Lupus Anticoagulant and the Fibrinolytic System in Young Patients With Stroke

Domenico Ferro, MD; Claudio Quintarelli, MD; Maurizia Rasura, MD; Giovanni Antonini, MD; and Francesco Violi, MD

Background and Purpose: Our purpose was to assess the presence of lupus anticoagulant and fibrinolytic system abnormalities in young patients with stroke.

Methods: We studied 33 consecutive ischemic patients aged <50 years. Lupus anticoagulant was screened by four different coagulation tests, and the fibrinolytic system was studied by analyzing tissue plasminogen activator antigen and plasminogen activator inhibitor activity.

Results: Six patients (18%), two of whom were affected by systemic lupus erythematosus, had lupus anticoagulant. Plasminogen activator inhibitor activity was significantly higher in those positive for lupus anticoagulant than in those negative for lupus anticoagulant and control subjects (p<0.001).

Conclusions: In young patients with stroke, lupus anticoagulant is associated with an imbalance of the fibrinolytic system as a result of higher levels of plasminogen activator inhibitor. (Stroke 1993;24:368–370)

KEY WORDS • anticoagulants, lupus • cerebral ischemia • young adults

In a series of stroke registries recently reviewed, 2–7% of brain infarcts in young adults have been attributed to hematological causes. Among these, fibrinolytic system abnormalities are variably reported, and antiphospholipid antibodies and lupus anticoagulant (LA) are the acquired prothrombotic conditions most frequently detected. LA is an acquired circulating serum gamma globulin not strictly related to systemic lupus erythematosus (SLE) that in vitro prolongs phospholipid-dependent coagulation tests and, paradoxically, is associated with an increased tendency to venous and arterial thromboses.

Screening of young stroke patients for LA has yielded widely varying results, probably as a result of the different sensitivity and specificity of each laboratory test. To further analyze this problem, we studied certain coagulation and fibrinolytic parameters and the presence of LA in young adults who had suffered from ischemic stroke.

Subjects and Methods

From February 1989 to May 1991, 33 consecutive subjects (27 men, six women; aged 23–49 years) with ischemic stroke gave informed consent to participate in the study. We considered that a patient had suffered from ischemic stroke when he or she had had an acute focal neurological deficit lasting >24 hours and the cerebral infarction was confirmed by computed tomography. Patients aged >50 years with transient ischemic attack and nonischemic brain diseases were excluded.

LA coagulation screening tests, anticardiolipin antibodies (aCL), circulating titer, and coagulation and fibrinolytic patterns were studied at least 3 months after the onset of the ischemic event. Any drug that could affect clotting and the fibrinolytic system or platelet function was discontinued for at least 2 weeks before the study.

The LA study was carried out by performing four different coagulation tests: activated partial thromboplastin time (aPTT), kaolin clotting time, dilute Russell’s viper venom time, and dilute aPTT, assessed as previously described. Samples yielding abnormal results were reassessed by mixing fresh patient’s plasma in a 1:1 ratio with fresh pooled normal plasma, and clotting times were considered abnormal if longer than the mean+2SD of 25 control subjects matched for age and sex. The presence of LA was diagnosed by the abnormality of two or more coagulation screening tests and by the confirmatory test with 0.05 mM phosphatidylserine-phosphatidylcholine liposomes. To evaluate aCL, the enzyme-linked immunosorbent assay technique validated in an international workshop was used. Results are expressed as the number of standard deviations above the mean in normal human serum (reference value, <3SD).

Prothrombin activity (Baldacci, Pisa, Italy; reference value, 75–120%), fibrinogen studied according to the Clauss method (Immuno, Pisa, Italy; reference value, 180–400 mg/dl), and factor VII activity assessed by use of tissue thromboplastin of rabbit brain origin (Baldacci; reference value, 75–125%) were measured by use of the Schnitzer and Gross coagulometer.

The tissue plasminogen activator (t-PA) antigen (Imubind-5-tPA, American Diagnostica) and plasminogen activator inhibitor (PAI) activity (Kabi Diagnos-
The t-PA (Sweden) and the assays were compared with a control group of 25 normal subjects matched for age and sex.

**Statistical Analysis**

Statistical analysis was performed by means of the unpaired two-tailed test and the Mann-Whitney test. Data are presented as mean±SD and 95% confidence limits. Significance was defined as p<0.05.

**Results**

Six subjects (18%) (five men, one woman; aged 23–47 years) were LA positive (LA(+)) (Table 1). Twenty-seven subjects (21 men, six women; aged 38–49 years) were LA negative (LA(-)). High aCL circulating levels were found in eight of 33 stroke patients (24%), and in six of 33 young stroke patients (18%), and eight of 33 patients (24%) showed high titers of aCL. Only two patients had simultaneous LA(+) and high aCL titers. This agrees with previous reports that considered LA and aCL as potentially different entities, sometimes heterogeneous.2 In accordance with previous studies, which suggested that the coagulation approach was more specific than immunologic assays in identifying LA patients suffering from or at risk for thrombotic events,3 we considered as LA(+) only the patients who showed abnormal coagulation tests.

