Recurrent Cerebral Infarctions in Two Brothers with Antiphospholipid Antibodies That Block Coagulation Reactions

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SUMMARY  Inhibitors blocking coagulation reactions, often called lupus anticoagulants, are readily identifiable but rarely considered as risk factors for cerebral infarction. These inhibitors are inconsistently found in a number of diseases (often autoimmune) and after treatment with certain drugs and appear to be closely associated with, or identical to, antibodies to certain phospholipids. We have observed two brothers with these inhibitors who both experienced recurrent cerebral infarctions. Such familial occurrence has rarely been reported. In addition, some other family members were found to have depressed factor XII levels. Using the technique of double immunodiffusion, we found that the serum from these brothers formed precipitin lines against certain phospholipid substrates, lending further support to the antiphospholipid nature of this inhibitor.

Inhibitors which block coagulation reactions, often called lupus anticoagulants (LA), are a heterogeneous group of immunoglobulins that may act by interfering with the activation of prothrombin by the prothrombinase complex (factor Xa, factor V, calcium, phospholipid). Some of these inhibitors bind to the phosphate esters of a variety of biological molecules and have been termed antiphospholipid antibodies.

In this report we use the term “blocking inhibitors” (BI) rather than LA because they are more often than not associated with disorders other than systemic lupus erythematosus (SLE) and because of their ability to block coagulation reactions. Initially described in two patients with SLE by Conley and Hartman in 1952, these inhibitors have since been associated with a variety of immunological disorders, malignancies, drugs (including phenothiazines, penicillin derivatives, phenytoin, hydralazine, procainamide, isoniazid), and pregnancy. Their occurrence in SLE has been estimated to be 5-10%. Of all blocking inhibitors (about 300 cases) reviewed in this laboratory, less than 20% were found in patients with documented SLE (unpublished data).

BIs are usually recognized by their effects upon the activated partial thromboplastin time (APTT) — prolongation that does not fully correct when mixed 1:1 with normal plasma — and by their frequent association with biological false-positive tests for syphilis and occasional association with thrombocytopenia. About 15% of sera containing these inhibitors forms a precipitin line against phosphatidylserine using double immunodiffusion techniques (J.H.L., personal communication).

Despite abnormal coagulation tests, patients with the inhibitor usually do not have abnormal bleeding tendencies. Those few patients with this in-
Prepared by dissolving or suspending 5 mg in 1 ml barbital buffer (pH 8.6). Platelet extract and brain suspension were used because they contain, among other things, complex phospholipid mixtures. Platelet extract was prepared by washing one unit of platelets in 250 ml citrate-saline 3 times. After the final centrifugation the prepared by washing one unit of platelets in 250 ml citrate–saline 3 times. After the final centrifugation the platelets were separated from visible RBC’s and suspended in 20 ml of barbital buffer. After sonification and freeze-thawing 3 times, the supernatant was used. The insoluble material was allowed to settle and the supernatant was used. Both platelet extract and brain suspension have been stored freeze-thawed 3 times. The insoluble material was allowed to settle and the supernatant was used. Both platelet extract and brain suspension have been stored frozen for four years and continue to react with our positive controls. A positive patient control was included on each plate. This was serum from a patient with chronic lymphatic leukemia which formed a precipitin line with all of the center well reagents.

Case Reports

Case 1

A 39-year-old right-handed man was hospitalized in January 1984 following the acute onset of right-sided weakness and slurred speech. He had been well until 1976 when he suffered an anterior wall myocardial infarction. His rapid plasma reagin (RPR), a screening test for syphilis, was reactive at 1:2; coagulation tests were not performed. In 1977 cardiac catheterization revealed complete occlusion of the left anterior descending artery. All other arteries were widely patent. The procedure was complicated by brachial artery thrombosis for which he was treated for about a year with warfarin. In July 1983 he had an episode of right-sided weakness. His medications at the time of admission included propranolol 20 mg four times daily and dipyridamole 25 mg four times daily. Other than Case 2, there was no family history of bleeding, thrombotic or autoimmune disorder, although one distant relative had "an unusual facial rash" and Raynaud’s phenomena.

