Clinical and Laboratory Findings in Patients With Antiphospholipid Antibodies and Cerebral Ischemia

The Antiphospholipid Antibodies in Stroke Study Group

We reviewed the clinical and laboratory data of 128 patients with cerebrovascular disease and antiphospholipid antibodies. Cases were evenly divided between men and women, and the mean age of the study group was 46 years. Cerebral infarction occurred in 97 patients, and transient hemispheric ischemic attacks without stroke were recorded in 19; 12 suffered ocular ischemia. Systemic lupus erythematosus was diagnosed in 16% of all cases. Histories of systemic thromboembolic events and recurrent miscarriages were noted in 14% of the patients and in 19% of the women, respectively. Evidence of cerebral infarction preceding the index event was present in 30% of cases. During a mean follow-up of 16 months, nine of 96 (9%) patients sustained new cerebral infarctions. Of 72 echocardiographic studies, 16 (22%) showed valvular abnormalities. Cerebral angiography detected intracranial lesions in 24 of 49 patients (49%). These data indicate that antiphospholipid antibodies can be identified in stroke patients without known autoimmune disorders. They also suggest that antiphospholipid antibody-associated cerebrovascular ischemia may be recurrent and often occurs in patients with systemic thromboembolic events. Our findings should help design a prospective clinical trial that will assess the risk of recurrent thromboembolism in this population, identify stroke risk factors, and address therapy. 

Antiphospholipid antibodies are immunoglobulins of the IgG, IgM, and IgA classes with specificities for anionic and neutral phospholipids and include anticardiolipin antibodies and lupus anticoagulants. Originally detected in patients with systemic lupus erythematosus (SLE), they have since been described in other autoimmune disorders, as well as malignancy, myocardial infarction, and other illnesses. A number of investigators have associated these antibodies with a tendency for thromboembolism and laboratory studies have assessed their effects on hemostatic pathways. Recent reports have described antiphospholipid antibodies in patients with seizures, headache, subdural hematoma, and a variety of neurological syndromes. Patients with cerebral arterial or venous thromboembolic events and antiphospholipid antibodies increasingly have been identified. However, most studies present only a small number of cases, and the clinical, laboratory, and radiological characteristics of the association remain relatively unknown. The data available to assess the prevalence of these antibodies in patients with cerebrovascular disease or other neurological disorders are limited. Although antiplatelet agents, anticoagulants, and corticosteroids have been used empirically to treat patients with stroke, the efficacy of proposed therapeutic modalities remains to be determined.

The Antiphospholipid Antibodies in Stroke Study (APASS) Group includes investigators in 21 medical centers and was organized to study the association of antiphospholipid antibodies with neurological disorders. To better define the clinical characteristics of this association, we review selected features from 128
patients with these antibodies and ischemic cerebrovascular disease.

Subjects and Methods
We reviewed the medical records of patients who presented with symptoms of acute ocular or cerebral ischemia and had evidence of antiphospholipid antibodies within 30 days from onset of symptoms. Patients were not selected as part of a prospective study and were not evaluated with a predetermined battery of tests. The series therefore represents only a collection of case presentations. Eleven centers entered patients in this study. Patients were evaluated from 1983 to 1989. A two-page data collection form was completed for each patient by the participating investigators, and the data was entered into a Professional Filing System database system (Software Publishing Corp., Mountain View, Calif.).

The diagnosis of transient ischemic attack was made when a focal and presumably ischemic neurological deficit of sudden onset resolved within 24 hours, and the brain computed tomographic (CT) scan, when available, did not show findings consistent with new infarction. Internal carotid artery territory transient ischemic attacks were divided into transient hemispheric and amaurosis fugax attacks. When symptoms lasted more than 24 hours, cerebral or retinal infarction was diagnosed irrespective of brain CT findings. All laboratory tests, including cerebral angiograms and CT scans, were performed within 1 month after the index cerebrovascular event.

The index event was defined as the stroke, retinal infarction, or transient ischemic episode that prompted the battery of tests. The series therefore represents only the complete neurological evaluation. The diagnosis of SLE was based on the 1982 American Rheumatism Association criteria. Hypertension was defined as a systolic blood pressure above 140 mm Hg or a diastolic above 90 mm Hg during index admission, or a previous history of high blood pressure requiring medical treatment. Anticardiolipin antibody titers were determined in 94 patients and were elevated in 81 (86.2%); although the IgG isotype was detected in 64 of 94 (68.1%) patients and were elevated in 81 (86.2%); although the IgG isotype was detected in 64 of 94 (68.1%) patients, including 22 of 115 (19.1%) had hypercholesterolemia, and seven of 118 (5.9%) had diabetes mellitus.

