Frequency, Etiology, and Prevention of Stroke in Patients With Systemic Lupus Erythematosus

Nancy Futrell, MD, and Clark Millikan, MD

We retrospectively and prospectively reviewed the incidence of stroke in 105 patients with systemic lupus erythematosus (SLE). Stroke occurred in 14 (15%) of 91 consecutive patients with documented SLE; nine (64%) of the 14 had multiple cerebral infarcts. Factors associated with stroke and the frequency of stroke were systemic thrombosis (30%), elevated partial thromboplastin time (36%), spontaneous abortion (50%), age over 60 years (57%), transient ischemic attacks (57%), previous stroke (64%), and cardiac valvular disease (86%). The major period of risk for the first stroke was during the first 5 years of SLE. The most frequent etiology was a cardiogenic embolus or an antibody-mediated hypercoagulable state, with cerebral vasculitis occurring only in association with infection. Because of the decreased fibrinolysis seen in patients with SLE, anticoagulant therapy may be the most effective preventive treatment currently available. Anticoagulant therapy seemed to prevent recurrent focal cerebral ischemia in our patients and was associated with relatively few and minor complications. Patients who have had a stroke are at high (64%) risk for a recurrent stroke. Anticoagulant therapy is recommended for all of these patients. (Stroke 1989;20:583–591)

Central nervous system (CNS) involvement in systemic lupus erythematosus (SLE) was first described by Kaposi1 in 1869. The first reference to recurrent focal cerebral ischemia in SLE was made in 1903 by Osler,2 who reported a patient with five or six episodes of aphasia and hemiplegia; because vasculitic changes had been seen in the skin of SLE patients, Osler postulated that similar vascular changes in the brain could be responsible for the focal neurologic symptoms. Libman and Sacks3 described endocarditis in SLE in 1924; hyalinized blood along with platelet thrombi were seen in the heart, and these authors suggested that the left leg paralysis in one of their patients was caused by a cerebral embolus from the heart. In 1963, the association of the lupus anticoagulant (LA) and thrombosis in patients with SLE was described by Bowie et al.4 In 1968, Johnson and Richardson5 reported the neuropathologic findings in 24 cases of SLE and noted that true arteritis of cerebral vessels was rare. Richardson6 has also reported three cases of cerebral infarction that were apparently caused by emboli from Libman-Sacks endocarditis. In 1988, Devinsky et al7 reported an autopsy study of 50 SLE patients; 10 patients had embolic cerebral infarcts, five caused by Libman-Sacks endocarditis and four from other cardiac sources. There were no cases of active intracranial vasculitis.

Stroke is now generally recognized as a complication of SLE.8-21 We studied 105 patients with SLE, 18 of whom had strokes. By dividing the patients into subgroups with specific risk factors (coagulopathy, cardiac valvular disease, transient ischemic attacks [TIAs], previous stroke, and advanced age), groups of patients with stroke frequency ranging from 35% to 100% were identified. The recognition of these high-risk groups provides the basis for specific recommendations for preventive therapy in patients with SLE.

Subjects and Methods

All inpatient and outpatient records were reviewed for 105 patients with SLE. A comprehensive summary, including all pertinent clinical and laboratory findings related to SLE and all nervous system signs and symptoms, was made for each admission or major outpatient visit for each patient.
Group A comprised 91 patients with SLE documented by four or more American Rheumatological Society criteria for the diagnosis of SLE identified by consecutive hospital admissions to the University of Utah. Total follow-up was 599 patient-years. Eight of the 14 with stroke were followed prospectively for 1–6 years. Group B included 14 patients with SLE who were referred to the University of Utah or the University of Miami for evaluation of nervous system complaints. Total follow-up was 40 patient-years.

Stroke was diagnosed in SLE patients who had a clinical history compatible with stroke and a computed tomogram (CT scan) of the head demonstrating one or more infarcts. SLE patients with cerebral hemorrhage are listed separately. We used standard criteria for the diagnosis of TIA. Patients with a history compatible with TIA who also had strokes were classified with both groups.

