Ischemic Stroke Associated With Anticardiolipin Antibodies

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Anticardiolipin antibodies are a group of antiphospholipid autoantibodies seen primarily in patients with systemic lupus erythematosus and other autoimmune diseases. We report 3 patients, 2 without systemic lupus, who suffered ischemic brain infarction associated with these antibodies in the absence of detectable lupus anticoagulant activity. Anticardiolipin antibodies, possibly associated with a lupus anticoagulant-like thrombotic tendency, may be a newly recognized cause of ischemic stroke. (Stroke 1987;18:1101-1106)

Antiphospholipid antibodies are a group of circulating autoantibodies seen primarily in patients with systemic lupus erythematosus (SLE),1-3 other autoimmune diseases,3,9-13 and a variety of seemingly unrelated diseases.14-16 Among these autoantibodies, anticardiolipin antibodies (ACAs) have been closely associated with recurrent thrombotic complications including stroke in patients with SLE.2 ACAs also share the same or closely related antigenic specificities with another group of serum immunoglobulins, the lupus anticoagulants (LA).1,3 Purified ACA may have LA activity,17 and accumulating evidence suggests that patients with LA are at risk for recurrent thrombotic events including stroke.1,4,18-22 ACA may therefore be an occult cause of thrombotic cerebrovascular disease, especially in young patients. We describe 3 patients, 2 without SLE, in whom ACAs were associated with ischemic cortical stroke in the absence of detectable LA.

Subjects and Methods

ACAs were assayed by the enzyme-linked immunosorbent assay (ELISA) method of Loizou et al23 with slight modification. Serum dilutions of 1:25 instead of 1:100 were used because of the greater reproducibility of results, and the plates were evaporated with cold air instead of nitrogen.

Normative data were based on 36 controls. An IgG ACA binding index of 1.86-2.44 and an IgM ACA binding index of 2.59-3.65, 3-5 standard deviations (SD) above the control mean for both, were considered borderline positive. We considered ACA levels >5 SD above the control mean to be elevated.

Case 1

A 44-year-old black woman woke with left-sided weakness and numbness that lasted for hours. There was no history of heart disease, rheumatic fever, oral contraceptive or alcohol use, migraine, or diabetes mellitus. She had suffered 3 first-trimester spontaneous abortions. Mild hypertension had been diagnosed 8 months previous. There was a 25-pack-year history of cigarette use. Left-sided hyperreflexia, left arm pseudoathetosis, and left-sided extinction to visual and tactile double simultaneous stimulation were present on neurologic examination.

Complete blood and platelet counts, hemoglobin electrophoresis, prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, fasting glucose, triglycerides, Westergren erythrocyte sedimentation rate (ESR), serum protein electrophoresis, complement studies, and rheumatoid factor were all normal. Serum VDRL was positive; fluorescent treponemal antibody absorption test was negative. Antinuclear antibody (ANA) was weakly positive at 1:80 homogeneously. Electrocardiogram (ECG) was normal. Chest x-ray revealed a 5-cm anterior mediastinal mass, unchanged from 2 years previous. M-mode and two-dimensional echocardiography were normal except for a small posterior pericardial effusion. Head computed tomography (CT) scan revealed a lesion in the right parietal region consistent with an ischemic infarction (Figure 1). Cerebrospinal fluid (CSF) obtained under normal pressure was sterile with 7 white blood cells/mm3 (all lymphocytes). CSF protein, glucose, and IgG index were normal. No oligoclonal bands were present. CSF VDRL was nonreactive. Cerebral arteriography was remarkable only for a paucity of arterial vessels filling the right parietal region with a probable branch occlusion.

Because of her history of multiple spontaneous abortions and a false-positive VDRL, ACAs were assayed. IgG ACAs were present at levels of 7.2 SD above the control mean. She was placed on warfarin...
and hydrochlorothiazide and triamterene (Dyazide). She refused corticosteroids at this time.

Three months later she developed acute left-sided weakness, clumsiness, and numbness. She was confused and denied any deficits. There was a minimal right gaze preference and a mild right hemiparesis. There were no new abnormal laboratory findings. Intravenous heparin was given for 7 days after a head CT scan showed no change from previous admission. Warfarin was continued.

