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 (a0.84 g/L; odds ratio, 6.4; 95% CI, 2.5 to 16.3; /<.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, 1.41 to 11.7; />.<01). Smoking history

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.2,6 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

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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 (ethylenediaminetetraacetic 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 (45)</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±0.05</td>
<td></td>
<td>0.18±0.06</td>
<td>&lt;.1</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.

†Taking antihypertensive medication before admission or health screen.

§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 reported in Table 3. 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>No</td>
<td>1.0</td>
<td>2.1-7.5</td>
</tr>
<tr>
<td>(&gt;10 pack-years)</td>
<td>Yes</td>
<td>4.0</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>&lt;5.4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.4-6.2</td>
<td>1.5</td>
<td>0.3-6.5</td>
</tr>
<tr>
<td></td>
<td>&gt;6.3</td>
<td>15.7</td>
<td>2.8-89</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>&gt;0.84</td>
<td>1.6</td>
<td>0.4-5.6</td>
</tr>
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CI indicates confidence interval. History of hypertension and HDL cholesterol concentrations were not significant independent risk factors in these subjects.

Discussion

The autopsy incidence of cerebral aneurysms is about 5%.[1] The rupture of these aneurysms is the principal cause of SAH. The only large prospective study of SAH has indicated that both hypertension and smoking were important risk factors. The adverse effects of smoking on SAH also have been shown in other studies.[1,12] Current smoking of >20 cigarettes per day was particularly strongly associated with the risk of SAH. Our study revealed a history of heavy smoking in both British and Danish patients; in particular, 71% of patients with ruptured cerebral aneurysm were smoking before admission (plasma cotinine concentration >200 nmol/L). Smoking, and hypercholesterolemia and hypertension, are the major risk factors for atherosclerosis.[13] Hypercholesterolemia may be evidenced by increased concentrations of apo B and decreased concentrations of HDL cholesterol, both of which are considered important risk factors for atherosclerosis.[14,15] Both genetic and environmental factors, together with complex interactions between these factors, contribute to the development of atherosclerosis. A similar situation could prevail for cerebral aneurysms, and the investigations reported here were initiated to assess some possible genetic factors contributing to the development and rupture of cerebral aneurysms. The background environmental factor of smoking was similar in the two patient populations studied, British and Danish (Table 1). However, other factors strongly influenced by the environment (eg, plasma cholesterol) were different in the two populations. Therefore, the healthy subjects taken from a cardiovascular screening program endorsed by employers in the London area can function as control subjects for the British patients only, particularly with respect to factors influenced by the environment. When British patients were compared with British control subjects, smoking together with increased concentrations of cholesterol and apo B emerged as the important independent risk factors associated with rupture of a cerebral aneurysm. Both smoking and increased cholesterol concentrations were more potent risk predictors than hypertension or HDL cholesterol concentrations. However, many patients may have had unrecognized hypertension before the sudden rupture of a cerebral aneurysm. For this reason, together with the relatively small numbers in the case-control study, our conclusions must be tempered with caution. A high prevalence of smoking and high apo B concentrations also were observed in the Danish patients. These patients with ruptured cerebral aneurysm seem at increased risk of atherosclerosis: 7 patients already had suffered a myocardial infarction, and another had had an aortic aneurysm repaired.

Earlier this century atherosclerosis was considered a risk factor for cerebral aneurysm, but more recently the consideration that weakness of the cerebral arterial wall caused by inherited abnormalities in type III collagen has been both favored and disputed. For a disease with an autopsy incidence of 5%, it was perhaps not surprising that 7% of patients with cerebral aneurysm reported having first-degree relatives who were affected similarly. However, this study was not designed to investigate familial aggregation of cerebral aneurysms but rather to assess
the contribution of genetic factors to the risk of rupture of cerebral aneurysms through a study of relevant polymorphic genetic markers. Because the frequency of polymorphic genetic markers was closely similar in the British and Danish patients, the results have been aggregated. The similar frequency of two widely spaced polymorphic markers in the type III collagen gene in the patients, control subjects, and normal population provides no support for the hypothesis that a common mutation in this gene predisposes to weakness in the cerebral arteries and hence aneurysm rupture.

Apolipoproteins, the protein components of lipoproteins, control lipid metabolism. Apo B is the protein component of low-density lipoprotein particles whereas apo C-III, an inhibitor of lipoprotein lipase, is found in very-low-density lipoprotein particles. Polymorphic variation in these genes has provided indications of the genetic component to atherosclerosis and hyperlipidaemia. In particular, associations have been reported between the Xba I polymorphism in the apo B gene and coronary artery disease and between the Pvu II polymorphism of the apo C-III gene and hypertriglyceridaemia. Polymorphic variants of haptoglobin have long been used for disease linkage studies, particularly for the disordered lipid metabolism resulting from mutation in lecithin: cholesterol acyltransferase and for aortic aneurysms. However, the distribution of apo B and C-III genotypes and haptoglobin phenotypes provides no evidence for a genetic predisposition to cerebral aneurysm caused by variation at these loci. Interestingly, there was an unexpectedly high frequency of the α2-antitrypsin Z allele, present in 4 of 50 patients phenotyped. Any disturbance of protease/antiprotease balance could potentiate the damaging effects of smoking or atherosclerosis on the weakening of connective tissue in the arterial wall.

Atherosclerosis is often evident in cerebral aneurysms. While such atherosclerosis may be aggravated by flow disturbance, it also will be aggravated by smoking and increased cholesterol concentrations. Our study indicates that both current smoking and dyslipidemia should be considered as more important factors than mutations of type III collagen in contributing to the rupture of cerebral aneurysms.

Acknowledgments

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