Are Cerebral Aneurysms Atherosclerotic?

Jane Adamson, MSc; S.E. Humphries, PhD; J.R. Ostergaard, MA; B. Voldby, PhD; P. Richards, FRCS; J.T. Powell, MD

Background and Purpose The aim of our study was to investigate plasma and genetic risk factors for rupture of cerebral aneurysms.

Methods In London, a case-control study was made of 56 consecutive patients admitted to a regional neurosurgical service for treatment of ruptured cerebral aneurysm and of 93 control subjects. A further 40 consecutive patients admitted in Arhus with ruptured cerebral aneurysm also were studied.

Results The British case-control study showed that smoking was associated with an increased risk of ruptured cerebral aneurysm (odds ratio, 9.1; 95% confidence interval [CI], 3.4 to 23.8; P<.001 for a history of >10 pack years). After age and sex adjustment, factors associated with ruptured cerebral aneurysm included a cholesterol concentration in the highest tertile (>6.3 mmol/L; odds ratio, 10.2; 95% CI, 3.9 to 26.7; P<.001), an apolipoprotein B concentration in the highest tertile (>0.84 g/L; odds ratio, 6.4; 95% CI, 2.5 to 16.3; P<.001), and concentrations of HDL cholesterol in the lowest tertile (<1.1 mmol/L; odds ratio, 3.6; 95% CI, 1.4 to 8.2; P<.01). History of hypertension was of less importance (odds ratio, 4.0; 95% CI, 1.4 to 11.7; P<.01). Smoking history (P<.001) and increased concentrations of cholesterol (P<.0001) were the most important independent risk factors associated with ruptured cerebral aneurysm on multivariate analysis. The histories of hypertension and smoking, together with apolipoprotein B levels, in the Danish patients were similar to those in the British patients. In the entire patient group, the frequencies of two polymorphic variations in the type III collagen gene and polymorphisms at the apolipoprotein B, apolipoprotein C-III, and haptoglobin gene loci were not different from control subjects or the normal population; allele frequencies in British and Danish patients were similar.

Conclusions An atherosclerotic profile including increased total cholesterol concentration and a long smoking history may contribute to the rupture of cerebral aneurysms. This study provides no support for the hypothesis that inherited abnormalities of type III collagen are a common cause of cerebral aneurysms. (Stroke. 1994;25:963-966.)

Key Words • atherosclerosis • cerebral aneurysm • genetics • risk factors • smoking • subarachnoid hemorrhage

Rupture of a cerebral aneurysm is the most common cause of subarachnoid hemorrhage (SAH), particularly in persons over 30 years of age in whom it accounts for 70% to 90% of all SAH.1,2 The incidence of SAH resulting from ruptured cerebral aneurysm increases with age and is more common among women than men.1,2 The reasons for the development and rupture of cerebral aneurysms are not clear, but three main risk factors have been considered: congenital or inherited defects weakening the arterial wall, hypertension, and atherosclerosis.3

Inherited abnormalities in type III collagen have been suggested as an important factor contributing to an altered vascular extensibility and weakening of the cerebral artery wall.4,5 The widespread recognition and treatment of hypertension and improved neurosurgical management may have had an impact on the apparent decline in mortality from SAH, which has been reported in Sweden and elsewhere.5,6 Atherosclerosis is a widespread disorder in Western societies that results from complex interactions between environmental and genetic risk factors. We have investigated a cohort of 96 patients for plasma and genetic risk factors that may predispose to the weakening of cerebral artery walls. The genetic risk factors include polymorphic variation in the type III collagen gene and polymorphic variations in apolipoprotein genes.

Subjects and Methods

Consecutive patients with ruptured cerebral aneurysms proven by angiography were recruited from Charing Cross Hospital (n=56) between October 1989 and December 1991. Consecutive patients from Arhus Kommunehospital (n=40) were recruited during 1991 to increase the number of patients for the genetic studies. The patients or their relatives were interviewed about medical, family, and social history and a single anticoagulated (ethylene diaminetetraacetic acid) blood sample obtained on admission. The patients included 43 men and 53 women (median age, 48 years; range, 25 to 70 years); none were diabetic. No patient was taking lipid-lowering drugs. Among the women, 18 (34%) were postmenopausal; none were taking hormone replacement therapy, and of the remainder only 5 (9%) were taking oral contraceptives. Healthy control subjects, 56 men and 37 women, were recruited consecutively from an occupational cardiovascular screening program (1989 to 1990) and had a median age of 44 years (range, 25 to 64 years); the screening procedure for carotid, coronary, and peripheral arterial disease was as described previously.7

From the blood sample, plasma was separated for the determination of cholesterol, high-density lipoprotein (HDL) cholesterol, by Mg2+ dextran precipitation, apolipoprotein (apo) B by end-point immunonephelometry, cotinine by gas-liquid chromatography, and haptoglobin and α1-antitrypsin phenotype by polyacrylamide gel electrophoresis. Genomic DNA was isolated from the peripheral leukocytes. Polymorphic variation at the Ava II
TABLE 1. Demographic Features and Plasma Variables in British and Danish Patients With Cerebral Aneurysm and Control Subjects