His general examination revealed a blood pressure of 110/70 mm Hg, telangiectasias of the oral mucosa, and absent right radial, right brachial and right and left dorsalis pedis pulses. His speech was non-fluent with pauses and incorrect attempts for word insertions. He was able to repeat short phrases but had mild difficulty with object naming. Comprehension of verbal but not written commands was intact. He was able to spell short words but was unable to write them. Finger agnosia, acalculia and right-sided agraphesthesia were present. Other findings included moderate right lower facial weakness, right homonymous hemianopsia, increased tone with weakness of the right arm (and to a lesser degree of the leg), hyperactive muscle stretch reflexes (especially on the right), bilateral extensor plantar responses and mildly impaired pin-prick sensation on the left side of his body.

Pertinent laboratory results included: WBC, 3,900/cu mm; hematocrit, 43.9%; serum creatinine, 1.5 mg/dl; erythrocyte sedimentation rate (ESR), 49 mm/hr; antinuclear antibody (ANA), positive at 1:40 with speckled pattern; anti-DNA, negative; gamma globulin level, 1.96 gm/dl (normal = 0.7–1.6 gm/dl); immune complexes, positive; RPR, positive at 1:4; FTA-ABS, negative; direct and indirect antiglobulin test, negative; lipoprotein electrophoresis, normal. A circulating inhibitor with antiphospholipid activity was identified (table 1). The LA test was positive. Other abnormal findings in the coagulation tests are summarized in table 2. Dipyridamole was discontinued four days before the coagulation tests were performed. He had received two units of fresh frozen plasma and 20 mg of parenteral vitamin K three days before testing.

Cerebrospinal fluid (CSF) assessment revealed 1 RBC/cu mm, 6 lymphocytes/cu mm, total protein 40.5 mg/dl, gamma fraction 4.9 mg/dl (normal = less than 10% total protein), calculated IgG index 0.29, glucose

**TABLE 1** Demonstration of Antiphospholipid Antibodies by Double Immuno-diffusion

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Positive control</th>
<th>Normal</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lα-Phosphatidyl-L-Serine (5 mg/ml)</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phosphatidyl ethanolamine (5 mg/ml)</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lα-Phosphatidyl ethanolamine (5 mg/ml)</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Platelet extract</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Human brain</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 2** Coagulation Abnormalities

<table>
<thead>
<tr>
<th>Coagulation tests</th>
<th>Normals</th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding time</td>
<td>3.0–9.5 min</td>
<td>9.0</td>
<td>15.0</td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>10.0–13.0 sec</td>
<td>11.9</td>
<td>10.7</td>
</tr>
<tr>
<td>Partial thrombo-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plastin time</td>
<td>24.0–34.0 sec</td>
<td>54.0</td>
<td>57.6</td>
</tr>
<tr>
<td>1:1 mix</td>
<td>&lt;39.5 sec</td>
<td>39.7</td>
<td>43.4</td>
</tr>
<tr>
<td>Factor XII</td>
<td>0.5–1.5 U/ml</td>
<td>1.35</td>
<td>0.46</td>
</tr>
<tr>
<td>Platelet count</td>
<td>150–450 × 10³/µl</td>
<td>133</td>
<td>128</td>
</tr>
<tr>
<td>Platelet aggrega-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tions*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADP (2 × 10⁻⁴ M)</td>
<td>&gt;60%</td>
<td>77</td>
<td>53</td>
</tr>
<tr>
<td>collagen (1.9 mg/ml)</td>
<td>&gt;60%</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>nstocetin (15 mg/ml)</td>
<td>&gt;60%</td>
<td>74</td>
<td>82</td>
</tr>
<tr>
<td>thrombin (10 U/ml)</td>
<td>&gt;60%</td>
<td>92</td>
<td>68</td>
</tr>
<tr>
<td>arachidonic acid (5 mg/ml)</td>
<td>&gt;60%</td>
<td>20</td>
<td>0</td>
</tr>
</tbody>
</table>

