Lupus Anticoagulant and Anticardiolipin Antibodies in Young Adults With Cerebral Ischemia

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Retrospective surveys have reported an association between focal cerebral ischemia and antiphospholipid antibodies, mainly in patients with systemic lupus erythematosus or with prolonged partial thromboplastin time in routine screenings. Recent prospective and controlled studies have confirmed the association of antiphospholipid antibodies with cerebral ischemia in the young, as well as in patients of other ages, although the relevance of this association in older patients has been recently questioned. Patients with cerebral ischemia and antiphospholipid antibodies are younger than the general stroke population.

Little information is available about the prevalence of antiphospholipid antibodies in unselected, young populations with cerebral ischemia. Nor are there many studies looking at the characteristics of young patients with antiphospholipid antibodies based on the presence of conventional risk factors for and pathological mechanisms of cerebral ischemia. Although it has been observed that patients with cerebral ischemia and antiphospholipid antibodies frequently suffer from recurrent cerebral ischemic or systemic thrombotic events, a recent prospective study has concluded that these patients have a good prognosis.

The aims of our study were to determine the frequency of lupus anticoagulant, anticardiolipin antibodies, or both in an unselected young population with cerebral ischemia; to investigate the presence of these antiphospholipid antibodies in relation to conventional risk factors for and pathological mechanisms of cerebral ischemia; and the risk of recurrence of cerebral ischemia or systemic thrombotic events in patients with antiphospholipid antibodies compared with those without.

Background and Purpose: Our study evaluates in an unselected young population with cerebral ischemia the frequency of antiphospholipid antibodies; the relationship of antiphospholipid antibodies to conventional risk factors for and pathological mechanisms of cerebral ischemia; and the risk of recurrence of cerebral ischemia or systemic thrombotic events in patients with antiphospholipid antibodies compared with those without.

Methods: We prospectively tested for antiphospholipid antibodies in 55 of 59 young (aged 15–44 years) adults consecutively examined for ischemic stroke (n=44) or transient ischemic attack (n=11). These patients underwent a complete clinical and laboratory assessment for cerebral ischemia and had a 3-year mean follow-up.

Results: Ten patients (18%), all with stroke, had antiphospholipid antibodies. Antiphospholipid antibodies were significantly more frequent in women than in men (Fisher’s test, p = 0.014). Two patients with antiphospholipid antibodies had a new diagnosis of systemic lupus erythematosus. On angiography, none of the patients with antiphospholipid antibodies had extracranial lesions. Patients with antiphospholipid antibodies had significantly more prior cerebral events (Fisher’s test, p = 0.014), and, by survival analysis, higher probability of cerebral ischemic or systemic thrombotic events during follow-up than patients without (log rank test, p < 0.005).

Conclusions: We conclude that the prevalence of antiphospholipid antibodies is rather high in young adults with cerebral ischemia; that patients with cerebral ischemia and antiphospholipid antibodies may have unrecognized systemic lupus erythematosus; and that, among young patients with cerebral ischemia, patients with antiphospholipid antibodies constitute a subgroup at high risk of cerebral ischemic or systemic thrombotic recurrence. Prevention in this latter group may require close follow-up and treatment. (Stroke 1992;23:189–193)
ventional risk factors for and pathological mechanisms of cerebral ischemia; and to evaluate the recurrence of cerebral ischemia or systemic thrombotic events in young patients with antiphospholipid antibodies compared with those without.

**Subjects and Methods**

Between January 1985 and June 1989, 59 patients (age range 15–44 years) were consecutively examined at the Department of Neurology of the University of Florence for transient ischemic attack (TIA) or ischemic stroke and entered into a computerized Young Stroke Registry.19 We were able to test for both lupus anticoagulant and anticardiolipin antibodies in only 55 of the 59 patients because two died in the first few hours after the stroke event and two were on anticoagulants. These 55 patients (36 men and 44 patients with ischemic stroke. We defined stroke and TIA according to the criteria of the World Health Organization20 and the Stroke Committee,21 respectively. The diagnosis of ischemic stroke was based on computed tomography (CT).22 In all patients, the CT was performed within 2 weeks after the last neurological event. Particular care was taken to exclude patients with acute focal events caused by nonischemic causes (epilepsy, trauma, tumors, or intracerebral or subarachnoid hemorrhage) or with TIA-mimicking symptoms such as dizzy spell, isolated loss of consciousness, or generalized weakness.

