Lupus Anticoagulants, Anticardiolipin Antibodies, and Cerebral Ischemia

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We studied 23 patients suffering cerebral ischemia who also had laboratory evidence of either a lupus anticoagulant (LA) or an abnormal anticardiolipin antibody (ACA). Four patients had lupus or a lupus-like illness, three had drug-induced lupus, and 16 had no overt evidence of collagen-vascular disease. Cerebral ischemic events were multiple in 71% of the patients; two patients presented with multi-infarct dementia. Recognized cerebrovascular disease risk factors were present in 57% of the patients. The partial thromboplastin time was prolonged in only 35% of the patients. An LA was identified in 15 of 21 patients tested, and an elevated ACA titer was identified in 10 of 12 patients tested. Simultaneous assays for LA and ACA were discordant in eight of 10 patients tested. LA- and ACA-associated brain ischemia is often recurrent, but other risk factors for cerebrovascular disease are often present. The laboratory findings in such patients may display considerable heterogeneity. (Stroke 1989;20:225–229)

Lupus anticoagulants (LAs) and anticardiolipin antibodies (ACAs) are circulating immunoglobulins that cross-react with phospholipids and may display anticoagulant properties in vitro by interfering with phospholipid-dependent coagulation tests. Since the initial recognition of the LAs by Mueller et al and Conley and Hartmann, these factors have been associated with systemic and cerebral thromboembolism and recurrent spontaneous abortion despite their in vitro "anticoagulant" properties. In the central nervous system arterial and venous thrombosis, arterial embolism, and intracranial hemorrhage have all been reported. Initially an LA was most commonly recognized in lupus patients presenting with thrombosis and laboratory evidence of a circulating inhibitor of coagulation, hence the term "lupus anticoagulant". Subsequently, sensitive radioimmunoassays in these patients demonstrated abnormally elevated titers of antibodies directed against phospholipid moieties such as cardiolipin. Recently, associations of both the LAs and the ACAs with brain ischemia in patients without lupus have been reported. Other reports have noted that there may be considerable heterogeneity in the laboratory profile of these patients.

We report the clinical and laboratory findings in 23 LA- and/or ACA-positive patients with brain ischemia. These patients were examined to search for a characteristic neurologic profile, to assess the coincidence of recognized risk factors for cerebrovascular disease, and to compare the results of various laboratory studies.

Subjects and Methods

Eleven patients suffering brain ischemia were identified retrospectively from a total of approximately 270 LA-positive nonobstetrical patients at the Hospital of the University of Pennsylvania screened from 1978 to 1986 in an uncontrolled fashion. Generally, these patients first came to attention because of an abnormally prolonged partial thromboplastin time (PTT). Six of these 11 underwent neurologic evaluations at the time of presentation. In the other five patients, a history of brain ischemia was established by review of the records.

Between October 1986 and December 1987, 12 patients suffering brain ischemia were identified as being LA- or ACA-positive from a prospective screening of approximately 60 patients at the Hospital of the University of Pennsylvania selected in an uncontrolled fashion. All 12 underwent a thorough neurologic evaluation including history, physical examination, blood tests, and imaging studies. This roster of 23 patients was also cross-checked against other hospital and departmental records. Data were sought concerning the neurologic syndromes, medical histories, and results of other laboratory tests where available. The laboratory
results reported here were obtained as close to the
time of ischemic ictus as possible. In the prospec-
tive group, blood tests were obtained 1-60 days
after the ischemic ictus.

All 23 patients underwent PTT determinations
using General Diagnostics APIT Reagent and the
Coag-a-mate X-2 automated analyzer (Organon
Teknika Corp., Durham, North Carolina). Before
1986 the presence of a circulating coagulation inhib-
itor (rather than a coagulation factor deficiency)
usually was suspected when a prolonged PTT failed
to correct during a mixing study performed with
equal parts of the patient’s plasma and pooled
normal plasma. After the mixing study, the pres-
ence of an LA was sought using the dilute tissue
thromboplastin inhibition test (TTI); this procedure
has been described. In our laboratory, three
dilutions (1:10, 1:100, and 1:1000) are made for the
TTI and the reagent Simplastin Excel (Organon
Teknika) is employed. The reported TTI value is
the average of the results of the second and third
dilutions. We considered a ratio of patient result to
control of ≥1.3 to be abnormal. Screening for an
LA was not entirely confined to those patients
exhibiting an abnormal PTT.

Beginning about April 1986, sensitive solid-phase
radioimmunoassay became available for the detec-
tion of elevated concentrations of antibodies cross-
reacting with bovine cardiolipin phospholipid. This assay has been proven to be sensitive in tests
conducted against international standards (courtesy
of Dr. Nigel Harris, University of Louisville, Lou-
isville, Kentucky). Results of this assay are reported
as percentages of radioactivity bound; we consid-
ered binding of >3.0 standard deviations from mean
control values to be abnormal.

