Levels of \( \alpha_1 \)-Antitrypsin in Plasma and Risk of Spontaneous Cervical Artery Dissections
A Case-Control Study

Nicolás Vila, MD; Mónica Millán, MD; Xavier Ferrer, MD; Nadal Riutort, MD; Domingo Escudero, MD

Background and Purpose—Abnormalities of dermal connective tissue have been detected in patients with spontaneous cervical artery dissections (sCAD), suggesting an underlying structural defect of the arterial wall. \( \alpha_1 \)-Antitrypsin (A1-AT) is a circulating serine proteinase inhibitor of proteolytic enzymes that helps to maintain the integrity of elastic and collagen fibers.

Methods—To test the hypothesis that moderate deficiency of A1-AT may be a risk factor for sCAD, 22 cases with sCAD and 113 controls were included in the study.

Results—Patients with sCAD had significantly mean lower levels of A1-AT compared with controls (116.0±24.9 versus 141.1±31.7 mg/dL; \( P<0.01 \)). Low levels of A1-AT (<90 mg/dL) were more frequently observed in patients with sCAD compared with controls (27.3% versus 2.7%; \( P<0.001 \)). A positive correlation between age and plasma levels of A1-AT was found (\( r=0.22; P<0.01 \)). A1-AT levels were not affected by sex or vascular risk factors, including smoking habit. On multivariate analysis, A1-AT <90 mg/dL was associated with sCAD independently of age, sex, or vascular risk factors (odds ratio, 17.7; 95% confidence interval, 2.9 to 105.6).

Conclusions—Low plasma levels of A1-AT may be a risk factor for sCAD. (Stroke. 2003;34:e168-e169.)

Key Words: alpha 1-antitrypsin • aneurysm, dissecting • risk factors

Ge}netic and environmental factors have been proposed in the pathogenesis of spontaneous cervical artery dissections (sCAD). Abnormalities of dermal connective tissue have been detected in most patients with sCAD, suggesting an underlying structural defect of the arterial wall. In such patients, damaged collagen and elastic fibers might predispose to arterial wall rupture in points of weakness after mechanical stress. The presence and intensity of vascular risk factors (smoking, homocysteine, hypertension, oral contraceptives, infections, etc) might explain the sCAD cluster at the middle of life despite the congenital structural defect of the vessel. Genetically determined alterations of the extracellular matrix may be an important field to investigate the genesis of sCAD.

\( \alpha_1 \)-Antitrypsin (A1-AT) is a circulating serine proteinase inhibitor of proteolytic enzymes that contributes to the maintenance of the integrity of connective tissues. Deficiency of A1-AT may result in degradation of the arterial wall through inadequate protection against the proteolytic effect of elastase and collagenase. A1-AT deficiency is a genetic and systemic disorder characterized not only by lung and liver disease but also by vascular manifestations, including sCAD, fibromuscular dysplasia, or aneurysms. However, A1-AT deficiency ranges from severe forms with very low circulating levels (10% of normal) in homozygous patients to other forms with moderately low concentrations (60% to 70% of normal) in heterozygous patients. To evaluate whether moderate deficiency of A1-AT may be a risk factor for sCAD, we performed a prospective case-control study comparing plasma levels of A1-AT in consecutive patients with sCAD and controls.

Methods
We examined 22 consecutive patients with stroke and sCAD confirmed by conventional angiography or MR angiography and cervical MRI. Controls (n=113) were stroke patients without sCAD admitted during the same period of time who had complete neurovascular studies (carotid ultrasounds, MR angiography, or conventional arteriography).

We recorded demographic data and presence of vascular risk factors. A blood sample was taken at least 2 weeks after stroke onset in cases and controls to avoid the effect of the acute-phase response on plasma protein levels. A1-AT determinations were performed at the hospital laboratory following a standard immune nephelometric technique. Established normal values for A1-AT were between 90 and 200 mg/dL. Levels <90 mg/dL were classified as low; levels ≥90 mg/dL were classified as normal. The study was approved by the local ethics committee.

