Multiple Cerebral Infarctions and Dementia Associated With Anticardiolipin Antibodies

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Antibodies to negatively charged phospholipids including cardiolipin have been recognized in the sera of patients with systemic lupus erythematosus (SLE) and a variety of other disorders. These antibodies can be detected by various tests such as enzyme-linked immunosorbent assays (ELISAs) and radioimmunoassays. Similar antibodies are recognized as a cause of the false-positive RPR (VDRL) test and often account for the so-called lupus anticoagulant that is detected as a prolonged activated partial thromboplastin time (APTT) test that does not correct when the subject's plasma is mixed with normal plasma. Presumably this phenomenon is caused by antibodies that react with the phospholipids used in the standard APTT test.

Patients with circulating anticardiolipin antibodies (ACAs) may experience recurrent arterial and venous thromboemboli including cerebral infarction and spontaneous abortion. Besides SLE, these antibodies have been associated with other disorders including the acquired immunodeficiency syndrome (AIDS), malaria, and acute infections. While the exact nature of the association between the presence of ACAs and thrombotic events is uncertain, several lines of investigation suggest an important role for these antibodies in the pathogenesis of vascular thrombosis.

We describe 4 patients without clinical or laboratory evidence of SLE who had multiple cerebral infarctions, dementia, and persistently elevated titers of circulating ACAs. Because of the strong association with thrombosis, ACAs might be an unrecognized cause of cerebral infarction in patients other than those with SLE.

Subjects and Methods

All patients were seen and examined by one or more of the authors, and available clinical and laboratory information including complete blood counts (CBC), platelet counts, chemistry screen, APTT, computed tomographic (CT) scans, and cerebral angiograms was abstracted from the medical records.

ACAs were assayed by modification of the method of Harris et al using an ELISA that detects all classes of antibodies. In brief, the wells of 96-well microtiter plates were coated with cardiolipin and washed with buffer containing 1% bovine serum albumin; a 1:40 dilution of the test serum was added and incubated for 2 hours at 25°C. The supernatant was then aspirated, the plate was washed, and affinity-purified F(ab')2 fragment of goat anti-human immunoglobulin linked to horseradish peroxidase was added and incubated for 1 hour at 25°C. The supernatant was removed, the plate was washed, and 2,2'-azino-bis(3-ethylbenzthiazolinesulfonic acid) (ABTS, Sigma Co., St. Louis, Mo.) was added and incubated for 30 minutes at 25°C. The reaction was stopped and the plates were read at 405 nm using an ELISA reader. Each plate contained controls including normal pooled serum as well as multiple positive controls. Results were expressed as arbitrary units relating the ratio of the sample optical density to that of the normal pooled serum. A ratio of >2 units was considered positive for ACA and was >3 SD above normal when a group of 45 normal subjects were tested. Except for Case 1, in which the ACA was assayed post mortem, elevated ACA titers were confirmed on multiple determinations in all cases.

Case Report 1 — Anticardiolipin Titer 8.6 Units

R.G., a 59-year-old man, became confused and paraplegic over 1 week. On examination, he was alert...
but did not initiate movement or speech. He followed simple commands with difficulty. He responded to questions inconsistently and only in 1- or 2-word phrases. His arms were normal in strength but he was apraxic. He had a flaccid paraplegia with brisk deep tendon reflexes and bilateral Babinski's signs.

CT scan of his head disclosed an area of low density in the anterior portion of the left frontal lobe and a much smaller area of low density in the same region of the right frontal lobe (Figure 1, left). Complete myelogram was normal. Cerebrospinal fluid (CSF) examination showed no white blood cells, a total protein of 97 mg%, a normal IgG index, no oligoclonal bands, a nonreactive VDRL test, and a glucose level of 75 mg%. Cerebral arteriography revealed nearly complete occlusion of the proximal portions of both anterior cerebral arteries (Figure 2). Leptomeningeal and cerebral cortex biopsy disclosed no evidence of vasculitis but showed infarcted brain tissue.

Erythrocyte sedimentation rate (ESR) was 115 mm/hr. Rheumatoid factor was positive at 1:8, and there was a mild indirect Coomb's-positive hemolytic anemia. Antinuclear antibody (ANA), complement levels, cryoglobulins, VDRL, fluorescent treponemal antibody absorption, mycoplasma titers, and mono spot tests were normal or negative. IgG Epstein-Barr virus titer was positive at 1:2,560, but the IgM titer was <1:20. His APTT was normal.

A tentative clinical diagnosis of cerebral vasculitis was made and prednisone, initially 100 mg/day, was begun. During the ensuing weeks, there was little change in his neurologic condition. He died of cardiac arrest 5 months after the onset of his neurologic illness.