Results

The study group is profiled in Table 1. There were
12 men and 11 women, with a mean age of 56.9
(range 28-86) years. Two patients had systemic
lupus erythematosus (SLE), one had discoid lupus,
and one had a “lupus-like” collagen-vascular
disease. Three patients had clinical or serologic
evidence of a drug-induced lupus syndrome. Recog-
nized risk factors for cerebrovascular disease,
such as hypertension and organic heart disease,
were noted in 11 of 19 patients without collagenvascular disease.

The syndromes of cerebral ischemia in the 23
patients are summarized in Table 2. Overall, 17
patients suffered cerebral infarction alone whereas
three suffered transient ischemic attacks (TIAs)
alone. There were multiple cerebral infarctions in
12 of the 17 patients who suffered infarction alone.
For the patients with TIA only, two of the three
suffered multiple events. Three patients suffered
both cerebral infarction and TIA. Three of the four
patients with SLE or a lupus-like syndrome pre-
sented with a single cerebral infarction. Cerebral
infarction was localizable to the brainstem or basi-
lar circulation in four of the 17 patients with infarc-
tion alone. Two patients suffered amaurosis fugax.

Three patients were demented at the time of
initial presentation. One suffered carcinoma, but
the other two had no other apparent contributing factors. In both of these patients a clinical diagnosis
of multi-infarct dementia was entertained before the
discovery of the LA or ACA. Postmortem exami-
nation demonstrated nonbacterial vegetative
endocarditis in one patient in the absence of clinical or laboratory signs of SLE.

Two patients suffered from vasculitis. One (Patient
15) had giant-cell arteritis demonstrated by tempo-
ral artery biopsy. The other (Patient 23) suffered
multiple cerebral infarctions and had arteriographic
evidence of primary intracranial arteries; celiac
arteriogram was normal.

The laboratory results are also summarized in
Table 1. Overall, the PTT was prolonged in 35% of
the patients. The TTI, performed in 21 patients, was
abnormal in 15; of these 15 patients, the PTT was
prolonged in eight and normal in seven. ACA was
assayed in 12 patients and was abnormal in 10; the
PTT was abnormal in only one of the 12 patients.
Ten patients underwent simultaneous TTI and ACA
assays. The TTI and ACA assays were both abnor-
mal in two and the TTI was positive while the ACA
assay was negative in two; in the other six the ACA
assay was positive while the TTI was negative, and
in all of these patients the PTT was normal. In eight
of the 10 patients with a positive ACA assay, the
abnormal ACA was immunoglobulin G (IgG); in the
two patients without evidence of IgG, one had an
IgM while the other had both IgA and IgM. Of 16
patients without lupus or drug-induced lupus, the
ANA was abnormal in three; none of these three
had clinical evidence of SLE. Two patients exhib-
ted positive serum microhemagglutination assay for
Treponema pallidum antibodies. Both had received adequate penicillin treatment, and cerebro-
spinal fluid examination was normal in each patient.
In the one patient with clinically definite SLE who
underwent simultaneous TTI and ACA assays, only
the TTI was abnormal.

Discussion

The exact roles, if any, for the LA or ACA in the
pathogenesis of cerebral ischemia remain uncertain.
No controlled studies have established either entity
as a distinct risk factor for cerebral ischemia; that
task was not within the scope of our study. Rather,
we offer the following observations of LA- and
ACA-associated cerebral ischemia: 1) the syn-
dromes of cerebral ischemia occurred in the major-
ity of our patients, 2) lupus and lupus-like illnesses
coexisted in a minority of patients, 3) laboratory
findings (e.g., PTT) were heterogeneous, and 4)
subacute presentations such as multi-infarct demen-
tia may occur.

These clinical and laboratory observations stand
in some contrast to those of previously published
Currently, there is considerable uncertainty surrounding the optimal laboratory strategy for the diagnosis of both the LA and antiphospholipid antibodies. Some of the differences between our results and those of previous reports are likely the product of differing criteria for patient selection. Most previous reports have dealt with lupus patients presenting with thrombocytopenia and were found concurrently to have a prolonged PTT that failed to correct with normal plasma mixing studies. Screening for these factors based on coagulation studies is still widely espoused. However, coagulation studies alone may lack sensitivity in detecting these factors, and this approach may lead to both false-positive and false-negative errors. A number of reports have shown that there can be considerable heterogeneity in the laboratory profile of LA- and ACA-positive patients.

Shapiro and Thiagarajan have recognized that most LA factors are Igs with antiphospholipid specificity, and it has been suggested that these factors can be considered as one and the same. We have viewed the LA and ACA as being potentially different entities, and evidence of each was sought by separate laboratory techniques. The use of the TTI to detect the LA has been long established in our experience of LA- and ACA-positive patients.