All patients had a standard clinical and laboratory assessment, including collection of historical data on cerebrovascular risk factors, miscarriage, and deep vein thrombosis; neurological and cardiac evaluation; standard blood and urine tests; electrocardiogram; two-dimensional echocardiography; brain CT scan; and continuous-wave Doppler sonography of the cervical arteries. Forty-five patients (82%) underwent selective conventional cerebral angiography and six (11%) transcranial Doppler. Circulating immune complexes and antinuclear antibodies were tested in 33 patients (60%).

We defined the presumed etiopathogenic types of cerebral ischemia according to Bogousslavsky et al,23 with modifications: 1) atherothrombosis, if angiography revealed nonstenosing ulcerated plaque, stenosis ≥50%, or occlusion of the congruent extracranial or large intracranial artery and the absence of other etiology; 2) possible atherothrombosis, if two or more risk factors (among hypertension, diabetes mellitus, smoking, and dyslipidemia) were present and other etiology was absent; 3) embolic heart disease, if cardiac abnormalities that are conventionally accepted as potential sources of emboli24 were demonstrated by two-dimensional echocardiography or electrocardiogram and other etiology was absent; 4) lacunar infarction, in patients with clinical and CT lacunar infarction in the territory of a deep perforating artery and in the absence of other etiology; 5) arterial dissection, defined on the basis of the typical angiographic signs25 and in the absence of other etiology; 6) migraine, when cerebral ischemia occurred during a migraine attack and in the absence of other etiology; 7) systemic lupus erythematosus, according to the 1982 American Rheumatism Association criteria26 and in the absence of other etiology; 8) mixed, if the above etiologies were combined; and 9) undetermined, if no etiology could be determined.

After the index event, all the patients were regularly followed with visits every 3 months. Any cerebral ischemic (TIA or stroke) or systemic thrombotic (myocardial infarction, peripheral artery, or vein thrombosis) event occurring during the follow-up was registered.

Fifty-six healthy volunteers (43 men and 13 women; mean age 40±5 years) previously tested for anticardiolipin antibodies and 55 healthy volunteers (35 men and 20 women; mean age 37±8 years) previously tested for lupus anticoagulant served as controls. A history of stroke/TIA, malignant disorders, human immunodeficiency virus, or autoimmune disease was cause for excluding potential control subjects.

Venous blood samples were collected by a standard venipuncture technique on average 99 days (range 6–278 days) after the index event. Lupus anticoagulant was determined using the diluted tissue thromboplastin inhibition test.27 When ratio of patient’s to control’s clotting time was higher than 1.2 in 1:100 dilution and higher than 1.3 in 1:1,000 dilution, the patient was classified among patients with lupus anticoagulant. The presence of circulating immunoglobulins G and M anticardiolipin antibodies was determined by a solid-phase radioimmunoassay.28 Values higher than 20 GPL units or 20 MPL units for immunoglobulin G or M, respectively, were considered abnormal according to Harris,29 and the patients with these values were labeled as having anticardiolipin antibodies.

For data analysis, patients with either lupus anticoagulant, anticardiolipin antibodies, or both were defined as patients with antiphospholipid antibodies, whereas those with neither lupus anticoagulant nor anticardiolipin antibodies were defined as patients without antiphospholipid antibodies. We compared these two groups for demographic characteristics (age and sex) and risk factors, as expressed by the following variables: 1) continuous variable: age; 2) categorical variables: sex, hypertension (history or blood pressure ≥160/90 mm Hg in at least two recordings), diabetes (history or fasting blood glucose ≥120 mg/dl), smoking (current or at any time smoking >20 cigarettes), hypercholesterolemia (fasting total cholesterol >230 mg/dl), low high density lipoprotein cholesterol (fasting high density lipoprotein cholesterol <40 mg/ dl), or hypertriglyceridemia (fasting triglycerides >170 mg/dl).

To evaluate the recurrence of cerebral ischemic or systemic thrombotic events during follow-up, we per-
formed a survival analysis in the two groups with and without antiphospholipid antibodies.