*The concentrations of working solutions which were diluted 1:10 in the tests are listed in parentheses.
Case 2

A 41-year-old, right-handed brother of the first patient was admitted in January 1984 for re-evaluation of aphasia and right-sided weakness. He had been well until January 1980 when he experienced a three hour episode of dysarthria and right arm weakness. Four vessel cerebral angiography at that time was normal. He was treated with aspirin and dipyridamole and did well until January 1982 when he was admitted for evaluation of intermittent claudication. Angiography revealed stenosis of the distal aorta and he underwent an uncomplicated aortic endarterectomy. The APTT in the hospital laboratory at that time was 37.6 secs with a control of 26.6 secs. At discharge all medications were stopped. He was re-admitted two months later because of expressive aphasia and right-sided weakness. His APTT was still prolonged at 32.0 secs with a control of 27.0 secs. A left cervical bruit was heard and four vessel cerebral angiography revealed a minimal smooth plaque of the left common carotid artery bifurcation and occlusion of major left posterior Sylvian branches. CT of the brain revealed a lucency in the left posterior Sylvian region. His RPR was positive at 1:4 and his FTA-ABS was negative. He had been treated with warfarin until four weeks prior to the current admission. His past medical history was otherwise significant for an uncomplicated tonsillectomy, bilateral inguinal herniorrhaphy and lumbar laminectomy. He was on no medication at the time of admission.

His blood pressure was 130/99 mm Hg. No cervical bruits were heard. The remainder of his general examination was unremarkable. His speech was fluent but with a staccato rhythm. He was able to repeat simple phrases but had mild difficulty with object naming. Acalculia, finger agnosia and right-left disorientation were present. Other significant findings included mild right lower facial and arm weakness, brisk right muscle stretch reflexes, and an extensor plantar response on the right.

Pertinent laboratory results included: WBC, 5200/cu mm; hematocrit, 43.3%; serum creatinine, 1.3 mg/dl; ESR, 17 mm/hr.; ANA, positive at 1:100 with a homogeneous pattern; anti-DNA, negative, gamma globulin level, 1.57 gm/dl; immune complexes, positive; RPR, positive at 1:1; FTA-ABS, negative; direct and indirect antiglobulin test, negative; lipoprotein electrophoresis, Type IV hyperlipidemia. A circulating inhibitor with antiphospholipid activity was identified (table 1). The LA test was positive. Other abnormal findings in the coagulation tests are summarized in table 2. Aspirin 10 grains daily was started three days before the coagulation tests were performed.

CSF assessment revealed 2 RBC/cu mm, 2 lymphocytes/cu mm, total protein 26.5 mg/dl, gamma fraction 1.6 mg/dl, glucose 55 mg/dl (simultaneous serum glucose 130 mg/dl), negative VDRL, and negative immune complexes.

The ECG and echocardiogram were normal. Four vessel cerebral angiography revealed minimal atherosclerotic changes of the distal common carotid and proximal internal carotid arteries, bilaterally. CT of the brain demonstrated areas of low attenuation in the distribution of the distal left middle cerebral artery and in the posterior right frontal region, the latter with gyral enhancement, compatible with two separate areas of infarction at different stages of evolution.

Discussion

The two cases presented illustrate features frequently associated with blocking inhibitors (of the lupus anticoagulant type): an abnormal APTT with incomplete correction when mixed with normal plasma, abnormal LA test (dilute thromboplastin), thrombocytopenia, biological false-positive tests for syphilis, and lack of a bleeding tendency. It should be noted that commercial reagents used in the APTT vary in their
ability to detect these inhibitors. Therefore, weak inhibitors may be missed if only the APTT is used for screening their detection.