She had been depressed since her first stroke, and she was readmitted for suicidal ideations 2 months after her second stroke. In the hospital her prolonged PT fell to normal in spite of maintaining the same dose of warfarin. She became less responsive and did not follow simple commands. A right homonymous hemianopia and dense right-sided weakness were present. Lupus serologies, CSF analysis, and coagulation parameters remained unchanged. Head CT scan revealed a new left middle cerebral artery (MCA) territory infarction. Cerebral arteriography was significant only for a left MCA angular branch occlusion. The relation between the abnormal chest mass and recurrent strokes was raised; mediastinal biopsy revealed a thymoma.

In addition to warfarin she was treated with subcutaneous heparin, 60 mg prednisone daily, ranitidine, and nortriptyline. During removal of the thymoma she suffered her fourth ischemic stroke, which involved the entire left MCA territory. Neither intraoperative hypotension nor cardiac arrhythmia had occurred. Postoperative cerebral angiography was not performed. She has remained globally aphasic without new thrombotic events through 1 year of follow-up. ACAs could not be detected after removal of the thymoma.

Case 2

A 29-year-old black woman with a 9-year history of SLE suddenly fell to the ground, unable to speak or stand. Several days of headache had preceded this event. Ten months previous she had complained vaguely of "visual problems;" 8 months earlier she had intermittent right leg numbness. Four to 6 weeks prior to admission she was noted by her family to have a personality change. Azathioprine had been started 6 months before this admission but was discontinued after 3 months of use.

Medical history was significant for lupus nephritis, thrombocytopenia, splenectomy, and a first-trimester spontaneous abortion. There was no history of hypertension, cardiac disease, migraine, oral contraceptive use, or diabetes mellitus. She had smoked 10 cigarettes daily for 17 years. Her medications included Dyazide, orphenadrine, hydroxychloroquine, and prednisone. There was a history of noncompliance.

Examination revealed a soft systolic cardiac murmur. Blood pressure was 100/64 mm Hg. She had a fluctuating level of attention and concentration and would stutter severely upon attempting to speak. There was impaired memory and language function and left arm dyspraxia. A right homonymous hemianopia and hemiparesis were noted with dystonic right hand posturing.

Laboratory studies revealed mild leukocytosis and anemia. Platelet count, serum glucose, cholesterol, triglycerides, and sickle-cell preparation were normal. Westergren ESR was elevated to 42 mm/hr. ECG and echocardiography were normal. Head CT scan revealed multiple areas of low attenuation and a new contrast-enhancing area in the left MCA territory representing the most recent ischemic event (Figure 2). PT and activated PTT were normal on several occasions. ANA was weakly positive. ACA levels were > 5 SD above the control mean. Cerebral angiography revealed occlusions of the right internal carotid artery at its origin (Figure 3) and proximal left anterior cerebral artery (Figure 4). The left carotid bifurcation and vertebrobasilar circulation were normal.

On 80 mg prednisone daily, warfarin, azathioprine, 325 mg aspirin daily, and 50 mg dipyridamole t.i.d., repeat ACA titers were normal. No new ischemic events have occurred on this therapy during 1 year of follow-up.

Case 3

A 56-year-old black man developed acute mesenteric artery thrombosis. Three weeks later he suddenly became agitated and was noted to have left-sided weakness. On transfer to our care he was lethargic. His response to pain was diminished on his left side. Left-sided spasticity was noted. Severe ischemic signs in his right leg led to a diagnosis of thromboembolic occlusion of the right femoral artery.

At age 47 he had been evaluated for multiple presumably embolic events of the right arm and left foot.
Aortography revealed arterial occlusion below the popliteal bifurcation, and heparin was given. At that time blood and platelet counts, ANA, VDRL, and serum protein electrophoresis were normal. Sickle-cell trait was found. He subsequently developed mild hypertension and mild renal insufficiency.