Autopsy. At autopsy bilateral cerebral infarctions were found in the distribution of the anterior cerebral arteries. Despite the presence of widespread atheroma of precerebral arteries and the middle cerebral arteries, both anterior cerebral arteries were widely patent and without evidence of atheroma, whereas the smaller cerebral vessels in this distribution showed occlusions with fibrin thrombi (Figure 3). There was no evidence of vasculitis. Similar findings, including widespread foci of myocardial infarction with multiple recanalized thromboemboli and fibrin thrombi of arterial-sized blood vessels, were present in other organs.

Case Report 2 — Anticardiolipin Titer 8.7 Units  
M.M., a 43-year-old man and a former computer programmer, became totally disabled because of multiple strokes. He experienced his first apparent stroke at age 33 when he developed the sudden onset of aphasia and right hemiparesis. A CT brain scan showed a lucency in the distribution of the left middle cerebral artery consistent with cerebral infarction. A complete cerebral angiogram was normal. Three years later, at age 36, a second stroke produced severe dysarthria and repeat CT scan showed bilateral lucencies in the territory of the middle cerebral arteries. Repeat cerebral angiography showed no evidence of atherosclerosis or angiitis and was interpreted as normal. He subsequently developed episodes of blurred vision, progressive difficulties with memory, and emotional lability. A recent stroke at age 42 resulted in worsening of a left hemiparesis, and he currently requires custodial care. He has severe dysarthria and is unable to speak intelligibly. His affect is labile, and his memory and receptive language function are severely impaired. He is unable to write and has facial diparesis and moderate spastic quadriplegia. Repeated cardiac examinations and Holter monitoring have been normal. Throughout the course of his illness, results of laboratory studies including CBC, urinalysis, hepatic and renal function, electrocardiography (ECG), ESR, serum protein electrophoresis, VDRL, cholesterol, and triglycerides have been normal. Coagulation studies showed normal fibrinogen, complement C3 and C4, prothrombin.

Figure 1. Left: Case 1. Computed tomography (CT) scan showing cortical infarcts in distributions of both anterior cerebral arteries. Middle: Case 2. CT scan demonstrating multiple cortical infarcts in distributions of both middle cerebral arteries. Right: Case 3. CT scan revealing multiple cortical infarcts in distributions of right and left anterior and middle cerebral arteries and right posterior cerebral artery.
time, euglobulin clot lysis test, Antithrombin III, and Factors VIII and IX. Late in his course a slight elevation in the APTT, 46.6 seconds, was noted. An ANA was 1+ with a speckled pattern. On one determination, the platelet count was reduced to 78,000/µl and platelet survival time was reduced to 4.2 days, half the normal time. Cerebral angiograms performed at age 38 were normal except for retrograde filling of the opercular arteries bilaterally. A recent CT brain scan showed multiple cortical infarctions and cerebral atrophy (Figure 1, middle).

Case Report 3 — Anticardiolipin Titer 3.0 Units

A.G., a 69-year-old man, has experienced 6 years of progressive intellectual impairment, memory loss, and difficulty in walking. His illness was heralded by the sudden onset of right-sided weakness, mostly involving the right lower extremity. Other than his initial
symptoms, for which he did not seek medical consultation, no other clinical stroke-like episodes are described. He developed progressive difficulties with gait and intellectual impairment manifested by poor judgment in managing his monetary affairs, but no urinary incontinence or loss of bladder control. His health otherwise had been vigorous except for mild hypertension with no history of cardiac disease, arrhythmia, or diabetes mellitus. He smokes one-half pack of cigarettes per day.

His neurologic examination demonstrated a flat affect, depressed mood, and mild impairment of memory and intellect. There was a right hemiparesis and a right hyperreflexia with bilateral Babinski’s signs. His gait was broad-based and unsteady; his steps were short, and there was a tendency for retropulsion. He exhibited mild dysarthria but no bulbar paresis nor lability of affect. Results of laboratory studies including liver function tests, urinalysis, chest x-ray, serum protein electrophoresis, ANA, CBC, ESR, VDRL, ECG and echocardiography, serum B-12 and folate, and digital subtraction carotid angiography were normal. CT scan of his brain showed multiple small cortical infarctions and cerebral atrophy (Figure 1, right).

The patient is clinically stable and using a medical regimen of 240 mg propranolol, 150 mg dipyridamole, and 300 mg aspirin daily.

Case Report 4 — Anticardiolipin Titer 3.8 Units

B.R., a 28-year-old woman, developed sudden weakness of the left hand 2½ years ago. Her weakness gradually has worsened over that period, and she has experienced increased clumsiness in the entire left side of her body. Her memory and cognitive function have similarly declined so that she can no longer take care of herself or her family. Other than the initial apoplectic onset, discreet episodes of worsening were denied by the patient and other reliable family members. A false-positive VDRL was noted at application for her marriage license 10 years previous. She gave no history of spontaneous abortions, had used oral contraceptives in the past, and smoked 3 packs of cigarettes per day. Her health otherwise had been excellent.

