88 (median, 50; range, 3 to 449) percentage units for the percent stenosis.

Based on combined data from both projections, the univariate risk factors for the occurrence of atherosclerosis are presented in Tables 1 and 2. Male sex, arterial
TABLE 3. Independent Determinants of the Presence of Cervical Atherosclerosis by Stepwise Multiple Logistic Regression Analysis in 294 Patients With Transient Ischemic Attack or Minor Ischemic Stroke

<table>
<thead>
<tr>
<th>Determinant</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>1.11/1 y*</td>
<td>1.06-1.16</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.8/1 mmol/L*</td>
<td>1.1-2.8</td>
</tr>
<tr>
<td>Duration of smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 y</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt;0-20 y</td>
<td>1.6</td>
<td>0.7-3.6</td>
</tr>
<tr>
<td>&gt;20 y</td>
<td>3.3</td>
<td>1.4-7.6</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 g/wk</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>&gt;0-50 g/wk, regular†</td>
<td>0.3</td>
<td>0.1-0.8</td>
</tr>
<tr>
<td>&gt;0-50 g/wk, irregular‡</td>
<td>0.6</td>
<td>0.2-1.4</td>
</tr>
<tr>
<td>&gt;50 g/wk</td>
<td>1.0</td>
<td>0.4-2.9</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>2.4</td>
<td>1.1-5.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.9/1 kg/m²*</td>
<td>0.8-1.0</td>
</tr>
<tr>
<td>Family history of stroke</td>
<td>1.8</td>
<td>0.9-3.6</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval. Other factors tested in the same logistic regression analysis were sex, diabetes mellitus, current smoking, habitual snoring, cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and the ratio of high density lipoprotein cholesterol to total cholesterol.

*Change in risk for atherosclerosis per unit change in a variable.
†At least once a week to daily consumption.
‡Not more than three times per month.

hypertension, diabetes mellitus, current smoking, duration of smoking (more than 20 years), family history of stroke, habitual snoring, age, obesity, and high cholesterol, LDL cholesterol, and triglyceride levels increased the risk of present atherosclerosis, whereas light drinking (average amount not exceeding 50 g/week), high HDL cholesterol level, and high ratio of HDL cholesterol to total cholesterol were in an inverse association with the presence of atherosclerosis on univariate testing (Tables 1 and 2).

The results from a multiple stepwise logistic regression analysis are shown in Table 3. Age, serum triglycerides, smoking in years, arterial hypertension, and regular light alcohol intake (inversely) emerged as significant independent determinants of the presence of atherosclerosis, whereas the contributions of body mass index and family history of stroke were marginal.

Table 4 presents the significant factors associated with the severity of atherosclerosis when the three different methods for grading atherosclerosis as the dependent variable and the multiple stepwise linear regression analyses were used. Age and the ratio of HDL to total cholesterol showed independent associations with the severity of atherosclerosis regardless of the scoring method. Current smoking and sex emerged as significant determinants of the length of the lesions and of the percent stenosis of the arteries, whereas arterial hypertension was found to be in a significant association only with the length of the lesions (Table 4).

**Discussion**

Based on multivariate analyses, age, serum triglyceride levels, smoking history of more than 20 years, and arterial hypertension were independent determinants of the presence of extracranial atherosclerosis among 294 patients with TIA or minor ischemic stroke. The contributions of family history of stroke and body mass index (inversely) were marginal. Regular light alcohol consumption was in an independent inverse association with the presence of atherosclerosis.

The severity of atherosclerosis was assessed using three separate severity scores for the total thickness, the total length, and the sum of the relative stenosis of all atherosclerotic plaques, expressed as percentage units. A slight variability in the combination of significant predictors of atherosclerosis between the scores was noticed. Age was associated positively and the ratio of HDL cholesterol to cholesterol was associated negatively with the length and with the thickness of the lesions as well as with the percent stenosis of the arteries, whereas current smoking status and female sex were associated only with the length and with the percent stenosis, and arterial hypertension was associated only with the length of the lesions.

