Recurrent Ischemic Attacks in Two Young Adults with Lupus Anticoagulant

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SUMMARY  Two young adults with lupus anticoagulant had multiple attacks of cerebrovascular ischemia in different arterial territories. Cerebral angiography was normal. One patient had a new episode during anticoagulant therapy, but has remained asymptomatic on antiplatelet treatment. In the other, further events occurred during treatment with platelet-inhibiting drugs, but there have been no recurrences with adequate anticoagulant therapy.

Lupus anticoagulants are possible causes of otherwise unexplained thromboembolic events. Due to the variable mode of action of these immunoglobulins, platelet-inhibiting drugs may in some cases be considered as a prophylactic alternative to anticoagulant treatment.

THROMBOEMBOLISM due to arteriosclerotic lesions accounts for most cases of ischemic cerebrovascular accidents, but other causes are not infrequent in young adults.1,2 Among hemostatic abnormalities, lupus anticoagulants have been found in association with thrombotic events.3,4 These acquired circulating anticoagulants are immunoglobulins, either IgG or IgM,5 and were initially described in patients with systemic lupus erythematosus (SLE).6 Although the paradox of thrombosis occurring in the presence of coagulation inhibitors has not been adequately explained, anticoagulant therapy has been used in order to prevent further episodes.4

We report the cases of two young women with lupus anticoagulant and recurring cerebrovascular accidents, who presented unusual therapeutic problems.

Case Reports

Case 1

A 39-year-old woman experienced one episode daily for three consecutive days of bilateral scintillating scotomata, without headache, lasting a few minutes each time. Seven months later she had a myocardial infarction. Coronary angiography was normal. Mild hypertension (150/100 mm Hg) was diagnosed and treated with diuretics. Six months later she had another attack of scintillating scotomata, this time followed by a persistent defect of the left visual field.

She had smoked 10 cigarettes daily until her myo-
cardiac infarction. Her past history revealed no evidence of lipid abnormalities, diabetes mellitus, or migraine. She had never taken oral contraceptives, or any other drugs except diuretics. Her only sister had died, aged 25, of SLE. Neurological examination on admission showed only a left homonymous hemianopia. Blood pressure was 140/90 mm Hg. Routine blood chemistry tests were normal, except for an ESR of 20 mm/hr. Coagulation studies (table) demonstrated the presence of a lupus-like circulating anticoagulant. A test for antinuclear antibodies was strongly positive, with a homogeneous and speckled pattern. Anti-DNA antibodies were within the normal range, as were serum complement and immunoglobulins. Cryoglobulins, anti-mitochondrial, anti-smooth muscle and Sm antibodies were not detected.

ECG documented the earlier myocardial infarction; echocardiogram was normal. A CT scan revealed an area of infarction in the right occipital lobe. After contrast injection, enhancement was observed in the right temporo-insular area. Four-vessel transfemoral angiography was normal. The patient was discharged with a diagnosis of possible SLE. Ten days afterwards she suddenly experienced speech difficulty and transient bilateral visual obscuration. In addition to left hemianopia, neurological examination showed mild aphasia and a right superior quadrantanopia, both of which regressed in a few days. A CT scan (fig.) showed three hypodense areas, in the right occipital and temporo-insular zones and in the left temporal lobe. Treatment was started with acenocoumarol, with thrombotest values ranging between 5% and 15%. One month later the patient developed transient bilateral amaurosis: during this attack she fell and fractured her right tibia. A CT scan was unchanged, as were hematstatic and immunological tests. Acenocoumarol was discontinued, and antiplatelet therapy was started with acetylsalicylic acid (ASA), 500 mg daily. On follow-up examination 18 months later the patient is in good health and has had no further ischemic attacks despite persistence of circulating anticoagulants.

Case 2

A 32-year-old woman developed transient aphasia and right hemiparesis lasting about 20 minutes. A left carotid angiography disclosed no abnormality. SLE had been diagnosed five years earlier, and she was taking prednisone, 20 mg daily, with complete remission of systemic symptoms.

