Alpha-1–antitrypsin phenotypes among patients with intracranial aneurysms

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A deficiency of α₁-antitrypsin has been implicated in the development of arterial aneurysms, including intracranial aneurysms. The authors determined the prevalence of α₁-antitrypsin deficiency of different phenotypes in 100 consecutive patients with intracranial aneurysms and compared the distribution of α₁-antitrypsin phenotypes to that in the general population (904 people).

The study population consisted of 44 men and 56 women with a mean age of 52 years (range 15–81 years). The heterozygous α₁-antitrypsin deficiency states (PiMS and PiMZ) were more common in patients (16%) than in the general population (7%), providing an odds ratio of 2.56 (95% confidence interval (CI) 1.32–4.75; p = 0.005). In addition, one patient (1%) was homozygous for the deficient allele (PiZZ) compared to an expected number of 0.015, providing an odds ratio of 67.0 (95% CI 2.0–363.3; p = 0.015). These findings lead the authors to suggest that the heterozygous and homozygous α₁-antitrypsin deficiency states are genetic risk factors for the development of intracranial aneurysms.

KEY WORDS • alpha-1–antitrypsin deficiency • cerebral aneurysm • genetics subarachnoid hemorrhage

SUBARACHNOID hemorrhage (SAH) caused by the rupture of an intracranial aneurysm is a devastating disease with a mortality rate exceeding 50%. The etiology and pathogenesis of intracranial aneurysms are poorly understood but may involve hemodynamic factors and an underlying arteriopathy. The nature of this putative arteriopathy, however, usually remains elusive. Recently, a deficiency of α₁-antitrypsin has been implicated in the development of arterial aneurysms, including intracranial aneurysms. The α₁-antitrypsin gene is a highly polymorphic gene located on chromosome 14; more than 75 allelic variants of this gene have been identified. The allele has been designated protease inhibitor (Pi). Patients who are homozygous for the deficient α₁-antitrypsin allele PiZ have a severe α₁-antitrypsin deficiency and characteristically develop hepatic cirrhosis or panlobular emphysema. Patients who are heterozygous for PiZ, however, often remain asymptomatic and undetected throughout life, particularly if they are nonsmokers. (Smoking has been shown to decrease the efficacy of α₁-antitrypsin.) The present prospective study was undertaken to determine the prevalence of α₁-antitrypsin deficiency of different phenotypes among patients with intracranial aneurysms. None of these patients has been reported previously.

Clinical Material and Methods

Patient Population

We studied 100 consecutive patients (44 men and 56 women) with intracranial aneurysms admitted to a Mayo Clinic–affiliated hospital (St. Mary’s Hospital, Rochester, MN) between March 1994 and April 1995. The diagnosis of aneurysm was confirmed by angiography, surgery, or postmortem examination. All patients had their α₁-antitrypsin phenotype determined by isoelectric focusing in polyacrylamide gels (pH 3.5–5).
casian blood donors from Minnesota. These blood donors were primarily of German or Scandinavian heritage.

Statistical Analysis

The distribution of α₁-antitrypsin phenotypes was compared between the two populations by the Fisher’s exact test, because we expected some small frequencies. This test was also used to compare clinical characteristics between patients with α₁-antitrypsin deficiency and those without it. Confidence intervals (CIs) for odds ratios were estimated by exact methods, using commercially available software (StatXact, 1989; Cytel Software Corp., Cambridge, MA). Because the expected frequency of the PiZZ phenotype was so small, we computed the odds ratio for PiZZ according to the ratio of observed-to-expected frequencies and computed the 95% CI on this relative risk by use of the binomial distribution.

Results

The study population consisted of 44 men and 56 women with a mean age of 52 years (range 15–81 years). Clinical characteristics of the patients are shown in Table 1.

Comparison of Patient and General Populations

The distribution of Pi phenotypes is summarized in Table 2. Overall, the frequencies of the Pi phenotypes differed significantly between patients and the general population (p = 0.003). In particular, the frequency of the combined heterozygous α₁-antitrypsin deficiency states (PiMS and PiMZ) was higher in patients (16%) than in the general population (7%), providing an odds ratio of 2.56 (95% CI 1.32–4.75; p = 0.005). In addition, one of the 100 patients was homozygous for the PiZ allele, an occurrence that is significantly higher than the expected number of cases (0.015%4,5), providing an odds ratio of 67 (95% CI 2.0–363.3; p = 0.015).

Men were overrepresented in the group of patients with α₁-antitrypsin deficiency (44 (76%) of 17 patients) compared to those without α₁-antitrypsin deficiency (31 (37%) of 83; p = 0.006). There were no other significant differences between patients with and without an α₁-antitrypsin deficiency in the characteristics listed in Table 1.

Systemic disorders that have been associated with intracranial aneurysm development were present in five (5%) of the 100 patients (Table 3). All these disorders were known prior to the diagnosis of intracranial aneurysm.