For statistical bivariate analysis, \( \chi^2 \) test, Student’s \( t \) test, or the Mann-Whitney test was used as appropriate. Pearson’s correlation coefficient analyzed the association between continuous variables.
In this study, we detected that 1 of every 3 patients with sCAD had reduced levels of A1-AT. Because blood determinations were done after the effects of the acute phase of stroke, we speculate that levels of A1-AT detected in plasma reflect genetically determined activity. We could not correlate protease inhibitor (PI) phenotypes with A1-AT levels because only a few sCAD patients had these determinations. However, our results are in the same direction as previous case reports in which an association between deficient protease inhibitor phenotypes (PIZ and PIS) of A1-AT and the presence of sCAD was observed.4,5,7,8

An association between age and A1-AT levels was found in all subjects, suggesting that levels of A1-AT, like other acute-phase proteins, increase with age. Because sCAD cases were younger than controls, it is possible to speculate that low levels of A1-AT in sCAD reflect their younger age. However, low levels of A1-AT remained in the predictive multivariate model of sCAD as a risk factor independently of age. Cigarette smoking decreases the efficacy of A1-AT, resulting in a situation similar to the genetically determined A1-AT deficiency.9 In this study, we did not find different levels of A1-AT according to smoking habit, and low levels of A1-AT remained independently associated with sCAD when smoking was entered into the model.

In conclusion, this study suggests that low plasma levels of A1-AT may be a risk factor for sCAD.

Acknowledgments

We thank all residents and nurses of neurological department for their support and contribution to this work.

References


The relation between low levels of A1-AT and sCAD was assessed by logistic regression analysis, entering into the model all variables with values of \( P < 0.1 \) on bivariate testing, including age, risk factors, and A1-AT <90 mg/dL. Odds ratios and 95% confidence intervals were calculated from \( \beta \) coefficients and their SE. A value of \( P < 0.05 \) was established as statistically significant.

### Results

The main characteristics of cases with sCAD and controls are shown in Table 1. Patients with sCAD were younger and less frequently had vascular risk factors. Patients with sCAD had significant mean lower levels of A1-AT in plasma compared with controls. Low levels of A1-AT (<90 mg/dL) were detected more frequently in patients with sCAD compared with controls (27.3% versus 2.7%; \( P < 0.001 \)). A positive correlation between age and plasma levels of A1-AT was found (\( r = 0.22, \ P < 0.01 \)). A1-AT levels were not affected by sex or vascular risk factors, including cigarette smoking. On multivariate analysis (shown in Table 2), low levels of A1-AT (<90 mg/dL) were associated with the presence of sCAD independently of age, sex, or vascular risk factors.

### Discussion

The main finding in the present study is the association between low plasma levels of A1-AT and risk of sCAD. This result suggests that A1-AT deficiency may be considered another potential biochemical factor with genetic influence in the complex pathogenesis of sCAD. Patients with moderately low levels of A1-AT may have a permanent status of proteolytic activity against the connective tissue of the arterial wall. Increased elastolytic activity may result in fragmentation of the arterial elastic fibers and degradation of the extracellular matrix as demonstrated in experimental studies.9 These aberrations of elastic fibers have been also observed in skin biopsies of patients with sCAD.2

### Table 1. Demographics, Risk Factors, and A1-AT Levels in sCAD Cases and Controls

<table>
<thead>
<tr>
<th></th>
<th>sCAD Cases</th>
<th>Controls</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>50.6±12.7</td>
<td>64.9±11.6</td>
<td>0.001</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>16 (72.7)</td>
<td>87 (77)</td>
<td>0.6</td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td>15 (68.2)</td>
<td>105 (92.9)</td>
<td>0.01</td>
</tr>
<tr>
<td>A1-AT (mean±SD), mg/dL</td>
<td>116.0±24.9</td>
<td>141.1±31.7</td>
<td>0.01</td>
</tr>
</tbody>
</table>

The relation between low levels of A1-AT and sCAD was assessed by logistic regression analysis, entering into the model all variables with values of \( P < 0.1 \) on bivariate testing, including age, risk factors, and A1-AT <90 mg/dL. Odds ratios and 95% confidence intervals were calculated from \( \beta \) coefficients and their SE. A value of \( P < 0.05 \) was established as statistically significant.

### Table 2. Multivariate Analysis of Factors Associated With sCAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>( \beta )</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1-AT &lt;90 mg/dL</td>
<td>2.8</td>
<td>17.7</td>
<td>2.9–105.6</td>
</tr>
<tr>
<td>Age</td>
<td>-0.090</td>
<td>0.9</td>
<td>0.87–0.95</td>
</tr>
<tr>
<td>Risk factors</td>
<td>-1.92</td>
<td>0.14</td>
<td>0.34–0.65</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval.

In conclusion, this study suggests that low plasma levels of A1-AT may be a risk factor for sCAD.
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