The following definitions were formulated for this study: hypertension: blood pressure of >140/90 mm Hg on multiple occasions; cardiac valvular lesions: clearly abnormal valve(s) by echocardiography, including stenosis and/or insufficiency (mitral valve prolapse alone was not classified as abnormal); renal disease: proteinuria, cellular casts, decreased creatinine clearance, elevated blood urea nitrogen and creatinine concentrations, or abnormal renal biopsy; LA: elevated partial thromboplastin time (PTT) that failed to correct with the addition of fresh frozen plasma; systemic vascular occlusion or spontaneous abortion; coagulopathy: LA or systemic vascular occlusion or spontaneous abortion; and SLE onset: generally, the time at which SLE was diagnosed; occasionally, the medical history and the record of previous physical examinations and laboratory work allowed us to retrospectively date SLE onset to before the formal diagnosis. The earliest date at which four or more SLE criteria could be documented was used as the time of SLE onset in this study.

Results

Of the 91 Group A patients, 14 (15%) had strokes; nine (64%) of those 14 had multiple infarcts. Four of the 14 also had a history of TIA(s), and three more had TIA(s) but no strokes. One of the 14 with a platelet count of 3,000/mm³ had a cerebral hemorrhage. The mean age at the time of the first stroke was 40 years. The mean age of onset of SLE was 37 years in the 14 patients with strokes compared with 25 years in the rest of the Group A patients. The range of time between the onset of SLE and the first stroke was 0–25 (mean 3.8) years. Four of the 14 patients presented with a stroke and SLE was diagnosed subsequently; the other 10 patients had their initial stroke 0–1 years (two), 1–2 years (two), 2–5 years (four), 9 years (one), and 25 years (one) after SLE onset.

Yearly stroke rates were calculated for Group A based on the years between the onset of SLE and the first stroke using the number of stroke-free patients still being followed for a given number of years. The yearly stroke rates were 6.6% (six of 91) during Year 1, 3.1% (two of 65) during Year 2, 2.8% (four of 48) during Years 3–5, 0.6% (one of 31) during Years 6–10, and 0.6% (one of 12) during Years 11–25.
The 14 stroke patients in Group A were compared with the 77 nonstroke patients (Table 1), looking for differences in disease manifestations that could be related to stroke occurrence. Hypertension or renal disease did not change the risk of stroke. Potential stroke risk factors were evaluated (Table 2), with stroke frequency calculated for each risk factor. TIAs, previous stroke, and cardiac valvular lesions (particularly with coagulopathy) were associated with an extremely high stroke frequency (57-100%). Of the 60 SLE patients in Group A who had none of these risk factors, only one (1.7%) had a stroke.

Echocardiography was done in 40 of the 91 Group A patients, including 10 of the stroke patients. Definite (not subtle) cardiac valvular lesions were found in seven patients, including six of the stroke patients, and one stroke patient had a cardiomyopathy. In the 30 patients without stroke, the indications for echocardiography were the evaluation of cardiac murmurs or pericardial friction rubs.

Stroke(s) occurred in four of the 14 patients in Group B; two had a single stroke and two had multiple strokes. Mean age at the time of first stroke was 30 years. The time from the onset of SLE to the first stroke was 1, 3, 3, and 9 years in the four patients. One intracerebral hemorrhage occurred in a patient with a platelet count of 6,000/mm³; a 2-cm hematoma, not seen on CT scan, was found at autopsy in this patient.

Echocardiography was done in six of the Group B patients. Two had cardiac valvular lesions and infective endocarditis; one had multiple strokes and the other had multiple systemic emboli. This second patient was comatose and had received pancuronium bromide (Pavulon) before being seen by the authors. A CT scan was not obtained before her death, and her brain was excluded from the autopsy by her family. Although she may have had cerebral infarcts, this was not documented and she was not included as a stroke patient.

Among all 105 SLE patients (Groups A and B), 18 had strokes, with 11 of the 18 (61%) having multiple strokes. Risk factors were listed for each of these 18 stroke patients (Table 3). All 18 had at least one risk factor. The major lupus-associated stroke risk factors (TIAs, coagulopathy, cardiac valvular lesions, and age of >60 years) were present in 17 (94%) of the 18 stroke patients. Twelve had clinical or laboratory signs of coagulopathy or had a TIA before their first stroke (four spontaneous abortion, four TIA, one DVT, one superior vena cava occlusion, two LA). Five patients had no clinical or laboratory evidence of coagulopathy before their stroke, with two of these developing evidence of coagulopathy (spontaneous abortion and systemic emboli) after their first stroke. One patient had multiple TIAs and strokes, but the temporal relation of these events was not recorded.

Five of the 18 stroke patients, including one with multiple infaracts, died, two of cardiac disease (both >60 years old), one of an intracerebral hemorrhage (platelet count 3,000/mm³), one of infection (while on immunosuppressive drugs), and one of fulminant SLE with renal failure. Five of the 13 surviving stroke patients are severely disabled from multiple cerebral infarcts, with two requiring permanent nursing care.