Discussion

The results of this study indicate that α₁-antitrypsin deficiency is a genetic risk factor for the development of intracranial aneurysms. Although we have not proved a causal relationship, there is a biologically plausible explanation for the association between α₁-antitrypsin deficiency and intracranial aneurysms. The proteins elastin and collagen are the main components of the arterial wall. Alpha₁–antitrypsin is a powerful inhibitor of circulating proteolytic enzymes (proteases), particularly elastase but also collagenase, trypsin, and chymotrypsin. By disturbing the protease/antiprotease balance, a deficiency of α₁-antitrypsin could thus result in degradation of the arterial wall.
Alpha-1–antitrypsin deficiency and aneurysms

### TABLE 3

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Frequency Among Patients With Intracranial Aneurysms (100 patients)</th>
<th>Reported Frequency in General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>autosomal dominant polycystic kidney disease</td>
<td>2% 1:400 (0.25%)</td>
<td></td>
</tr>
<tr>
<td>neurofibromatosis type 1</td>
<td>1% 1:3000 (0.03%)</td>
<td></td>
</tr>
<tr>
<td>systemic lupus erythematosus</td>
<td>1% 1:2400 (0.04%)</td>
<td></td>
</tr>
<tr>
<td>Klippel's syndrome</td>
<td>1% 1:1000 (0.1%)</td>
<td></td>
</tr>
<tr>
<td>α₁-antitrypsin deficiency (PiZZ)</td>
<td>1% 1:6700 (0.015%)</td>
<td></td>
</tr>
</tbody>
</table>

A potential limitation of our study is the choice of control population, composed of individuals primarily of German or Scandinavian heritage who had their Pi phenotype determined at another institution in Minnesota. However, the great majority of patients in the present study were also Caucasian and mainly of Northern European descent, reflecting the common referral base of our study population and the population reported by Dykes and colleagues. In addition, we used similar methodologies to perform Pi phenotyping.

Several investigators have studied the possible link between α₁-antitrypsin deficiency and arterial disease. Cohen and associates reported that the PiMZ phenotype occurred significantly more often in patients with abdominal aortic aneurysms than in the general population; however, this could not be confirmed in a larger study. Recently, we reported three cases of patients with aneurysmal SAH among a group of 362 patients with symptomatic α₁-antitrypsin deficiency, a higher number than would be expected on the basis of the incidence rate of aneurysmal SAH in our community (10 per 100,000 persons per year). In a postmortem study, we found that arterial fibromuscular dysplasia was more common in patients with severe α₁-antitrypsin deficiency than in the general autopsy population, providing further support for the presence of an arteriopathy in patients with α₁-antitrypsin deficiency. Elzouki and Eriksson, however, detected no intracranial aneurysms during their postmortem examinations of 30 patients with severe α₁-antitrypsin deficiency.

In the present study, we found a significant association between the heterozygous α₁-antitrypsin deficiency states and intracranial aneurysms. Heterozygosity for the PiZ or PiS allele was approximately 2.5 times more common in patients with intracranial aneurysms than in the general population. In addition, one of the 100 patients with intracranial aneurysms was homozygous for the PiZ allele, compared to an estimated population frequency of PiZZ that is one of 6700 persons. Because of the rarity of PiZZ, this was a statistically significant difference; however, the range of the 95% CI for the odds ratio was wide. Adamson and colleagues mentioned a high frequency of α₁-antitrypsin deficiency among a group of British patients with intracranial aneurysms, but no control group was reported and it is not clear whether these patients were hetero- or homozygous for PiZ. Baker and coworkers measured serum elastase and α₁-antitrypsin levels in patients with intracranial aneurysms and found an increased elastase/α₁-antitrypsin ratio in those patients compared to that of a control population; however, the α₁-antitrypsin phenotypes were not determined.

Intracranial aneurysms are more common in women than men, indicating that the importance of certain risk factors for aneurysm development may be dissimilar between the sexes, such as the presence of sex hormones or a genetic susceptibility. In the present study, there was a clear male preponderance among the patients with the PiMS, PiMZ, or PiZZ phenotypes and, in our previous study, all three patients with α₁-antitrypsin deficiency and ruptured intracranial aneurysms were men. These findings indicate that α₁-antitrypsin deficiency may especially be a risk factor for the development of intracranial aneurysms in men.

In addition to our findings of α₁-antitrypsin deficiency in patients with intracranial aneurysms, we identified systemic disorders that have been associated with aneurysmal disease in 5% of patients. We suggest that patients with intracranial aneurysms may be quite heterogeneous with regard to the nature of their underlying arteriopathy. Possibly, a wide variety of abnormal extracellular matrix proteins and protease inhibitors, of which α₁-antitrypsin is just one, could predispose an artery to aneurysm formation.

In conclusion, the heterozygous and the homozygous α₁-antitrypsin deficiency states are genetic risk factors for the development of intracranial aneurysms.

### References

9. Kueppers F: Determination of α₁-antitrypsin phenotypes by iso-
10. Laurent P, Bieth JG: Cigarette smoke decreases the rate constant for the association of elastase with α1-proteinase inhibitor by a non-oxidative mechanism. Biochem Biophys Res Commun 126:275–281, 1985

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