Prospective Study of Anticardiolipin Antibodies in Stroke

Michael J. Kushner, MD

Over 2 years, 104 patients underwent clinical evaluation and laboratory screening for the presence of abnormal anticardiolipin antibodies to determine the profile of laboratory and clinical findings in patients with stroke and other neurologic disorders. Seven with incomplete or ambiguous data were excluded; of the remaining 97 patients, 31 were ≥65 years old. Nine patients suffered systemic lupus erythematosus, 45 suffered brain ischemia, and 43 suffered other nonischemic neurologic disorders. Cardiac arrhythmia, myocardial infarction, and cardiac valvulopathy were grounds for exclusion. The presence of anticardiolipin antibodies was not influenced by age. In the 88 patients without lupus, anticardiolipin antibodies were significantly more common in the group suffering brain ischemia than in the group with nonischemic neurologic disorders (29% versus 5%, p<0.01, χ² test). These controlled data demonstrate an association between the presence of circulating anticardiolipin antibodies with stroke, but not with other neurologic conditions. (Stroke 1990;21:295-298)

Anticardiolipin antibodies (ACAs) and the lupus anticoagulant (LA) are circulating immunoglobulins that have been associated with thromboembolic disorders despite their in vitro anticoagulant properties. The LA was first recognized in patients with systemic lupus erythematosus who also exhibited prolonged times for various blood coagulation studies. Subsequent work by Shapiro and others has demonstrated that immunologic testing provides a simpler and sensitive method to detect ACAs, and that the ease of these immunologic tests makes them more suited to widespread clinical screening.

Early reports linked ACAs to a number of disorders such as recurrent fetal wastage and systemic thromboembolism in patients with and without lupus. However, recent data from controlled clinical series have suggested that associations between systemic thromboembolic complications and the presence of an ACA may not be as strong as previously suspected.

The exact role, if any, for ACAs in the pathogenesis of brain ischemia (BI) remains uncertain. ACAs have been cited as occurring with a high incidence in lupus patients suffering cerebral infarction, but they also often occur frequently in lupus patients without evidence of BI. Small series also have sought to associate an ACA with a variety of other neurologic conditions such as migraine, transient ambyloplia, seizures, and dementia.

Lacking in this previous body of work is controlled data that establishes a direct association between the presence of an ACA and BI or other neurologic conditions. I report the results of a prospective investigation undertaken to define the associations of ACAs in neurologic patients with and without BI.

Subjects and Methods

Acquisition of data and the methods of handling patient-related clinical data conformed to the practices of, and were approved by, the Committee on Studies Involving Human Beings of the University of Pennsylvania.

Patients undergoing evaluation for neurologic disease within the Department of Neurology of the University of Pennsylvania were examined prospectively between October 1, 1986, and December 20, 1988. Medical history, neurologic history, presenting illnesses, and the results of routine laboratory tests including blood tests and imaging studies were obtained from extant clinical records. The final neurologic diagnosis was based on the cumulative impression given by the historical findings, the clinical signs, and the results of laboratory tests. All available clinical data was used to stratify the patients according to the presence of BI as opposed to other central nervous system diseases such as multiple sclerosis and neurodegenerative disorders, among others.

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Patients with obvious cardiac pathology such as recent myocardial infarction, atrial fibrillation, rheumatic heart disease, and prosthetic heart valve were excluded. Grounds for exclusion from the study also included the presence of intracranial vascular malformation, systemic or cerebral neoplasm, or human immunodeficiency virus and pregnancy or parturition. Patients with other risk factors for vascular disease such as hypertension, diabetes mellitus, and collagen-vascular diseases were eligible for inclusion.

Partial thromboplastin time (PTT) was determined using General Diagnostics APTT Reagent and the Coag-a-mate X-2 automated analyzer (Organon Teknika Corp., Durham, North Carolina). 24

The presence of circulating ACA(s) was determined by laboratory methods that have been described previously. 25 Solid-phase radioimmunoassay was used to detect antibodies cross-reacting with bovine cardiolipin phospholipid. 26,27 This assay has been proven to be sensitive in tests conducted against international standards. Results of this assay are reported as a percentage of radioactivity bound. Binding of >5.0 standard deviations from the mean control values for any clone (IgG, IgA, or IgM) was considered abnormal in this analysis.

Also examined, when available, were the results of other blood tests including serum chemistries, complete blood counts, platelet counts, treponemal studies, and autoimmune evaluations. Timing of the ACA testing ranged from 1 day to 3 months after a neurologic event.

The medical history, neurologic findings, and results of laboratory tests were entered into a computerized database using D-BASE III. Statistical analysis was performed using the STATGRAPHICS software package (Statistical Graphics Corp., Rockville, Maryland). Comparisons within and between groups were made using the \( \chi^2 \) test.