### Table 1. Clinical and Laboratory Profile of 23 Patients With Cerebral Ischemia

<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Systemic disease</th>
<th>Vascular risk factors</th>
<th>Cardiac disease</th>
<th>Brain ischemia</th>
<th>Other nervous diseases</th>
<th>Laboratory profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/43/F SLE</td>
<td>Smoking</td>
<td>MVP</td>
<td>Infarct</td>
<td>Optic neuropathy</td>
<td>33.2 1.4 ND</td>
<td>ANA 1:2560</td>
</tr>
<tr>
<td>2/32/F Lupus-like syndrome</td>
<td>—</td>
<td>—</td>
<td>Infarct</td>
<td>Seizure, migraine</td>
<td>46.3 1.4 ND</td>
<td>ANA 1:1240</td>
</tr>
<tr>
<td>3/64/F Discoid lupus</td>
<td>HT</td>
<td>—</td>
<td>Multiple infarcts</td>
<td>—</td>
<td>26.8 1.4 ND</td>
<td>ESR 69</td>
</tr>
<tr>
<td>4/65/M DIL-procaine</td>
<td>HT</td>
<td>CAD</td>
<td>Multiple TIAs, multiple infarcts</td>
<td>Depression</td>
<td>55.1 1.9 ND</td>
<td>Platelets 57×10^4</td>
</tr>
<tr>
<td>5/73/M DIL-procaine</td>
<td>—</td>
<td>AFIB, CHF, MVP</td>
<td>Dementia</td>
<td>—</td>
<td>63.1 2.7 ND</td>
<td></td>
</tr>
<tr>
<td>6/70/M DIL-procaine</td>
<td>Smoking</td>
<td>Ml, angina</td>
<td>Multiple TIAs</td>
<td>—</td>
<td>57.9 1.9 ND</td>
<td></td>
</tr>
<tr>
<td>7/72/M —</td>
<td>—</td>
<td>RHD</td>
<td>Multiple TIAs</td>
<td>—</td>
<td>42.0 2.5 ND</td>
<td></td>
</tr>
<tr>
<td>8/86/F</td>
<td>—</td>
<td>—</td>
<td>Infarct, TIA</td>
<td>—</td>
<td>49.5 1.8 ND</td>
<td></td>
</tr>
<tr>
<td>9/81/M</td>
<td>—</td>
<td>HT</td>
<td>Multiple infarcts</td>
<td>—</td>
<td>36.1 1.7 ND</td>
<td>+MHATP</td>
</tr>
<tr>
<td>10/66/F</td>
<td>—</td>
<td>HT</td>
<td>Multiple infarcts, MID</td>
<td>Depression</td>
<td>23.0 1.0 IgM</td>
<td></td>
</tr>
<tr>
<td>11/52/M</td>
<td>—</td>
<td>HT</td>
<td>Multiple strokes, multiple TIAs</td>
<td>—</td>
<td>23.9 1.0 IgA, IgM</td>
<td></td>
</tr>
<tr>
<td>12/57/F</td>
<td>—</td>
<td>HT, smoking</td>
<td>Multiple strokes</td>
<td>—</td>
<td>26.5 1.1 IgG</td>
<td></td>
</tr>
<tr>
<td>13/44/F</td>
<td>—</td>
<td>HT</td>
<td>Multiple strokes</td>
<td>—</td>
<td>27.7 1.5 IgG, IgA</td>
<td>+MHATP</td>
</tr>
<tr>
<td>14/28/M</td>
<td>—</td>
<td>—</td>
<td>Bithalamic</td>
<td>—</td>
<td>31.7 1.6 IgG, IgA, IgM</td>
<td></td>
</tr>
<tr>
<td>15/45/M</td>
<td>—</td>
<td>—</td>
<td>TIA</td>
<td>GCA</td>
<td>33.3 1.4 ND</td>
<td></td>
</tr>
<tr>
<td>16/72/F</td>
<td>—</td>
<td>—</td>
<td>Multiple infarcts, MID</td>
<td>—</td>
<td>33.4 1.5 ND</td>
<td>ANA 1:640</td>
</tr>
<tr>
<td>17/39/F SLE</td>
<td>—</td>
<td>—</td>
<td>Infarct</td>
<td>Hydrocephalus</td>
<td>35.2 1.5 Negative</td>
<td>ANA 1:1040</td>
</tr>
<tr>
<td>18/66/F</td>
<td>—</td>
<td>HT</td>
<td>Infarct</td>
<td>—</td>
<td>33.2 1.2 IgG</td>
<td></td>
</tr>
<tr>
<td>19/66/M</td>
<td>—</td>
<td>HT</td>
<td>Infarct</td>
<td>—</td>
<td>33.4 1.2 IgG</td>
<td></td>
</tr>
<tr>
<td>20/43/M</td>
<td>—</td>
<td>—</td>
<td>Multiple infarcts</td>
<td>—</td>
<td>24.7 1.2 IgG, IgM</td>
<td>ANA 1:640</td>
</tr>
<tr>
<td>21/62/M</td>
<td>—</td>
<td>—</td>
<td>Multiple infarcts</td>
<td>—</td>
<td>25.2 1.2 IgG</td>
<td></td>
</tr>
<tr>
<td>22/40/M</td>
<td>—</td>
<td>—</td>
<td>Infarct, TIA</td>
<td>—</td>
<td>32.3 1.1 IgG</td>
<td></td>
</tr>
<tr>
<td>23/43/M</td>
<td>—</td>
<td>—</td>
<td>Multiple infarcts</td>
<td>PICA</td>
<td>20.3 1.5 Negative</td>
<td></td>
</tr>
</tbody>
</table>