Sixty-three men and 65 women satisfied the inclusion criteria. Their mean age was 45.8 years (SD = ±17.0). The mean age was 48.8 years (SD = ±16.0) for men and 42.8 years (SD = ±17.5) for women at the time of the index cerebrovascular event. Age distribution is presented in Figure 1.

The index event was cerebral infarction in 97 patients, including two with cerebral venous thrombosis, and transient hemispheric attacks without stroke in 19. Seven patients had transient monocular visual symptoms, three had central retinal artery occlusions, and two had central retinal vein occlusion. Clinical evidence of cerebral infarction preceding the index event was found in 37 of 124 (29.8%) patients with available information, including 12 (9.7%) with more than one cerebral infarct. In addition, 19 (15.3%) patients gave histories of transient hemispheric attacks.

Follow-up information was available in 96 patients. The mean follow-up interval was 16.2 months (SD = ±12.4). Six (6.3%) patients had transient hemispheric attacks, and nine (9.4%) sustained a new cerebral infarction during the follow-up period.

Associated illnesses and risk factors included SLE, which had been diagnosed at the time of the index event in 19 of 117 (16.2%) patients, including 15 women. Their mean age was 40.8 years (SD = ±14.2). A history of cerebral infarction preceding the index event was found in nine (47.4%) of these patients, and transient hemispheric attacks without stroke in four (21.1%). Brain CT scans showed multiple areas consistent with infarction in seven (36.8%). A history of deep vein thrombosis was obtained from 18 of 125 (14.4%) patients, and miscarriage(s) from 12 of 63 (19.0%) women. Thirty-two of 122 (26.2%) patients were hypertensive, 22 of 115 (19.1%) had hypercholesterolemia, and seven of 118 (5.9%) had diabetes mellitus.

The activated partial thromboplastin time (aPTT) was prolonged in 60 of 119 (50.4%) patients tested. Anticardiolipin antibody titers were determined in 94 patients and were elevated in 81 (86.2%); although the IgG isotype was detected in 64 of 94 (68.1%) patients, 12 patients harbored only IgM antibodies and two had only IgA antibodies. The lupus anticoagulant was detected in 79 of 103 (76.7%) patients. Seventy patients had simultaneous anticardiolipin antibody and lupus anticoagulant testing: Thirty-two (45.7%) harbored both types of antibodies, 25 (35.7%) harbored the former only (including three with IgM antibodies), and 13 (18.6%) had only the latter.

Serological testing showed that antinuclear and anti-DNA antibody titers were elevated in 58 of 106 (54.7%) and 10 of 61 (16.4%) patients, respectively.
The venereal disease research laboratory or rapid plasma reagin test was positive in 21 of 108 (19.4%) patients tested. Antinuclear and anti-DNA antibody testing was negative in 24 of 60 (40.0%) patients who received both tests simultaneously. None of these patients had clinical evidence of autoimmune disorders. Their mean age was 42.1 years (SD=±13.1). Seventeen (70.8%) were men. Seven (29.2%) gave histories of stroke preceding the index event, and multiple CT areas of cerebral infarction were noted in seven of 23 (30.4%).

Electrocardiograms showed atrial fibrillation in five patients, all more than 45 years of age, and acute myocardial infarction in another two. Echocardiographic findings from 72 patients are summarized in Table 1.

Brain CT scans had been obtained in all but 12 patients and were normal in 35 (30.2%). Computed tomographic findings were consistent with a single cerebral infarction in 53 (45.7%) cases, and multiple infarctions in 28 (24.1%) patients.

Table 2 summarizes cerebral angiographic findings in 49 patients. Eighteen patients (36.7%) had normal studies; 24 (49.0%) had studies showing intracranial lesions, including 19 who had no cervical carotid disease, and 11 (22.4%) had arteriograms with extracranial lesions.

**Discussion**

This study presents selected clinical, laboratory, and radiological features of 128 patients with cerebral or ocular ischemia who were found to have antiphospholipid antibodies. Our data suggest that these patients share characteristics that may distinguish them from other patients with cerebrovascular disease.

A mean age of 45.8 years in our patients confirms the previous impression that antiphospholipid anti-

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**FIGURE 1.** Age distribution of 128 patients with antiphospholipid antibodies and cerebral or ocular ischemic events.