Examination showed an alert, oriented woman who could register only 2 of 3 objects at 1 minute and could not remember any objects after 5 minutes. She could recall the current president but no others, but did recollect her own and her son’s birthdays. Speech was unaffected, but she had difficulty following 3-step commands. There was a mild left homonymous hemianopsia, a left pronator drift, and moderate left hemihypesthesia to all primary sensory modalities involving both the arm and the leg. Her left hand was clumsy, but there was no dystaxia. Cardiac examination was entirely normal, but some copper-wiring changes were noted in the funduscopic examination.

Results of laboratory evaluations including routine CBC, differential, and screening panel were normal. CT scan showed multiple bihemispheric cortical and subcortical infarctions. The APTT test using 3 different commercial reagents was normal. ANA was negative. The patient is receiving 325 mg aspirin per day and 50 mg dipyridamole 3 times daily.

Discussion

These 4 patients experienced multiple unexplained cerebral infarctions that caused loss of intellect and a spectrum of associated motor, sensory, and language disabilities. The first patient had the unusual presentation of acute infarctions in the distribution of both anterior cerebral arteries, which produced immediate severe neurologic impairment and subsequent death. While an isolated cerebral vasculitis seemed likely, the brain pathologic examination revealed thrombi in multiple small arteries but no vasculitis. The remaining 3 patients had multiple cortical infarcts without heart disease or evidence of significant atherosclerosis. The gradual deterioration seen in 2 patients without the stepwise progression characteristic of multi-infarction dementia bears emphasis.

Despite the different clinical manifestations, all 4 patients had 2 features in common. First, their cerebral infarctions were primarily cortical and by pathologic demonstration, clinical features, and radiographic studies appeared to reflect small artery involvement. Second, all 4 patients had ACAs in their serum without evidence of SLE. While 1 patient had a Coomb’s-positive hemolytic anemia and an elevated ESR, the others had no evidence of an autoimmune disease. These cases suggest that there may be an association between the presence of ACAs and the occurrence of cerebral infarction. We believe that ACAs may play a pathologic role in the cerebral infarctions in these cases as they may in SLE. It remains to be seen if these antiphospholipid antibodies are in themselves pathogenic or whether they are only a marker for another as yet unknown pathologic process.

There remains a lively debate as to the significance of ACAs in the cause of vascular thrombosis.18-23 ACAs are part of a spectrum of antiphospholipid antibodies and include immunoglobulins of the IgG, IgM, and IgA classes. It has been demonstrated that monoclonal lupus autoantibodies and monoclonal antibodies from normal human tissue show polyspecificity for a variety of phospholipids as well as for DNA.5,24-27 There is some evidence of a relation between these antibodies and antibodies to some bacterial antigens such as Klebsiella Polysaccharide K, as well as to certain proteoglycans.28 It has been suggested that these antibodies cross-react with phospholipids contained in platelets and endothelium and thereby induce thrombosis.20,23 However, careful studies have not found a consistent relation between the presence of these antibodies and platelet function abnormalities, decreased endothelial cell prostacyclin production, and other related abnormalities.30

A variety of tests may be used to detect the presence of antibodies to negatively charged phospholipids.9,10 Standard laboratory tests that suggest the presence of these antibodies include the false-positive VDRL, ANA assay, prolonged APTT, and thrombocytopenia. These were mostly negative in our patients, although
Table 1. Clinical Manifestations of Anticardiolipin Antibody Syndrome

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<thead>
<tr>
<th>Nervous system manifestations</th>
<th>Systemic manifestations</th>
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<tr>
<td>Cerebral infarctions</td>
<td>Coronary thrombosis</td>
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<tr>
<td>Retinal artery thrombosis</td>
<td>Peripheral arterial thrombosis</td>
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<tr>
<td>Amaurosis fugax</td>
<td>Recurrent venous thrombosis</td>
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<tr>
<td>Dementia</td>
<td>Leg ulceration</td>
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<tr>
<td>Migraine headache</td>
<td>Livedo reticularis</td>
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<tr>
<td>Epilepsy</td>
<td>Spontaneous abortion</td>
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<tr>
<td>Chorea</td>
<td>Pulmonary hypertension</td>
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<td>Thrombocytopenia</td>
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Patient 1 had mild thrombocytopenia and Patient 2 had a positive ANA and a mild thrombocytopenia on 1 occasion. In this small series, the ACA assay appears to be a more sensitive indicator for the presence of these antibodies than other standard laboratory tests.

Hughes et al.30 have proposed the principal features of the anticardiolipin syndrome as outlined in Table 1. Most of the features of the syndrome result from vascular thromboses. The presence of ACAs is of clinical importance since persons with thrombotic events who have these antibodies appear to be at high risk for recurrent episodes of thromboses. Furthermore, an understanding of the precise role of these antibodies in the pathogenesis of vascular thromboses may lead to a better understanding of the mechanism of certain forms of stroke and other vascular diseases. This is particularly exciting in that these antibodies are not confined necessarily to autoimmune diseases and may appear as acute phase reactants after infections and various other diseases.

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