*Normal unless noted (where performed).
hospital, but it has been recognized that other tests (such as the Russell’s viper venom test and the platelet neutralization procedure) may be more sensitive than the TTI in detecting the LA.1,17 Shapiro and Thiagarajan1 found that the sensitivity of the TTI may fall to as low as 80% in the presence of IgM inhibitors, and Trippett et al28 have shown that the TTI cannot distinguish between true LA factors and circulating anti-Factor VIII antibodies. Thus, it is possible that screening for the LA using the TTI alone could lead to both false-negative and false-positive errors. In our series, false-positive TTI errors due to unsuspected anti-Factor VIII antibodies should have been a much rarer occurrence than false-negative TTI errors since no hemophiliacs or patients with a history of bleeding diathesis were studied.38 We feel that errors arising from the use of the TTI in our series are largely compensated for by the relatively large number of TTI-positive patients with cerebral ischemia included, although these attributes of the TTI could potentially limit future prospective studies.13,15-22 As yet, other antiphospholipid antibody assays have not been shown to be superior to the ACA assay.37

In the future, certain assays for the LA and ACA may be found to predict thromboembolism better than others.27,34,36 The phospholipid specificity of these antibodies may vary among patients, and only antibodies directed against certain phospholipid fragments or those attaining a certain titer may be clinically meaningful and detectable by current laboratory methods.37 While this is possible, it must be noted that other reports have demonstrated that nonischemic disorders may comprise the initial presenting problems in patients with the LA and ACA.39,40 As yet, the optimal laboratory testing methods have not been established.

It is likely that widespread prospective screening will be needed to resolve these clinical and laboratory issues in both lupus and nonlupus patients. These factors have been recognized in up to 2.0% of the general population and in 7-38% of lupus patients.26,34,41 It has also been reported that a higher incidence of ACAs and other autoantibodies can be found in aged normal individuals.42 The relation between age, cerebral ischemia, and the LA and ACA also bears further study. Of interest in our elderly patients was a presenting syndrome of multi-infarct dementia in two. Coull et al43 also described presenile and senile dementia in patients suffering multiple cerebral infarctions who also harbored an ACA.

Earlier selective reports dealing with cerebral ischemia in lupus have found these factors present in a majority of patients.14-25 In our group, lupus-like illnesses occurred in a minority. A role for these factors in the pathogenesis of cerebral ischemia in lupus is problematic since lupus patients may suffer from Libman-Sacks endocarditis and other lupus-associated hematologic abnormalities that are recognized risk factors for thromboembolism.23,44 We have studied eight patients with definite SLE suffering cerebral infarction prospectively as part of ongoing studies of cerebral blood flow in lupus.30,45 To date, only two of the eight have harbored either an LA or ACA. Likewise, the incidence of an abnormally prolonged PTT in our study group is much lower than that reported previously, but comparisons of the PTT across laboratories may be difficult because of the variability of results engendered by the use of different reagents and techniques.4,29

Our data demonstrate that younger individuals with stroke of inobvious cause can harbor either an LA or ACA without significant clinical history or preceding laboratory abnormality. It is likely that more LA- and ACA-positive stroke patients uninfluenced by recognized vascular disease risk factors will be identified as the result of widespread testing.

Therapy for LA- and ACA-associated thromboembolism remains uncertain. Reports of treatment success in LA-associated recurrent fetal wastage have raised hopes that LA-positive patients with thromboembolism, including cerebral ischemia, might benefit from similar therapy.10-12 Roles for antiplatelet drugs, immunosuppressant agents, and anticoagulants have all been advocated.5,6,16,20,46,47 Therapy with prednisone plus aspirin has been associated with normalization of laboratory abnormalities and subsequent successful delivery in cases of recurrent spontaneous abortion and other conditions.11,47 However, prospective and controlled data is lacking and no standard treatment strategy has emerged for LA- and ACA-associated brain ischemia. Any treatment directed toward these factors cannot ignore coexisting conditions that predispose to stroke.

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References


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