LA(+) patients are younger and have a history of more frequently recurrent cerebral ischemic episodes than LA(-) patients. These data confirm previous observations.8,9

Only two of six LA(+) patients were affected by SLE. This is in accordance with previous findings showing no close relation between LA and SLE in young patients with cerebral ischemia.9,8 The pathophysiological link between LA and thrombosis has not yet been

### TABLE 1. Coagulation Tests Screening for Lupus Anticoagulant and Anticardiolipin Antibodies Circulating Titer in Six Young Stroke Patients Positive for Lupus Anticoagulant

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3*</th>
<th>Patient 4</th>
<th>Patient 5*</th>
<th>Patient 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>aPTT (seconds)</td>
<td>25</td>
<td>27</td>
<td>28</td>
<td>25</td>
<td>36†</td>
<td>25</td>
</tr>
<tr>
<td>(RV, 24±3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCT (seconds)</td>
<td>62.4</td>
<td>80.2†</td>
<td>72.7†</td>
<td>88†</td>
<td>86†</td>
<td>71.5†</td>
</tr>
<tr>
<td>(RV, 48.8±8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilute RVVT (seconds)</td>
<td>33.8†</td>
<td>30.2†</td>
<td>37.3†</td>
<td>27</td>
<td>35.3†</td>
<td>31.6†</td>
</tr>
<tr>
<td>(RV, 26.4±1.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilute aPTT (seconds)</td>
<td>18.6†</td>
<td>21.7†</td>
<td>19.3†</td>
<td>20.1†</td>
<td>22.4†</td>
<td>25.5†</td>
</tr>
<tr>
<td>(RV, 9±2.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aCL titer (SD)</td>
<td>&lt;3</td>
<td>&lt;3</td>
<td>Ig G 33</td>
<td>&lt;3</td>
<td>Ig G 19.2</td>
<td>&lt;3</td>
</tr>
<tr>
<td>(RV, &lt;3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ig M 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ig A 14.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All abnormal values shown are obtained by mixing patient’s plasma in a 1:1 ratio with fresh pooled normal plasma. Reference values (RV) are expressed as mean±SD. aPTT, activated partial thromboplastin time; KCT, kaolin clotting time; RVVT, Russel’s viper venom time; aCL, anticardiolipin antibodies; Ig, immunoglobulin.

*Patient with systemic lupus erythematosus.
†Clotting times were considered abnormal if longer than mean+2SD of control subjects.

in six of 33 young stroke patients (18%), and eight of 33 subjects (24%) showed high titers of aCL. Only two patients had simultaneous LA positivity and high aCL titers. This agrees with previous reports that considered LA and aCL as potentially different entities, sometimes heterogeneous.2 In accordance with previous studies, which suggested that the coagulation approach was more specific than immunologic assays in identifying LA patients suffering from or at risk for thrombotic events,3 we considered as LA(+) only the patients who showed abnormal coagulation tests.

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### TABLE 2. Coagulation and Fibrinolytic Parameters in Young Ischemic Stroke Patients Positive and Negative for Lupus Anticoagulant

<table>
<thead>
<tr>
<th>Test</th>
<th>LA(+) (n=6)</th>
<th>LA(-) (n=27)</th>
<th>Control subjects (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin activity (%)</td>
<td>83±16</td>
<td>82±13</td>
<td>87±8 (84–91)</td>
</tr>
<tr>
<td>aPTT (seconds)</td>
<td>28±4</td>
<td>25±2</td>
<td>24±3 (23–28)</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>278±33</td>
<td>264±60</td>
<td>272±43 (244–302)</td>
</tr>
<tr>
<td>Factor VII activity (%)</td>
<td>87±13</td>
<td>106±31</td>
<td>92±11 (100–106)</td>
</tr>
<tr>
<td>t-PA antigen (ng/ml)</td>
<td>5.8±4.1</td>
<td>6.2±5.2</td>
<td>4.2±1.2 (3.6–4.7)</td>
</tr>
<tr>
<td>PAI activity (units/ml)</td>
<td>30.9±9.5*</td>
<td>12.7±7.1</td>
<td>9.5±4 (7.8–11.2)</td>
</tr>
</tbody>
</table>

LA(+), positive for lupus anticoagulant; LA(-), negative for lupus anticoagulant; aPTT, activated partial thromboplastin time; t-PA, tissue plasminogen activator; PAI, plasminogen activator inhibitor. Values in parentheses indicate ranges.

*P<0.001 compared with LA(-) patients and control subjects. No other statistical differences were found.
pletely clarified. Recently we suggested that an imbalance between t-PA and its inhibitor PAI could predispose to thrombosis in LA(+) patients. This seems to be confirmed by the present investigation, in which t-PA antigen levels were within normal range, whereas PAI activity, a marker of hypercoagulability previously related to venous and arterial thrombosis, was significantly higher in LA(+) patients than in LA(−) patients and control subjects.

In conclusion, our study shows that, among young stroke patients, the presence of LA is associated with an imbalance of the fibrinolytic system as a result of the increased levels of circulating PAI activity. The pathophysiological relevance of this association as a thrombotic risk factor in the pathogenesis of stroke in young adults needs to be verified in larger prospective studies.

Acknowledgments

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References

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