**Results**

One hundred four neurologic patients were screened for the presence of an ACA. Clinical data were lacking or ambiguous in seven, who were excluded from further analysis. There remained 97 women and 47 men ranging in age from 21 to 83 years; 31 patients were ≥65 years old. The clinical profile of the study population is summarized in Table 1. Nine patients suffered systemic lupus erythematosus. 28 Forty-five patients without lupus suffered BI; 42 had cerebral infarction and the other three had transient ischemic attacks. Forty-three patients without lupus suffered nonischemic neurologic disorders. Head computed tomography or magnetic resonance imaging was performed in eight of the nine lupus patients, in 44 of the 45 BI patients, and in 39 of the 43 patients with nonischemic neurologic disorders.

The laboratory findings by group are summarized in Table 2. The PTT was determined in eight of the nine lupus patients, in 44 of the 45 BI patients, and in 33 of the 43 patients with nonischemic neurologic disorders. No significant pattern of PTT abnormality emerged.

All 97 patients underwent ACA screening. The presence of an elevated concentration of a circulating ACA was significantly higher in the BI group than in the group with nonischemic neurologic disorders \( (p<0.01) \). Polyclonal ACA moieties were found in four of the 13 ACA-positive patients with BI as opposed to in neither of the two ACA-positive patients with nonischemic neurologic disorders.

For the entire study population, ≥65 years was not significantly associated with the presence of an ACA. No significant effect of age was noted on the presence of an ACA within either the BI or the nonischemic neurologic disorder groups. For the BI patients, there was no difference in mean age for ACA-positive versus ACA-negative individuals (mean ages 54.4 and 54.9 years, respectively). In the few lupus patients, ACAs were found only among those <65 years old.

**Discussion**

These results provide the first controlled data showing a significant association between the presence of circulating ACA and brain ischemia. My data suggest that these immunoglobulins may represent true risk factors for stroke. It seems now that orga-
nized testing of the efficacy of various treatment strategies directed toward the ACA, such as platelet inhibition, immunosuppression, and anticoagulation, is warranted in ACA-positive stroke patients.

Previously, a search for either the LA or an ACA was most commonly prompted by either a fruitless initial evaluation or the presence of a "suspect" clinical profile. As suggested by our previous study,25 the index of suspicion for these immunoglobulins must be broadened to include patients without glaring hematologic or clinical abnormalities. Another important inference in the current results is the lack of an association between an ACA and nonischemic neurologic disorders. The brain is rich in phospholipid, and conceptually it is possible that autoimmunization could manifest itself in positive ACA assays in patients with nonischemic neurologic disorders. My current results do not suggest this to be the case. Neither was a significant age effect noted on the laboratory profile.29

Whereas the bulk of previous experience has dealt with lupus patients harboring these immunoglobulins, it would likely prove difficult to establish an irrefutable association between an ACA (or the LA) and cerebral ischemia in lupus patients. Laboratory studies have demonstrated that the LAs and ACAs are common in lupus patients regardless of their neurologic history.17,20 Furthermore, lupus patients may have multiple disorders that may predispose to thromboembolism, including cardiac valvulopathy and platelet dysfunction, among others.17,30,31 Studies in patients without lupus would seem to offer better control of these potentially confounding factors. Indeed, more controlled data has become available as interest in these hematologic entities has broadened. Positive associations between an ACA and recurrent myocardial ischemia and postsurgical thromboembolic complications have been reported.10,11 In contrast to some previous reports, null findings have been reported recently on the relation between an ACA and thromboembolic complications in women with recurrent fetal wastage, combination therapy with platelet inhibitors and corticosteroids has been suggested to be efficacious.6 Obviously, ACA-positive patients must be identified by specific laboratory tests before therapy can be considered. While these tests are widely available, they remain specialized as yet and are not in general use as primary screening procedures. A number of procedures have been applied to immunologic studies of ACAs, while quantitative coagulation studies such as the dilute tissue thromboplastin inhibition assay (TTI), Stypven test (Russell's viper venom test), and kaolin clotting time are sensitive in detecting the LA.22-30 Some evidence suggests that coagulation screens are more specific than immunologic assays in identifying lupus patients suffering from, or at risk for, thromboembolism.37,38 These special clotting studies may not be suited to mass screening for this problem and may still need to be preceded by strong clinical suspicions before they are performed. It must be remembered that the presence of elevated concentrations of ACA is known to be influenced by a number of other factors unrelated to autoimmune or thromboembolic conditions including infection, immunodeficiency, and family history, among others.39-43

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References


TABLE 2. Summary of Laboratory Findings in 97 Neurologic Patients

<table>
<thead>
<tr>
<th>Test</th>
<th>Partial thromboplastin</th>
<th>Anticardiolipin antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number tested</td>
<td>Abnormal</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>(N=9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain ischemia (N=45)</td>
<td>44</td>
<td>3*</td>
</tr>
<tr>
<td>Nonischemic neurologic disorders</td>
<td>33</td>
<td>1</td>
</tr>
<tr>
<td>(N=43)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Two patients were being treated with warfarin at the time of testing.†p<0.01 different from nonischemic by χ² test.
42. Pascual DS, Garcia MCR, Lopez MT, Fontan G: Anticardio-

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