The 13 of the 105 patients who were treated with anticoagulant therapy for any indication are listed in Table 4. We review the case histories of those with TIAs or strokes. Patient 3 in Table 4 had received anticoagulant therapy numerous times for DVT and PE. She had numerous strokes while off anticoagulants but no strokes during the 4 years she received anticoagulant therapy. The source of her strokes was clearly cardiac, with vegetations seen on the mitral valve on echocardiography. Patient 4 in Table 4 had been having episodes of visual scotomas (5-10 minutes) twice weekly before anticoagulant therapy was started for a DVT. These episodes stopped but returned when anticoagulant therapy was discontinued because of hematuria. Patient 6 in Table 4 had three episodes of diplopia (15-60 minutes), one episode of right arm numbness (30 minutes), one episode of vertigo (10 minutes), and frequent episodes of hemeralopia during the 4 years before warfarin was started for a systemic arterial embolus. She had continued hemeralopia but no other episodes while receiving anticoagulant therapy for 13 months. She has had no warfarin for 1 year and

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**Table 2. Potential Risk Factors for Stroke in 91 Patients With Systemic Lupus Erythematosus**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Patients with risk factor</th>
<th>Patients with risk factor who had stroke</th>
<th>Stroke frequency (%)</th>
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<tr>
<td>False-positive VDRL</td>
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<td>3</td>
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<td>Systemic thrombosis</td>
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<td>30</td>
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<tr>
<td>Lupus anticoagulant</td>
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<td>36</td>
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<tr>
<td>Coagulopathy</td>
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<td>9</td>
<td>36</td>
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<tr>
<td>Spontaneous abortion</td>
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<td>50</td>
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<tr>
<td>Age $\geq$ 60 years</td>
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<td>4</td>
<td>57</td>
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<tr>
<td>Transient ischemic attacks</td>
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<td>4</td>
<td>57</td>
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<tr>
<td>Previous stroke</td>
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<td>64</td>
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<tr>
<td>Cardiac valvular disease</td>
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<td>6</td>
<td>86</td>
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Table 3. Risk Factors for Stroke in Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Patient</th>
<th>Multiple strokes</th>
<th>TIAs</th>
<th>LA (clinical)</th>
<th>Coagulopathy (clinical)</th>
<th>Abnormal heart valve</th>
<th>Age ≥ 60 years</th>
<th>High blood pressure</th>
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<td>Group A</td>
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Group B

<table>
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<tr>
<th>Patient</th>
<th>Multiple strokes</th>
<th>TIAs</th>
<th>LA (clinical)</th>
<th>Coagulopathy (clinical)</th>
<th>Abnormal heart valve</th>
<th>Age ≥ 60 years</th>
<th>High blood pressure</th>
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<td>+</td>
<td>+</td>
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</table>

TIA, transient ischemic attacks; LA, lupus anticoagulant.
*TTP, thrombotic thrombocytopenic purpura, known to be associated with strokes and with systemic lupus erythematosus.24-25

Table 4. Patients With Systemic Lupus Erythematosus Treated With Anticoagulants

<table>
<thead>
<tr>
<th>Patient</th>
<th>Stroke</th>
<th>TIAs</th>
<th>LA</th>
<th>Anticoagulant</th>
<th>Duration</th>
<th>Indication</th>
<th>CNS response</th>
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<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>H</td>
<td>2 weeks</td>
<td>DVT, PE</td>
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<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>H,W</td>
<td>2 months</td>
<td>PE</td>
<td>+</td>
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<tr>
<td>3*</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>W</td>
<td>4 years</td>
<td>PE, DVT</td>
<td>+</td>
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<tr>
<td>4†</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>W</td>
<td>6 weeks</td>
<td>DVT</td>
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<tr>
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<td>-</td>
<td>W</td>
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<td>DVT, PE</td>
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<tr>
<td>6</td>
<td>-</td>
<td>+</td>
<td>W</td>
<td>3 months</td>
<td>PE</td>
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<td>7</td>
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<td>W</td>
<td>8 weeks</td>
<td>Orthopedic surgery</td>
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<tr>
<td>8</td>
<td>+</td>
<td>-</td>
<td>W</td>
<td>3 years</td>
<td>TIAS</td>
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<td></td>
</tr>
<tr>
<td>9</td>
<td>+</td>
<td>-</td>
<td>W</td>
<td>3 years</td>
<td>PE</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>-</td>
<td>W</td>
<td>3 years</td>
<td>Strokes</td>
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<tr>
<td>11</td>
<td>+</td>
<td>-</td>
<td>W</td>
<td>3 years</td>
<td>Strokes</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>-</td>
<td>W</td>
<td>3 months</td>
<td>PE</td>
<td>+</td>
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</table>