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**TABLE 1.** Echocardiographic Findings in 72 Patients With Antiphospholipid Antibodies and Cerebral or Ocular Ischemic Events

<table>
<thead>
<tr>
<th>Findings</th>
<th>No. of patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>48 (66.7)</td>
</tr>
<tr>
<td>Mitral valve abnormalities</td>
<td>16 (22.2)</td>
</tr>
<tr>
<td>Myxomatous thickening</td>
<td>8</td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td>9</td>
</tr>
<tr>
<td>Mitral insufficiency</td>
<td>8</td>
</tr>
<tr>
<td>Aortic valve abnormalities</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>Aortic valve calcification</td>
<td>1</td>
</tr>
<tr>
<td>Aortic insufficiency</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac wall abnormalities</td>
<td>7 (9.7)</td>
</tr>
<tr>
<td>Akinetic segment(s)</td>
<td>4</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>3</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>1</td>
</tr>
<tr>
<td>Thrombus</td>
<td>3 (4.2)</td>
</tr>
</tbody>
</table>

*Numbers within parentheses represent ratios of specific findings to total number of studies expressed in percentages. Several patients had more than one abnormal echocardiographic finding.
Antiphospholipid Antibodies in Cerebral Ischemia

TABLE 2. Angiographic Findings in 49 Patients With Antiphospholipid Antibodies and Cerebral or Ocular Ischemic Events

<table>
<thead>
<tr>
<th>Findings</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>18</td>
</tr>
<tr>
<td>Intracranial lesions</td>
<td>24</td>
</tr>
<tr>
<td>MCA trunk stenosis/occlusion</td>
<td>4</td>
</tr>
<tr>
<td>MCA branch occlusion</td>
<td>11</td>
</tr>
<tr>
<td>ACA trunk stenosis/occlusion</td>
<td>2</td>
</tr>
<tr>
<td>PCA branch occlusion</td>
<td>3</td>
</tr>
<tr>
<td>ICA stenosis/occlusion</td>
<td>4</td>
</tr>
<tr>
<td>Basilar stenosis</td>
<td>2</td>
</tr>
<tr>
<td>&quot;Vasculitis&quot;</td>
<td>2</td>
</tr>
<tr>
<td>Extracranial lesions</td>
<td>11</td>
</tr>
<tr>
<td>ICA stenosis/occlusion</td>
<td>7</td>
</tr>
<tr>
<td>VA stenosis/occlusion</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
</tbody>
</table>

MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery; ICA, internal carotid artery; VA, vertebral artery. "Other" included the following diagnoses: ICA fusiform aneurysm, ICA intraluminal clot, VA dissection, and superior sagittal sinus, transverse sinus, and MCA arteriovenous malformation thrombosis. Several studies had more than one abnormal finding.

Anticardiolipin antibodies are frequently identified in "young" stroke patients who are less than age 50. However, 50 (39.1%) of our patients were in their sixth to ninth decades, indicating that these antibodies can be found in older stroke patients as well. Antiphospholipid antibodies may be undetected in older patients who are not screened as vigorously as young adults. That only five patients were less than age 20 may represent a selection bias, because most of the participating investigators were adult neurologists who do not routinely examine pediatric stroke patients.

Previous studies have suggested that, in patients with SLE and without SLE, the presence of antiphospholipid antibodies is associated with an increased risk for thromboembolic events. Almost 30% of our patients had clinical evidence of previous cerebral infarction at the time of the index event, but only 26.2% were hypertensive and 5.9% diabetic, the two factors commonly associated with an increased risk for recurrent stroke. Twelve patients (9.7%) had clinical evidence of multiple strokes, and CT scans showed findings consistent with more than one area of infarction in 24.1% of cases, indicating that many infarcts had not been clinically recognized. In addition, nine patients for whom follow-up information was available (9.4%) sustained new cerebral infarcts during a mean follow-up interval of 16.2 months. A follow-up of stroke patients less than age 40 and admitted consecutively at a university hospital reported a stroke incidence of 0.5% per year. Our findings are therefore in accord with reports suggesting that the presence of antiphospholipid antibodies characterizes a state of recurrent ischemic events. The thromboembolic events are not limited to the cerebral vasculature. Deep vein thrombosis occurred in 14.4% of our patients and miscarriage in 19.0% of the women. Miscarriages have been associated with decidual vasculopathy and placental infarction in some patients. Thus, antiphospholipid antibodies may be the hallmark of a systemic hypercoagulable state. A prospective clinical study is needed to determine whether the high rate of initial and recurrent vascular events observed in our selected population characterizes all stroke patients who have these antibodies.

