Cerebral Infarction in a Heterozygote With Variant Antithrombin III

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Background: We report a heterozygous case of familial qualitative deficiency of antithrombin III associated with cerebral infarction.

Case Description: A 33-year-old man had a history of recurrent transient ischemic attacks from the age of 28. Cerebral computed tomography at age 29 disclosed a low-density area in the left frontal lobe, and an internal carotid angiogram showed branch occlusion of the right anterior cerebral artery and stenosis of the left middle cerebral artery. Occlusion of the right middle cerebral artery developed thereafter. The plasma antithrombin III antigen concentration and progressive antithrombin activity were normal, but plasma heparin cofactor activity was low in the patient and his father. Nucleotide sequence analysis of the proband's deoxyribonucleic acid showed no mutation in exons II and VI of antithrombin III.

Conclusions: We conclude that abnormal antithrombin III with defective heparin binding, even though heterozygous may cause ischemic stroke in young adults. We named this antithrombin III variant "Antithrombin III Nagasaki." (Stroke 1992;23:1822-1825)

KEY WORDS • antithrombin III • cerebral infarction • hereditary disease • young adults

Quantitative deficiency of antithrombin III (AT-III) with a high incidence of thrombosis was first described by Egeberg,1 and Sas et al2 made the first report of a qualitative AT-III defect in a family with spontaneous thromboembolism. More than 30 families with AT-III abnormalities have now been reported, and the variants have been divided into five subtypes.3-5 AT-III deficiencies have been shown to be associated with a high incidence of thrombotic disorder; the prevalence of thromboembolism is reported to be about 50%. A striking difference, however, has been noted for subtype IIC. There is a very low prevalence in heterozygous cases (6%) and a high prevalence in homozygous cases (100%).5

We describe the case of a young man who suffered recurrent cerebral infarction and was shown to be a heterozygote of the subtype IIC AT-III deficiency.

Case Report

The proband was a 33-year-old male without previous episodes of cerebrovascular disorder. In November 1985, at age 28, he developed numbness and weakness in his right hand that disappeared in 10 minutes. After that he experienced several recurrent transient ischemic attacks (TIAs). In February 1986, he was admitted to our hospital for further evaluation of his TIAs. Cerebral computed tomography (CT) disclosed a low-density area in the left frontal lobe (Figure 1A). Cerebral angiography showed branch occlusion of the right anterior cerebral artery and focal stenosis in the proximal portion of the left middle cerebral artery (Figure 2A). The etiology, however, was undetermined at that time. On July 14, 1989, despite antiplatelet treatment, he suddenly experienced weakness in his left hand that improved in 1 minute. On July 16, he was again admitted to our hospital because of convulsion and loss of consciousness. He had smoked 30-40 cigarettes daily for 14 years. No consanguinity was found in his family history.

On admission, physical examination revealed obesity. His height was 177 cm and weight was 89 kg. He showed slightly disturbed comprehension and mild dysarthria, left hemiparesis, and bilateral Babinski's sign.

Results of routine laboratory examinations were all in the normal range except for a low level of high density lipoprotein cholesterol. Serological tests for antinuclear antibodies, lupus anticoagulant, and anticardiolipin antibodies were negative. An oral glucose tolerance test showed mild hyperglycemia. Cerebrospinal fluid findings were normal. Hemostatic test results for coagulation time, prothrombin time, activated partial thromboplastin time, fibrinogen, fibrin degradation products, plasminogen activity, protein C activity, protein S activity, and heparin cofactor II activity were all within the normal range. Platelet activation studies were normal. A roentgenogram of the chest, an electrocardiogram, and a transesophageal echocardiogram were normal. Brain CT disclosed low-density areas in the bilateral frontal lobes (Figure 1B). On day 5 after admission, his signs and symptoms improved, leaving slight dysarthria. On August 13, he suddenly developed numbness and
weakness in his left side that disappeared within 24 hours. Brain CT revealed a new low-density area in the right frontal lobe (Figure 1C). Treatment with warfarin was begun and he experienced no further TIAs. Carotid angiography in July 1989 disclosed new stenosis of the right middle cerebral artery (Figure 2B), with the stenosis of the left middle cerebral artery unchanged (Figure 2B). Repeat angiography in November 1989 showed complete occlusion of the right middle cerebral artery (Figure 2C).

The plasma concentration and functional activity of AT-III were measured in the proband and his parents (Table 1). The AT-III antigen concentration and progressive antithrombin activity were in the normal range for all of them. In contrast, heparin cofactor activity was low in the patient (67%) and his father (55%). Two-dimensional crossed immunoelectrophoresis of plasma in the absence of heparin showed no difference between the proband and his parents, whereas in the presence of heparin, two peaks were found in the patient and his
father. Affinity chromatography on heparin sepharose of the patient and his father revealed two AT-III populations, one of which was devoid of heparin cofactor activity (Figure 3). Nucleotide sequence analysis of the proband’s deoxyribonucleic acid showed no mutation in exons II and VI of AT-III.