The significance was tested by Student's $t$ test for continuous variables, Fisher's exact test for categorical variables, and the log rank test for survival analysis.30 The analyses were performed using the EPILOG PLUS software package (Epicenter Software, Pasadena, Calif.). The differences were considered significant at the $p<0.05$ level.

Results

Of the 55 patients tested, 10 (18%), all with stroke, had antiphospholipid antibodies: four had both lupus anticoagulant and anticardiolipin antibodies, four only lupus anticoagulant, and two only anticardiolipin antibodies. Among the six patients with anticardiolipin antibodies, three had immunoglobulins M and G antibodies, two had immunoglobulin G antibodies, and one had immunoglobulin M antibodies.

One (2%) of the 56 healthy controls tested for anticardiolipin antibodies had positive anticardiolipin antibodies compared with six (11%) of the 55 patients with cerebral ischemia (Fisher's test, $p=0.054$). One (2%) of the 55 healthy controls tested for lupus anticoagulant had lupus anticoagulant compared with eight (15%) of the 55 young ischemic patients (Fisher's test, $p=0.016$).

No patients with antiphospholipid antibodies had previously had infections, neoplasms, or primary immunodeficiency syndrome, nor had they taken any drug known as an inducer of antiphospholipid antibodies. One patient with both lupus anticoagulant and anticardiolipin antibodies had positive serum and negative cerebrospinal fluid microhemagglutination assays for Treponema pallidum antibodies. Two female patients were affected by systemic lupus erythematosus. In these patients stroke was the first manifestation of the disease.

The demographic characteristics and risk factors of patients with and without antiphospholipid antibodies are reported in Table 1. Antiphospholipid antibodies were significantly more frequent in women than in men (Fisher's test, $p=0.014$). Patients with antiphospholipid antibodies were younger than those without, but the difference was of borderline significance ($t$ test, $p=0.06$). Previous cerebral events were more frequently reported by patients with than by patients without antiphospholipid antibodies (Fisher's test, $p=0.014$). Several other risk factors tended to be more frequent in patients without antiphospholipid antibodies, but the difference was statistically significant only for hypertriglyceridemia (Fisher's test, $p=0.032$).

Of the factors known to be associated with antiphospholipid antibodies, thrombocytopenia, recurrent miscarriages, false-positive syphilis test, prolonged partial thromboplastin time, and deep vein thrombosis were concomitantly present in one patient with antiphospholipid antibodies and systemic lupus erythematosus. Prolonged partial thromboplastin time was found in two other patients with antiphospholipid antibodies. A history of deep vein thrombosis was present in four other patients with (one with systemic lupus erythematosus) and in one patient without antiphospholipid antibodies.

Eight (80%) of the 10 patients with and 37 (82%) of the 45 patients without antiphospholipid antibodies underwent angiography. The proportion of patients with abnormalities was essentially the same in the two groups (three of eight [37.5%] with antibodies; 17 of 37 [45.9%] without antibodies). In the former group, the abnormalities were all at the intracranial level (one occlusion and one stenosis of middle cerebral artery, one occlusion of the calcarine branch of posterior cerebral artery). In the latter group, four patients had angiographic alterations at the intracranial level (two occlusion of middle cerebral artery, one stenosis of posterior cerebral artery, one signs of vasculitis), and 13 at the extracranial level (three severe stenosis of internal carotid artery, four carotid plaque, two vertebral occlusion, and four carotid or vertebral dissection) (Fisher's test, $p=0.03$ for the frequency of extracranial versus intracranial lesions in the two groups).

The distribution of possible etiopathogenic types of cerebral ischemia in the groups with and without antiphospholipid antibodies is reported in Table 2. Patients with antiphospholipid antibodies received antiplatelet agents in seven (70%), anticoagulation in one (10%), and a combination of antiplatelet agents and corticosteroids in two (20%) cases. In the group without antiphospholipid antibodies, 34 patients (76%) were treated with antiplatelet agents, five (11%) with anticoagulation, two (4%) with endarterectomy and antiplatelet agents, and four (9%) with unspecified treatments.
TABLE 2. Possible Etiopathogenic Types of Cerebral Ischemia in Young Patients With and Without Antiphospholipid Antibodies

<table>
<thead>
<tr>
<th>Antiphospholipid antibodies</th>
<th>Present (n = 10)</th>
<th>Absent (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherothrombosis*</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Possible atherothrombosis</td>
<td>0</td>
<td>9</td>
</tr>
<tr>
<td>Embolic heart disease†</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Arterial dissection</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Lacunar infarction</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Migraine</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pregnancy/peripartum</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mixed‡</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Undetermined</td>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

*One of the two patients with antiphospholipid antibodies was an amphetamine abuser.
†Four patients (one with and three without antiphospholipid antibodies) had mitral valve prolapse, and one had sick sinus syndrome.
‡Atherothrombosis and lacunar infarction.