Only two of our patients had arteriographic findings suggestive of intracranial vasculitis. The finding of normal studies or cerebral angiograms showing intracranial infarcts without corresponding carotid artery stenotic lesions in 75.5% of patients suggests that either intravascular in situ thrombosis or cardiac embolism was the potential cause of cerebral ischemia. Lupus anticoagulants and anticardiolipin antibodies have been reported to alter thrombosis by several mechanisms. We searched for evidence of cardiac lesions that could lead to brain embolism. Clinical and electrocardiographic findings of acute myocardial infarction and atrial fibrillation preceding cerebrovascular symptoms were identified in two and five patients, respectively. Fifty-two percent of our patients with echocardiograms had abnormal studies. However, atrial or ventricular thrombi were identified in only three patients, and echocardiographic findings usually associated with cerebral embolism such as akinetic segments or septal defects were identified in only five. Mitral valve abnormalities consisting of a "myxomatous" thickening associated with prolapse or insufficiency were noted in 22.2% of studies and constituted the most common finding. Aortic valve calcification and insufficiency were found in two patients. Similar valvular involvement has also been identified in patients with active SLE. Pathological studies of a surgically excised mitral valve from a patient with SLE and anticardiolipin antibodies showed that the thickening consisted of layers of thrombus of different ages. However, both aortic valve thickening and mitral valve calcification without thickening have also been described in patients with acute ischemic cerebrovascular disease. Whether the mitral valve abnormalities are significantly more common in this disorder than in patients without antiphospholipid antibodies remains undetermined. We suggest that the cardiac chambers and valves may be the source of emboli causing cerebral or retinal ischemia in some patients with these antibodies.

Anticardiolipin antibody levels may be predictive of thrombotic symptoms. Harris et al found a strong correlation between IgG isotype levels and arterial or venous thrombosis in patients with autoimmune disorders and noted that antibody titers more than seven standard deviations above the mean of controls were highly specific and predictive for thrombosis. Briley et al reported that anticardiolipin antibody levels correlated with disease severity and that patients with higher titers appeared more likely to have multiple strokes. These conclusions were dif-

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different from the findings of Kalunian et al., who reported that measurement of all three isotypes optimized clinical correlations and that although the presence of these antibodies correlated with thrombosis, titers fluctuated widely and did not add to clinical utility. Other investigators have found that in patients with phenothiazine-induced autoimmune disorders, antibodies of the IgM isotype occur alone and are not associated with thrombotic events, suggesting that the three isotypes are not homogeneous with respect to ischemic events. We did not study the ability of anticardiolipin antibody titers to predict transient ischemic attacks or stroke, but found that although IgG was the most common isotype detected, some of our patients had only IgM or IgA isotypes. Approximately 46% of patients tested had both lupus anticoagulants and anticardiolipin antibodies; 18.6% had only the former, and 35.7% had only the latter, including three who had only the IgM isotype. These results suggest that high titers of a single anticardiolipin antibody isotype or the lupus anticoagulant can be associated with cerebral ischemic events. Until more data are available to clarify the significance of these tests, both lupus anticoagulants and all isotypes of anticardiolipin antibodies should be determined when indicated. In addition, our finding of prolonged aPTTs in only 50.4% of patients tested suggests that the aPTT is not a sensitive test to screen patients suspected of having antiphospholipid antibodies.

In their original communication, Conley and Hartman described the lupus anticoagulant in patients with SLE. Since then, antiphospholipid antibodies have frequently been reported in the context of autoimmune disorders. Only 16.2% of our patients had SLE and 16.4% had elevated anti-DNA antibody levels. However, antinuclear antibody titers exceeding a dilution of 1:32 provided laboratory evidence suggestive of an immunological disturbance in 54.7%. The subgroup of patients with SLE consisted predominantly of women (79.0%); approximately 47% had a history of cerebrovascular events preceding index presentation. Forty percent of our patients who received both the antinuclear antibody and anti-DNA tests had negative results. They had no clinical evidence of an autoimmune disease, were more frequently male (70.8%), and gave a history of stroke preceding the index event (29.2%). These preliminary analyses indicate that antiphospholipid antibodies can be detected in patients with cerebrovascular disease who may or may not have clinical evidence of autoimmune disorders. Thus, the population of patients with cerebrovascular disease and antiphospholipid antibodies may be heterogeneous with respect to pathogenesis and course of the disease.

In this report, we reviewed some of the clinical and laboratory features of patients with antiphospholipid antibodies and cerebral or ocular ischemia. Our preliminary findings should be interpreted with caution, because we retrospectively analyzed a highly selected population. The data may be used to design a prospective clinical trial that will assess the incidence and pathogenesis of primary and recurrent thromboembolic events in this population, identify potential subgroups, and determine the laboratory characteristics of antiphospholipid antibodies causally associated with stroke. Answers to these questions will help address therapy.

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References


KEY WORDS • anticoagulants, anticardiolipin antibodies • anticoagulants, antiphospholipid antibodies • cerebrovascular disorders
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