TIAs, transient ischemic attacks; LA, lupus anticoagulant; H, heparin; W, warfarin; DVT, deep venous thrombosis; PE, pulmonary embolus; CNS response, TIAs and strokes occurred before but none occurred during anticoagulant therapy.

*Complication, nasal bleeding with prothrombin time of 102 seconds; anticoagulant was continued.
†Complication, hematuria; anticoagulant was discontinued.
in Table 4 had multiple strokes from a definite cardiac source, with vegetations seen on echocardiography. She has had no strokes during 3 years of anticoagulation.

Neuropathologic evaluations were done at autopsy on six patients, two of whom had a history of stroke. One stroke patient had multiple cerebral infarcts and a thickened leaflet of the aortic valve. She had renal vasculitis but no cerebral vasculitis. The other stroke patient had a right temporal infarct, no cerebral vasculitis, and a normal heart. The only neuropathologic findings of “vasculitis” in the nervous system were related to infection; one patient had cytomegalovirus in the retina and brain, and one had Aspergillus in the brain and lung. The other two autopsies revealed no neuropathologic abnormalities. One was of a patient with the recent onset of generalized seizures, and the other was of a patient with no CNS problems.

**Discussion**

**Stroke occurs in 3–20% of patients with SLE.**

The low stroke rates in some studies may reflect the earlier tendency to consider all nervous system events in SLE patients as a single category. There is increasing awareness of the variable nature of nervous system involvement in SLE patients and of the need to carefully classify the CNS manifestations.[30] Several studies, mainly done before the recognition of the importance of stroke in SLE and before the availability of CT and magnetic resonance imaging, mention hemiparesis or hemiplegia in 4–13% of patients;[31–34] there is no mention of the temporal profile of these events. Other disorders that could produce hemiparesis (i.e., cerebral abscess) were present in some of the patients.[31] For these reasons and because some studies included only SLE patients with “neuropsychiatric manifestations,” the frequency of stroke in SLE cannot be determined from these studies. A higher frequency of strokes is reported in autopsy studies[35–37] and would not be expected to represent the frequency of stroke in the general SLE population.

Our study includes three SLE patients who had signs and symptoms that could have been caused by small cerebral infarcts and one comatose patient who may have had multiple embolic cerebral infarcts. These four patients were not included as stroke patients because CT had not been done to confirm the presence of cerebral infarct(s). Thus, we might have underestimated the stroke frequency in our patients. On the other hand, we would anticipate that these hospitalized patients at tertiary care centers may have a higher frequency of stroke than the general SLE population.

Yearly stroke rates calculated for the patients with SLE revealed a marked tendency for strokes to occur early in the course of SLE. Most patients who developed strokes had their first stroke during the first 5 years of the disease, with the highest stroke rate during the first year. SLE patients who did not have a stroke during the first 5 years of the disease had a yearly stroke rate of <1%. Those patients who had a stroke during the first 5 years of the disease continued to have a high risk of recurrent stroke for the duration of the period studied.

Eighteen of our 91 Group A patients were not evaluated for LA (four patients with and 14 patients without stroke). The stroke frequency in SLE patients with LA cannot be accurately determined from our data.

Seventeen (94%) of our 18 stroke patients had one or more stroke risk factors other than SLE and/or LA (hypertension, cardiac valvular lesions, cardiomyopathy, and thrombotic thrombocytopenic purpura). Levine and Welch[35] have reported stroke risk factors (hypertension, diabetes, and hypercholesterolemia) in four (80%) of their five patients and in >50% of the patients in the literature with LA and stroke. Levine and Welch suggest that other stroke risk factors may be synergistic with LA in producing stroke. Our data suggest that this is also true in SLE patients who have strokes.

Cerebral hemorrhage in SLE has been reported in 0.4–7% of patients with SLE.[12,16,21] The two cases in our study were both associated with thrombocytopenia. Although subarachnoid hemorrhage has been reported in SLE,[13,16,36] there was none in our patients.