During a mean follow-up of 35 months (range 14–47 months), four of the 10 patients with antiphospholipid antibodies suffered new cerebral ischemic or systemic thrombotic events (fatal stroke in one, stroke and subsequent myocardial infarction in one, TIA and subsequent deep vein thrombosis in one, and deep vein thrombosis in one) compared with two of the 45 patients without antiphospholipid antibodies (stroke in one and TIA in one) (log rank test, \( \chi^2 = 9.91, p < 0.005 \)). None of these recurrent events occurred between the index event and the antiphospholipid antibody testing.

Discussion

Our findings show that when a simultaneous determination of lupus anticoagulant and anticardiolipin antibodies is carried out, a rather high proportion (18%) of unselected young patients with focal cerebral ischemia (stroke or TIA) have antiphospholipid antibodies. This prevalence is higher than that reported in patients of all ages (from 7% to 9% in recent prospective surveys).\(^1,^{14,18}\) In young adults with cerebral ischemia Brey et al\(^{12}\) have found a 46% prevalence of antiphospholipid antibodies. This higher figure is caused by different selection criteria and more sensitive laboratory tests.\(^31\) Hart et al\(^{11}\) reported a low prevalence (4%) of lupus anticoagulant, but they screened only young stroke patients with prolonged partial thromboplastin time. The absence of antiphospholipid antibodies in our TIA patients is probably related to the small number of TIA cases we examined. Systemic lupus erythematosus might be a confounder for the higher frequency of antiphospholipid antibodies in our female patients; a higher female prevalence, however, is also reported in primary antiphospholipid syndrome.\(^32\)

In our series, lupus anticoagulant and anticardiolipin antibodies were variably associated. In other reports dealing with systemic lupus erythematosus patients, the percentage of positive lupus anticoagulant assay in the absence of anticardiolipin antibodies varies from 0%\(^1\) to 31%\(^{30}\) and that of positive anticardiolipin antibody assay in the absence of lupus anticoagulant from 17%\(^1\) to 73%.\(^{34}\) All of these data indicate that there is a heterogeneity in the laboratory profile of patients with antiphospholipid antibodies and that a simultaneous determination of different antiphospholipid antibodies should be performed to reduce the number of false-negative patients.

The angiographic study confirms the previously reported observation\(^6,^{16}\) that stabilized arterial lesions in young patients with cerebral ischemia and antiphospholipid antibodies are located mainly at the intracranial level.

Our findings also indicate that unselected young patients with cerebral ischemia and antiphospholipid antibodies are at high risk of cerebral ischemic or systemic thrombotic recurrences during the follow-up. This conclusion agrees with two previous studies in patients of similar age,\(^12,^{17}\) whereas it contrasts with a recent study\(^18\) reporting a good prognosis in middle-aged patients with antiphospholipid antibodies treated with 1 g/day aspirin. On the basis of our data, young patients with cerebral ischemia and with antiphospholipid antibodies should be intensively followed and treated to reduce the risk of recurrences. A controlled clinical trial (antiplatelet agents or anticoagulants, eventually associated with immunosuppressive drugs) could indicate the best treatment for these patients.

Acknowledgments

The authors wish to thank Dr. Giovanni Pracucci and Ms. Maria Costanzo for technical assistance.

References

Antiphospholipid Antibodies in Cerebral Ischemia


**Key Words** • anticoagulants, anticardiolipin antibodies • anticoagulants, antiphospholipid antibodies • anticoagulants, lupus • cerebral ischemia
Lupus anticoagulant and anticardiolipin antibodies in young adults with cerebral ischemia.

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*Stroke*. 1992;23:189-193
doi: 10.1161/01.STR.23.2.189

*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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