Laboratory studies revealed anemia, hypocalcemia, and mildly elevated fibrinogen. PT, activated PTT, platelets, fibrin degradation products, and serum cholesterol and lipids were normal. Serum creatinine was 4 mg/dl (350 mmol/1). ECG showed borderline left atrial enlargement without evidence of new or old ischemic changes. Head CT scan revealed a right frontoparietal infarct (Figure 5). CSF was normal. Antithrombin in, Protein C, and specific coagulation factors were all normal except for elevated Factor VIU activity. Platelet studies revealed spontaneous aggre-
FIGURE 5. Case 3. Head computed tomogram. Ischemic infarction in right frontoparietal region.

gation with hyperaggregation to all inducers. IgG ACA levels were 9 SD above the control mean. Echocardiography revealed a 0.5-cm round, freely mobile left ventricular mass, without a stalk, near the apex. The valves and wall motion were normal. Coronary arteries were normal by angiography. The mass was removed. Histologic examination revealed a necrotic, cellular mass infiltrated with neutrophils; myxomatous tissue was not present. His metabolic parameters and neurologic deficits improved. He was placed on aspirin and dipyridamole. He has been without new symptoms during 6 months of follow-up.

Discussion

The clinician investigating a patient with thrombosis, including thrombotic stroke, generally does not consider a primary immunologic disturbance as causative. An exception may be in the setting of known or preexisting autoimmune disease. Antibodies to cardiolipin have been recently associated with thrombosis. Antiphospholipid antibodies may be detected by radioimmunoassay (RIA) and ELISA. ELISA is currently considered the method of choice due to its higher sensitivity and specificity.

LA, closely related antigenically to the ACAs, was not detectable in any of our 3 cases. Thus, ACAs may be frequently present in the absence of LA. The routine activated PTT is therefore an inadequate screen for AC As. Recent reviews of their relation are available. Approximately 50-70% of patients with ACAs also have LA (prolonged PTT). ACA activity is inhibited by negatively charged phospholipids such as phosphatidylserine, phosphatidic acid, phosphatidylglycerol and (probably) phosphatidylinositol, but not by double-stranded DNA. The ACAs are therefore largely distinct from anti-DNA antibodies.

To our knowledge, only 2 previous reports have described patients with ACA-associated stroke in the absence of SLE or LA. Coull et al reported 3 patients without SLE who had multiple cerebral infarctions and ACAs; VDRL and PTT were normal in all 3. Autopsy on 1 revealed thrombotic occlusions of both anterior cerebral arteries as well as multiple small systemic arteries; there was no associated vasculitis. Two of 15 patients reported by Harris et al with stroke and ACAs did not have SLE, although both had "lupus-like illnesses."

One of our patients (Case 2) had SLE, whereas the other 2 did not. Both women had a history of first-trimester spontaneous abortions and recurrent strokes. Multiple large vessel thromboses documented by angiography in our patient with SLE, although not diagnostic, was consistent with in situ thrombosis from a coagulopathy. Similar arteriographic abnormalities have been seen in patients with stroke and LA. One of our patients resembled what Harris et al and Hughes et al have called the "antiphospholipid antibody syndrome:" thrombosis, false-positive VDRL, and recurrent spontaneous abortions. However, it is interesting to note our patient's thymoma, which may be associated with other autoantibodies. Case 3 probably had a cardioembolic stroke from the spontaneous intracardiac thrombus, although a primary thrombotic event.

Table 1. Conditions Associated With Anticardiolipin Antibodies

<table>
<thead>
<tr>
<th>Condition</th>
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<tr>
<td>Idiopathic thrombocytopenia purpura</td>
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<td>Degos' syndrome (malignant atrophic papulosus)</td>
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<td>Sjogren's syndrome</td>
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<td>Behcet's syndrome</td>
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<td>Waldenstrom's macroglobulinemia</td>
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<td>Lyme disease</td>
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<td>Rheumatoid, osteoarthritis, and psoriatic arthritis</td>
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<tr>
<td>Dermatomyositis and polymyositis</td>
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<td>Post vaccination</td>
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<td>Post Epstein-Barr virus infection</td>
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<tr>
<td>Sneddon's syndrome (livedo reticularis and strokes)</td>
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<tr>
<td>Thymoma</td>
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<td>Acquired immunodeficiency syndrome (AIDS)</td>
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Antiphospholipid antibodies may be detected by radioimmunoassay (RIA) and ELISA. ELISA is currently considered the method of choice due to its higher sensitivity and specificity. Approximately 50-70% of patients with ACAs also have LA (prolonged PTT). ACA activity is inhibited by negatively charged phospholipids such as phosphatidylserine, phosphatidic acid, phosphatidylglycerol and (probably) phosphatidylinositol, but not by double-stranded DNA. The ACAs are therefore largely distinct from anti-DNA antibodies.
within the MCA could not be excluded with certainty. He was tested for ACAs because of multiple thromboembolic phenomena without known cause. Elevated Factor VIII and a hyperaggregable platelet response are not infrequent following acute ischemia. However, either or both may have contributed to stroke if they were present before the stroke.

