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. Antibodies to negatively charged phospholipids including cardiolipin occur in the sera of patients with systemic lupus erythematosus (SLE) and a variety of other disorders. We report 4 patients who experienced cerebral infarctions and dementia in association with anticardiolipin antibodies. These patients did not have the characteristic lupus anticoagulant or systemic lupus erythematosus. The occurrence of anticardiolipin antibodies in patients with multiple cerebral infarctions who do not have evidence of a systemic vasculitis or inflammatory condition suggests that this association may be more common than previously recognized. It may be useful to test for the presence of anticardiolipin antibodies in patients who have unexplained cerebral infarctions. (Stroke 1987;18:1107-1112)

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-ethylbenzthiazolesulfonic 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 monospot tests were normal or negative. IgG Epstein-Barr virus titers were 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 aphasias 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 paresis 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 consulta-
tion, no other clinical stroke-like episodes are de-
scribed. 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, ar-
rhythmia, or diabetes mellitus. He smokes one-half
pack of cigarettes per day.

His neurologic examination demonstrated a flat af-
fect, depressed mood, and mild impairment of mem-
ory 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 includ-
ing 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 nor-
mal. CT scan of his brain showed multiple small corti-
sal infarctions and cerebral atrophy (Figure 1, right).

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 mar-
rriage 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 recol-
lect her own and her son’s birthdates. Speech was
unaffected, but she had difficulty following 3-step
commands. There was a mild left homonymous hemi-
anopsia, a left pronator drift, and moderate left hemi-
hypesthesia to all primary sensory modalities involv-
ing both the arm and the leg. Her left hand was clumsy,
but there was no dystaxia. Cardiac examination was
tirely 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 differ-
ent commercial reagents was normal. ANA was nega-
tive. 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 presenta-
tion 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 patho-
genic or whether they are only a marker for another as
yet unknown pathologic process.

There remains a lively debate as to the signif-
cance of ACAs in the cause of vascular thrombosis.19-23
ACAs are part of a spectrum of antiphospholipid anti-
odies and include immunoglobulins of the IgG, IgM,
and IgA classes. It has been demonstrated that mono-
clonal lupus autoantibodies and monoclonal antibodies
from normal human tissue show polyspecificity for a
variety of phospholipids as well as for DNA.5-25-27
There is some evidence of a relation between these
antibodies and antibodies to some bacterial antigens
such as Klebsiella Poly saccharide K, as well as to
certain proteoglycans.28-29 It has been suggested that
these antibodies cross-react with phospholipids con-
tained 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
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 10 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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References


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