The echocardiographic findings in Case 1 raise the possibility that cardiac embolization might have been the etiology of his cerebral infarcts. However, the seven-year interval between his myocardial infarction and first stroke suggest that this association would be highly unlikely, especially since a left ventricular aneurysm was not detected. The screening test for syphilis was reactive at the time of his cardiac catheterization. Although a more specific test was not performed, subsequent evaluation revealed that this was a biological false-positive result, suggesting that a BI may have been present when he experienced the myocardial infarction. Case 2 had laboratory evidence (prolonged APTT) suggestive of the existence of a BI two years prior to the current investigation. Since other laboratory abnormalities often associated with thrombotic diseases (antithrombin III, antiplasmin, plasminogen) were normal, we concluded that a BI was the predisposing factor for thrombotic disease in these two brothers.

Screening of all available members of the same family failed to detect others with BI or antiphospholipid antibodies. However, Case 2 and six family members were found to have abnormally low or low-normal factor XII levels. The relationship, if any, between our two cases with BI and their family members with abnormal factor XII levels is not clear.

These blocking inhibitors appear to be autoantibodies directed towards the phosphatase esters of a variety of biological molecules including the prothrombinase complex. The strong association between these inhibitors and biological false-positive tests for syphilis, the assay for which uses a cardiolipin (phospholipid) antigen, supports the role of phospholipid as the active site. Moreover, the fact that platelets supply the phospholipid framework for the intrinsic coagulation pathway, and the frequent occurrence of thrombocytopenia with BI, further strengthens this hypothesis. Consistent with these observations, the serum (56°C treated plasma) from both of our two cases with BI formed precipitin lines against certain phospholipid reagents.

The pathophysiologic mechanism by which BI predispose to arterial thrombosis has not been clearly defined but may involve inhibition of arterial prostacyclin (PGI\textsubscript{2}). The interaction of BI with various phospholipid substrates suggests that inhibition of arterial PGI\textsubscript{2} might result from interference with membrane phospholipid conversion to arachidonic acid, the precursor of PGI\textsubscript{2}. Using a more refined technique for the detection of antiphospholipid antibodies, Harris, et al\textsuperscript{28} demonstrated a significant correlation between patients with antiphospholipid antibodies, thrombocytopenia, biological false-positive tests for syphilis and thrombotic events. Furthermore, of nine patients with SLE and cerebral infarctions, eight had high levels of antiphospholipid antibodies suggesting that this might be a useful marker for those patients with BI at risk for cerebral infarction.

In management of patients with antiphospholipid coagulation inhibitors and thrombotic complications, the first step is to search for and treat underlying disease (particularly collagen-vascular) or to discontinue ongoing drug therapy with one of the implicated drugs.\textsuperscript{34} Prophylactic treatment of thrombotic manifestations is probably best accomplished with antiplatelet therapy. Aspirin is of possible use but the optimal antithrombotic dose has not been determined due to the known differential effects of aspirin on platelet thromboxane A\textsubscript{2} and vascular wall PGI\textsubscript{2} production.\textsuperscript{34} Other antiplatelet drugs might be considered. Steroids,\textsuperscript{17} cytotoxic agents\textsuperscript{35,36} and plasmapheresis\textsuperscript{22} — used either to treat the primary disease or the inhibitor’s effects — have been reported to correct

![Figure 1. Family pedigree indicating those with blocking inhibitor and abnormal factor XII levels.](image-url)

<table>
<thead>
<tr>
<th>Table 3 Summary of Coagulation Data from Family Members with Abnormal Factor XII Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family member*</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>III 6</td>
</tr>
<tr>
<td>III 7</td>
</tr>
<tr>
<td>II 2 (propositus)</td>
</tr>
<tr>
<td>III 1</td>
</tr>
<tr>
<td>II 6</td>
</tr>
<tr>
<td>II 4</td>
</tr>
<tr>
<td>II 1</td>
</tr>
</tbody>
</table>

*Identified by nomenclature used in fig. 1.
†See table 2 for the normal values.
‡As determined by the ability of serum to form precipitin lines with phospholipid reagents.
the coagulation test abnormalities in isolated cases or brief series, however, their use must be decided on an individual case basis.

Acknowledgments

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