Age has previously been found to be a well-established risk factor for carotid atherosclerosis, and our results are in agreement with these studies.5-7,9,11-14 We decided to include only patients up to 60 years of age in the present study, because in relatively young patients with less advanced atherosclerosis, it might be easier to detect the independent role of determinants of atherosclerosis. Despite the relatively low mean age (48.2 years), which could also weaken the possibilities of determining a correlation between age and atherosclerosis in this study, age emerged as an independent risk factor for the presence and the severity of atherosclerosis. Based on the logistic regression model, an in-

TABLE 4. Significant Independent Determinants of the Severity of Atherosclerotic Lesions in Cervical Arteries by Stepwise Multiple Linear Regression Analyses

<table>
<thead>
<tr>
<th>Determinant</th>
<th>Index of severity of atherosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Plaque length</td>
</tr>
<tr>
<td></td>
<td>SRC</td>
</tr>
<tr>
<td>Age (y)</td>
<td>0.30</td>
</tr>
<tr>
<td>HDL cholesterol/cholesterol</td>
<td>-0.25</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.26</td>
</tr>
<tr>
<td>Male sex</td>
<td>-0.25</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.15</td>
</tr>
</tbody>
</table>

SRC, standardized regression coefficient; HDL, high density lipoprotein. Other factors tested in the same linear regression analyses were diabetes mellitus, duration of smoking, family history of stroke, habitual snoring, body mass index, alcohol consumption, cholesterol, HDL cholesterol, low density lipoprotein cholesterol, and triglycerides.
crease of 11 percentage units (odds ratio, 1.11/1 y) in the risk of presenting extracranial atherosclerosis for each year of age was noticed.

Several lines of evidence relate blood lipids and lipoproteins to coronary atherosclerosis, but their role in cerebrovascular atherosclerosis has been controversial. In their recent review of 26 studies in which an association was sought between blood lipids and cerebrovascular atherosclerosis, Tell et al found such an association in all but three studies. The relation between lipids and atherosclerosis has been reinforced also in later studies.

Although all lipid and lipoprotein variables showed a strong univariate association with the presence of atherosclerosis in the present study, the independent contributions of most of them were much weaker, and only serum triglycerides remained in the logistic regression model as a significant factor. Concerning the degree of atherosclerosis, the ratio of HDL cholesterol to total cholesterol showed inverse associations with the thickness and the length of the lesions as well as with the percent stenosis of arteries, whereas the independent contributions of other lipids or lipoproteins had no significance. Ford et al studied the associations of risk factors with the average percentage of stenosis of the right and left internal carotid artery. They found a positive association between the degree of stenosis and age, history of smoking, and hypertension. The ratio of total cholesterol to HDL cholesterol also showed a positive association, whereas the association of HDL cholesterol with stenosis was inverse. However, only 4% of the variation in the extent of atherosclerosis was explicable on the plasma lipoprotein concentrations. Supported by several studies, a real relation appears to exist between cerebrovascular atherosclerosis and lipids or lipoproteins, although the association seems weaker and less consistent than that for more established risk factors.

Arterial hypertension is well established as a risk factor of ischemic stroke (probably the most important one), and it has also been associated with cerebrovascular atherosclerosis. Arterial hypertension was in an independent association with the presence of atherosclerosis in this study, and it also proved to be a determinant of the total length of atherosclerotic lesions, ie, the dissemination of atherosclerosis.

Regardless of differences in study designs and populations, there is a growing evidence for a strong association between smoking and extracranial carotid atherosclerosis. Our results are in agreement with these earlier findings. In the present study, a history of smoking of more than 20 years was a strong determinant of the presence of atherosclerosis, whereas current smoking was associated with the severity of atherosclerotic lesions.

Regular light drinking (up to 50 g weekly) appeared to have an independent inverse relation to the presence of atherosclerosis, whereas occasional drinking (although on an average not more than 50 g per week) showed a diluting effect on this association. Based on ultrasonographic evaluation of internal carotid arteries, light to moderate consumption of alcohol is suggested to be the first factor to be inversely associated with extracranial carotid atherosclerosis in symptomatic patients with cerebrovascular disease. Our angiographic eval-

uation of atherosclerosis in 11 major cervical arteries strongly supports this finding.

In some earlier studies, a positive family history of vascular disease has been in a univariate association with atherosclerosis in carotid arteries or in combined extracranial or intracranial atherosclerotic disease, but after carrying out multivariate analyses, its independent contribution has not been significant. Defined as a positive history of stroke in parents or siblings in the present study, family history of stroke showed a significant univariate association with the presence of cervical atherosclerosis, but in accordance with earlier studies, its contribution as an independent risk factor was attenuated, and it was only marginal after adjusting for other variables.