Two years later a similar attack occurred. A CT scan was normal and ASA, 500 mg daily, was added to the steroid therapy. One year afterwards she had two other transient episodes of aphasia and right hemiparesis. ASA was discontinued and sulfipyrazone, 800 mg daily, was begun. The next year, because of recurrence of systemic symptoms with lupus nephritis, methotrexate (40 mg i.m. weekly) was prescribed, with benefit. Six months later, the patient had, on the same day, two transient attacks of bilateral amaurosis with right hemiparesis and hypoesthesia. Four-vessel transfemoral angiography, a CT scan and EEG were normal, as well as ECG and echocardiogram. Hemostasis tests (table) demonstrated the presence of a lupus-like anticoagulant. Antiplatelet therapy was stopped and acenocoumarol was added to prednisone (20 mg daily) and methotrexate; however, thrombotest values fluctuated widely and the acenocoumarol dosage had to be frequently adjusted. Over the next six months the patient had several transient ischemic attacks, with right hemiparesis and aphasia, and bilateral amaurosis with mental confusion. Each time the value of the thrombost test performed before and on the day after the attack was above 40%. Replacement of acenocoumarol with warfarin resulted in thrombotest values constantly within the therapeutic range of 5–15%. During the following 2½ years cerebral ischemic events have not recurred, despite persistence of circulating anticoagulants. There have been no hemorrhagic complications, and neurological examination remains normal.

Discussion

Our two patients had multiple cerebral ischemic attacks in different arterial territories. Angiography showed no arteriosclerotic or arteritic lesions, and cardiac sources of emboli were not detected. Moreover, our patient 1 had normal coronary angiography at the time of her myocardial infarction. These clinical findings suggested a hypercoagulable state. In fact, both

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
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<tbody>
<tr>
<td>Platelets</td>
<td>90000/mm³</td>
<td>271000/mm³</td>
</tr>
<tr>
<td>Prothrombin time*</td>
<td>1.07</td>
<td>1.11</td>
</tr>
<tr>
<td>Tissue thromboplastin inhibition test (1:50 dilution)*</td>
<td>2.02</td>
<td>1.59</td>
</tr>
<tr>
<td>Tissue thromboplastin inhibition test (1:100 dilution)*</td>
<td>2.10</td>
<td>1.62</td>
</tr>
<tr>
<td>Activated partial thromboplastin time* (0.80–1.15)</td>
<td>2.13</td>
<td>1.44</td>
</tr>
<tr>
<td>Activated partial thromboplastin time, after 1:1 mixing with control plasma*</td>
<td>2.00</td>
<td>1.39</td>
</tr>
</tbody>
</table>

*Results are expressed as ratio of patient to reference normal plasma. Normal values are reported in parentheses.

![Figure Case 1. Selected slices of CT scan demonstrating three hypodense areas.](http://stroke.ahajournals.org/Downloaded-from)
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patients had lupus-like circulating anticoagulants, as diagnosed by the prolongation of the activated partial thromboplastin time, which was not corrected by 1:1 mixing with normal plasma, and by the abnormality of the tissue thromboplastin inhibition test. Although initially recognized in patients with SLE, where they occur in 5–10% of the cases, lupus anticoagulants have been subsequently observed in other autoimmune disorders, in association with drugs and neoplasia, and even in subjects without any underlying disease. Their precise mode of action on hemostasis tests has not been defined, but several studies suggest that they inhibit the phospholipid component involved in the in vitro activation of prothrombin.

A recent paper described a woman with a lupus anticoagulant impairing the synthesis or release of prostacyclin, a powerful inhibitor of platelet aggregation. The authors report decrease of prostacyclin production by plasma in four out of six patients with lupus anticoagulant. In such cases, treatment with platelet-inhibiting drugs appears warranted. Our patient 1 experienced no further episodes during prophylactic antiplatelet therapy. Low-dose ASA may be appropriate in order to achieve a selective inhibition of thromboxane and prevent the negative effects of prostacyclin deficit. In our patient 2, on the other hand, inadequate acenocoumarol levels, possibly due to the interaction of concomitant medications, led to several recurrences, which however stopped as soon as the thrombotic values were within the therapeutic range. In both cases treatment was protracted because of persistence of circulating anticoagulants.

Although cerebrovascular and coronary attacks in patients with SLE are usually ascribed to arteritis or atherosclerosis, circulating anticoagulants are probably involved in some cases and are sometimes the only relevant finding. Prevention of recurrent thromboembolic events in these patients should take into account that lupus anticoagulants do not seem to be a homogeneous group with regard to mode of action. Prophylactic treatment with platelet-inhibiting drugs may be sometimes considered, at least in cases where adequate anticoagulant therapy appears ineffective.

References

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