**Discussion**

Congenital AT-III abnormality is a heterogeneous disorder classifiable into five subtypes\(^5^a^5^b\): type I, low functional and immunological AT-III; subtype Ia, reduced synthesis, increased turnover of a normal molecule, or both; subtype Ib, reduced synthesis or turnover of AT-III or both, with abnormal heparin affinity; type II, low functional but normal immunological AT-III; subtype IIa, functional abnormalities involving both the active and the heparin-binding sites; subtype IIb, functional abnormalities limited to the active site; and subtype IIC, functional abnormalities limited to the heparin-binding site. The patient was classified as having the subtype IIC AT-III deficiency because of his normal AT-III antigen concentration, progressive antithrombin activity, and decreased heparin cofactor activity. In addition, he was considered a heterozygote because no consanguinity was found in his family, and the plasma from his mother showed a single peak with the same mobility as that of the control in the presence and absence of heparin.

So far, 18 families with subtype IIC deficiency have been reported.\(^6^\)\(^–^2^5^\) We reviewed the cases of 80 patients from 17 of these families for whom clinical data were available. A history of arterial or venous thrombosis or both was obtained for 15 of the 80 patients studied. Arterial thrombosis was present only in nine patients, four of whom were heterozygotes. Only three showed cerebral thrombosis, and they were homozygous for an arginine\(^4^7^\)\(^–^2^8^\)-cysteine mutation (Table 2).\(^1^3^\)\(^^1^4^\)\(^^2^0^\)\(^^2^3^\)\(^^2^2^\)\(^^2^3^\)\(^^2^5^\) The common clinical features in these cases, including the one reported here, are the occurrence of ischemic stroke in young adults and occlusion of the truncal rather than perforating arteries. The striking thing about our patient may be that he is a heterozygote who has a new mutation; nucleotide sequence analysis of the proband’s deoxyribonucleic acid showed no mutation in exons II and VI of AT-III.

Recently, the heparin-binding site was found to involve two distinct regions in the secondary structure of AT-III, encompassing arginine\(^4^7^\)\(^–^2^8^\) and arginine\(^1^2^6^)\(^–^2^6^\). The AT-III abnormality of our patient, therefore, seems to be associated with the latter region.

AT-III deficiency is known to predispose individuals to venous thrombosis, but its relation to arterial disease is not established. Whether reduced AT-III activity is the predisposing factor of stroke is still a matter of controversy.\(^2^7^\)\(^–^2^9^\) The presumed predisposing factors in our patient are smoking, obesity, low high density lipoprotein cholesterol level, and a mild glucose intolerance. The pathogenesis of his recurrent cerebral thrombosis is undetermined. Hart and Kanter\(^3^0\) reported that most patients with congenital AT-III deficiency and stroke have had previous venous thrombosis, with rare possible exceptions.\(^1^4\) Thereafter, another exception was reported.\(^3^1\) We conclude, therefore, that a subtype IIC AT-III abnormality, even in heterozygotes, may cause ischemic stroke in young adults when associated with other predisposing factors.

**Table 1. Antithrombin III Study of Patient and His Parents**

<table>
<thead>
<tr>
<th>AT-III antigen (mg/dl)</th>
<th>Heparin cofactor activity (%)</th>
<th>Progressive AT-III activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 32.9</td>
<td>67</td>
<td>117</td>
</tr>
<tr>
<td>Father 26.8</td>
<td>55</td>
<td>100</td>
</tr>
<tr>
<td>Mother 26.6</td>
<td>100</td>
<td>111</td>
</tr>
</tbody>
</table>

AT-III, antithrombin III.

**Table 2. Cerebral Infarction Associated With Subtype IIC of AT-III Deficiency in Four Reported Cases**

<table>
<thead>
<tr>
<th>Author of study</th>
<th>Age/sex of patient</th>
<th>Age at onset (years)</th>
<th>Obstructed artery</th>
<th>Heparin cofactor activity (%)</th>
<th>Zygosity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koide(^1^3)</td>
<td>23/F, 22</td>
<td>R MCA</td>
<td>26</td>
<td>Homo</td>
<td></td>
</tr>
<tr>
<td>Fischer(^1^4^)(^2^0)</td>
<td>41/M, 25</td>
<td>R, L MCA</td>
<td>&lt;10</td>
<td>Homo</td>
<td></td>
</tr>
<tr>
<td>Ueyama(^1^3^)(^2^3)</td>
<td>31/F, 17</td>
<td>R MCA</td>
<td>42</td>
<td>Homo</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>33/M, 28</td>
<td>R ACA; R, L MCA</td>
<td>67</td>
<td>Hetero</td>
<td></td>
</tr>
</tbody>
</table>

M, male; F, female; R, right; L, left; MCA, middle cerebral artery; ACA, anterior cerebral artery; Homo, homozygote; Hetero, heterozygote.
References

Cerebral infarction in a heterozygote with variant antithrombin III.
T Arima, M Motomura, Y Nishiura, M Tsujihata, K Okajima, H Abe and S Nagataki

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