<table>
<thead>
<tr>
<th></th>
<th>Danish Patients (n=40)</th>
<th>British Patients (n=56)</th>
<th>British Control Subjects (n=93)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>50 (26-69)</td>
<td>47 (25-70)</td>
<td>44 (25-64)</td>
<td>NS</td>
</tr>
<tr>
<td>Men, (%)</td>
<td>18 (45)</td>
<td>25 (46)</td>
<td>56 (60)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking history, (%)</td>
<td>36 (90)</td>
<td>51 (91)</td>
<td>45 (48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Preexisting hypertension, (%)†</td>
<td>4 (10)</td>
<td>14 (25)</td>
<td>6 (6)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Cholesterol, mmol/L†</td>
<td>5.68±1.37€</td>
<td>6.7±1.45</td>
<td>5.41±1.22</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L‡</td>
<td>0.95±0.27€</td>
<td>1.21±0.35</td>
<td>1.28±0.41</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>HDL cholesterol/cholesterol‡</td>
<td>0.17±0.06€</td>
<td>0.18±0.06</td>
<td>0.24±0.06</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Apolipoprotein B, g/L‡</td>
<td>0.79±0.20€</td>
<td>0.83±0.21</td>
<td>0.88±0.23</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Cotinine median (range), nmol/L</td>
<td>289 (40-1044)</td>
<td>280 (25-1897)</td>
<td>80 (25-1245)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

HDL indicates high-density lipoprotein; NS, not significant.

*British patients vs control subjects; sex, smoking, and hypertension from x² test, plasma variables from logistic regression.
†Taking antihypertensive medication before admission or health screen.
‡Values expressed as mean±SD.
§Significantly different from British patients, P<.05.
| Similar to British patients. |

The risk of ruptured cerebral aneurysm was associated with a history of smoking (odds ratio, 9.1 for >10 pack-year history; 95% CI, 3.4 to 23.8; P<.001) and with a history of hypertension (odds ratio, 4.0 for previous usage of antihypertensive medication; 95% CI, 1.4 to 11.7; P=.009). The risk of ruptured cerebral aneurysm with increasing concentrations of total cholesterol and apo B and decreasing concentrations of HDL cholesterol is shown in the Figure. The age- and sex-adjusted odds ratio increased very significantly for the highest tertile of cholesterol (≥6.3 mmol/L) to 10.2 (95% CI, 3.9 to 26.7) and for the highest tertile of apo B (≥0.84 g/L) to 6.4 (95% CI, 2.5 to 16.3) (Figure).

When all the above factors were included in a multiple regression analysis, the two most important independent predictors of ruptured cerebral aneurysm were history of smoking (P<.001) and increased concentrations of plasma cholesterol (P<.001). Apo B also remained an independent risk factor (P<.02) (Table 2).

Genetic Factors

Among the 96 patients, 7 (7%) reported having at least 1 first-degree relative with a previously ruptured cerebral aneurysm (3 mothers, 2 fathers, 2 brothers, 1 sister). Genetic variation at loci in the type III collagen gene and the apo B and C-III genes in the 96 patients is shown in Table 2. Allele frequencies in British and Danish patients were closely similar. Therefore, results for the two groups have not been reported separately. All genotypes were in Hardy-Weinberg equilibrium, and no difference in frequency compared with the frequencies of these polymorphisms either in the control group or those previously reported in healthy British populations was observed (Table 2). In a previous study it was observed that variation at the apo C-III locus was associated with differences in triglyceride levels. Triglyceride levels were not measured in this study because fasting blood samples were not available, but variation at the apo C-III locus was associated with ratios of apo B to cholesterol, patients with the rare allele having the highest ratios. When cholesterol levels
### TABLE 2. Independent Risk Factors for Ruptured Cerebral Aneurysm From 56 British Patients and 93 Control Subjects

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of smoking</td>
<td>Yes</td>
<td>1.0</td>
<td>2.1-7.5</td>
</tr>
<tr>
<td>(&gt;10 pack-years)</td>
<td>No</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>&lt;5.4</td>
<td>1.0</td>
<td>0.3-6.5</td>
</tr>
<tr>
<td></td>
<td>5.4-6.2</td>
<td>1.5</td>
<td>2.8-89</td>
</tr>
<tr>
<td></td>
<td>≥6.3</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>Apolipoprotein B, g/L</td>
<td>&lt;0.65</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.65-0.83</td>
<td>1.1</td>
<td>0.1-1.5</td>
</tr>
<tr>
<td></td>
<td>≥0.84</td>
<td>1.6</td>
<td>0.4-5.6</td>
</tr>
</tbody>
</table>

CI indicates confidence interval. History of hypertension and HDL cholesterol concentrations were not significant independent risk factors in these subjects.
We thank the British Heart Foundation for research support, the neurosurgeons at Charing Cross Hospital and Anders Port, the neurosurgeons at Aarhus University Hospital for permission to study their patients, Professor D. Edvinsson for the aprotinin A allele and increased cholesterol concentrations. Our study was supported by the British Heart Foundation, the Danish Medical Research Council, the Danish National Research Foundation, and the Royal Danish Academy of Sciences and Letters.

Gene

<table>
<thead>
<tr>
<th>Polymorphic Site</th>
<th>Type III CIII/CIIC polymorphism</th>
<th>Apolipoprotein B polymorphism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apolipoprotein B polymorphism</td>
<td>Apolipoprotein CIII polymorphism</td>
</tr>
<tr>
<td></td>
<td>Au I</td>
<td>Au II</td>
</tr>
<tr>
<td></td>
<td>Au II</td>
<td>Au III</td>
</tr>
<tr>
<td></td>
<td>Au III</td>
<td>Au IV</td>
</tr>
<tr>
<td>Frequency of Rare Allele in Control &amp; Healthy Population</td>
<td>0.27 (0.26)</td>
<td>0.29 (0.29)</td>
</tr>
</tbody>
</table>

We also thank Richard Edwards, Neil Poulter, and Martin Shipley for advice on statistical analysis and presentation. We thank the British Heart Foundation for research support, the Danish Medical Research Council, the Danish National Research Foundation, and the Royal Danish Academy of Sciences and Letters.

References

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