Male patients revealed significantly more atherosclerosis than women in univariate analysis, but male sex was not an independent risk factor for the presence of atherosclerosis in multivariate analysis. In fact, after assessing the severity of lesions in those patients who revealed atherosclerosis, female patients showed more advanced disease. Many studies related to ours show that men are at higher risk for cerebrovascular atherosclerosis than women. In an Italian multicenter study of risk factors and cerebral atherosclerosis, male sex was associated with the prevalence of extracranial and intracranial atherosclerosis, and it was the only significant factor for the presence of intracranial disease. Regardless of the difference in the prevalence of atherosclerosis between men and women, the extent and severity of the disease, as graded by angiographic scores, was equal in both sexes. A female preponderance for intracranial disease has also been suggested. Accordingly, conflicting results concerning the extent and severity of atherosclerosis between the sexes have been noted also earlier. One possible explanation for the higher degree of atherosclerosis in women in the present study is the relatively low mean age of our patients. Although atherosclerosis in this age group may be less common in women than in men, the disease might be more advanced before a woman suffers cerebrovascular symptoms.

History of snoring and sleep apnea are suggested to be in association with ischemic stroke. Sleep apnea is associated with nocturnal hypoxemic periods, which could theoretically promote atherosclerosis. However, in this study the significant univariate association between the history of habitual snoring and present atherosclerosis did not hold true after adjustments for other variables in the logistic model, indicating an essential interaction between snoring and other atherosclerosis-promoting factors. On the basis of these findings, factors other than augmented atherosclerosis may be involved in stroke events in patients with heavy snoring and sleep apnea.

In the present study, diabetes mellitus showed a univariate relation to the presence of atherosclerosis, but its contribution proved to be nonsignificant when adjusted for other variables in the multivariate analyses. Although we have used multivariate statistical testing, the associations between atherosclerosis and potential risk factors in this cross-sectional study do not necessarily correspond with true causal relations. Some other limitations of the present study must also be considered. We did not have asymptomatic patients evaluated by
aortic arch angiograms for use as control subjects, and we cannot rule out the possibilities that some of our patients with normal cervical arteries might have had intracranial atherosclerotic lesions or cardiac causes of their stroke events. Instead of comparing risk factors between groups with or without TIA or stroke and instead of determining the etiologic factors for stroke, we compared determinants of cervical atherosclerosis in patients with symptomatic cerebrovascular disease, using patients without any visible cervical atherosclerosis as the control group for those patients with an atherosclerotic disease. Accordingly, the conclusions must be limited to considerations of cervical atherosclerosis in symptomatic patients only, although no clear evidence indicates a difference of risk factors for atherosclerosis between subjects either asymptomatic or symptomatic for ischemic cerebrovascular diseases. The time interval between the acute-stage angiography and the collecting of blood samples (median time, 11 months) as well as the response rate of 69.5% of the original 423 patients invited to participate may also have some influence on our findings, especially concerning lipid or lipoprotein levels and body mass index. After suffering stroke, patients with high lipid values may have been subject to more effective diet counseling and weight reduction programs than those with more favorable lipid or lipoprotein profiles. This could also partly explain the marginal inverse association of body mass index with the presence of atherosclerosis based on multivariate testing. There may also have been some overrepresentation of patients with previous high lipid levels responding to invitations to blood sampling, which may have a diluting effect on the observed associations between lipid values and atherosclerosis. In general, these potential biases might have led to more conservative conclusions and by no means to overestimations of the risks.

Concerning the severity of present atherosclerosis, most of the significant associations between the disease and the risk factors were found when the total length of lesions was used as an indicator of the degree of the disease. The overall associations were weaker between risk factors and the percent stenosis of the arteries as well as the thickness of the lesions. Accordingly, of our three indexes, the length of the plaques might be most representative of the dissemination of atherosclerosis in neck arteries in patients with TIA or minor ischemic stroke. The presence of relatively few significant associations may suggest that other factors not identified and included in the present study could also be important determinants of cerebrovascular atherosclerosis.

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References


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