Although ischemic stroke was associated with ACA in all our patients, this does not necessarily imply causation. Autoantibodies may appear subsequent to tissue damage. LAs, similar antibodies, do not seem to be a consequence of thrombosis\(^{20,21}\); however, this possibility has not yet been definitively excluded for ACAs.

Several potential mechanisms of thrombosis induced by antiphospholipid antibodies have been reported\(^{5,9,20,23-37}\) (Table 2), although a unifying pathogenesis is lacking. The quantitative ACA titer may predict the probability of thrombosis.\(^{38}\)

There has been no consistently effective therapy to prevent recurrent thrombosis including stroke in patients with antiphospholipid antibodies, probably due in part to their various mechanisms of action. A controlled study is needed. Our patients empirically received either antiplatelet or anticoagulant therapy with or without corticosteroids and are currently being followed for further events. The patient with SLE was also given immunosuppressive agents, which may have contributed to the reduction in ACA level. Goei et al\(^{12}\) reported preliminary data suggesting that in patients with SLE or SLE-like disease, ACA varies little over time and is incompletely suppressed by high-dose corticosteroids. Corticosteroids may normalize the PTT and therefore could mask the presence of a concomitant LA.\(^{7}\) This still remains a possibility in our second case. Plasmapheresis has been reported to decrease the antibody titer in 2 patients.\(^{12}\) Patients treated with oral anticoagulation and antiplatelet agents including aspirin have had variable clinical responses.\(^{8,19,20,22}\) Six patients with ACAs sustained thrombotic events 6–12 weeks after warfarin withdrawal.\(^{29}\) At the time of their recurrent thromboses, all were on immunosuppressants and all had elevated ACA titers. No further thrombotic events occurred when warfarin was reinstituted. Asherson et al\(^{39}\) strongly suggest long-term anticoagulation pending the reduction of high antibody titers.

Table 2. Potential Mechanisms of Antiphospholipid Antibody-Induced Thrombosis

<table>
<thead>
<tr>
<th>Mechanism</th>
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<tr>
<td>Vascular wall prostacyclin inhibition(^3)</td>
<td>Levine et al. Anticardiolipin Antibodies and Stroke.</td>
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<tr>
<td>Direct binding to endothelial cell phospholipid(^9,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
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<tr>
<td>Altered platelet aggregation(^9,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
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<tr>
<td>Direct binding to platelet phospholipid(^9,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
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<tr>
<td>Prekallikrein inhibition(^3,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
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<tr>
<td>Functional alteration of Antithrombin III(^2,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
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<tr>
<td>Decreased fibrinolysis(^3,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
</tr>
<tr>
<td>Decreased plasminogen activator release(^3,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
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<tr>
<td>Inhibition of Protein C activation(^3,20)</td>
<td>Harris EN, Harris EN, Gharavi AE, Asherson RA, Harris EN, Gharavi AE.</td>
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In summary, patients with or without SLE may have isolated or recurrent thrombotic stroke in association with antiphospholipid antibodies even in the absence of LA activity. Clues to the presence of these antibodies include a false-positive VDRL, thrombocytopenia, spontaneous abortions, low-titer ANA positivity, and deep venous thrombosis. Highly sensitive methods are available to detect these circulating autoantibodies, and they should be sought in patients with otherwise unexplained ischemic stroke.

Note added in proof: Case 1 was previously reported.\(^{40}\)

Acknowledgments

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