In our study, SLE patients with spontaneous abortions had a significantly increased frequency of stroke. It is possible that a history of spontaneous abortions could have been more carefully taken in the stroke patients, falsely elevating this association. The risk of stroke following spontaneous abortion should be prospectively evaluated.

DVT, PE, and other systemic thromboses have been associated with SLE, with and without LA.[37–42] In our study, the rate of stroke was slightly elevated in patients with a history of systemic thrombosis, but this elevation failed to reach statistical significance. The frequency of systemic thrombosis in our patients was probably accurately reported since this problem almost always results in hospitalization. The risk of stroke after a DVT or a PE may be modified by the anticoagulant therapy that is usually given in this setting.

The category of coagulopathy includes SLE patients with either clinical or laboratory evidence of a hypercoagulable state. This resembles the guidelines for the diagnosis of SLE in that it includes both clinical and laboratory findings.[22] SLE patients with coagulopathy have a significantly increased frequency of stroke. The strong tendency for SLE patients with stroke to have other clinical and laboratory evidence of coagulopathy has been noted.[9] However, clinical signs of coagulopathy appeared after the first stroke in two (20%) of our 10 stroke patients with coagulopathy; therefore, the absence of clinical coagulopathy cannot be used as a negative predictor of stroke risk in a given patient.
Although the association between stroke and advanced age is well known, the risk of stroke in people over age 60 with SLE is markedly higher than that in people over age 60 without SLE. Our seven patients over age 60 also had an unusually late onset of SLE (range 47–65, mean 60 years of age). The high frequency of neurologic disease in late-onset SLE has been noted by McDonald et al., although the stroke frequency reported by these authors was only 10%, much less than the 57% we saw.

SLE patients with cardiac valvular lesions shown on echocardiography had a very high frequency of stroke (87%). This group included six of the 14 Group A stroke patients. This stroke frequency is much higher than that seen in patients with cardiac valvular lesions who do not have SLE. For example, 15–29% of patients with rheumatic heart disease will have embolic events, with approximately 40% of these being cerebral.43

It is known that Libman-Sacks endocarditis is frequently found in SLE (16–57% according to autopsy studies7,44–50), but the diagnosis cannot be made clinically.48,51 Thus, it is difficult to document the role of Libman-Sacks endocarditis in the production of embolic cerebral infarction. In the original description by Libman and Sacks3 in 1924, they postulated that the cerebral symptoms noted in one of their patients could have been due to cardiogenic emboli. In 1968, Johnson and Richardson5 reported that the microinfarcts seen in the brain had no consistent relationship to endocarditis at autopsy. By 1980, there were only two reported cases of embolic cerebral infarction from Libman-Sacks endocarditis.52,53 Some authors concluded that emboli from Libman-Sacks endocarditis are rare,54 but in 1982 Richardson4 reported three cases of cerebral embolism that were apparently emboli from Libman-Sacks endocarditis. The most recent series on the neuropathology of SLE was published in 1988 by Devinsky et al. and contains 50 patients; five patients had cerebral emboli from Libman-Sacks endocarditis and four had cerebral emboli from other cardiac sources (two from valvulitis and two from a mural thrombus). Cerebral embolism from Libman-Sacks endocarditis and other cardiac sources is probably much more frequent than previously estimated.

The idea of cerebral vasculitis as a cause of focal neurologic deficits in SLE was postulated by Osler,2 based on vasculitic changes seen in the skin of SLE patients. Johnson and Richardson4 found perivascular inflammatory infiltrates in the brains of three of 24 autopsies on SLE patients and pointed out that the alterations in blood vessels were not accompanied by inflammatory cells within the vessel wall and therefore cannot be classified as a vasculitis in the usual sense. Devinsky et al.7 found no acute vasculitis in the brain or spinal cord of 50 patients with SLE. Numerous authors have mentioned “cerebral vasculitis” or “lupus vasculitis” as a cause of focal neurologic deficits in their patients, but without pathologic confirmation.54–61

We found vasculitis in the nervous system at autopsy only in association with infection that invaded blood vessels (Aspergillus in the brain and cytomegalovirus in the eye and brain). Although rare cases of cerebral vasculitis in SLE may occur, the results of major autopsy studies suggest that vasculitis is an infrequent cause of stroke in patients with SLE.5,7,19,20,31,62–64

There is a striking incidence of thrombosis, including stroke, in SLE patients with LA.7,37–42 Anticardiolipin and other antiphospholipid antibodies, the concentrations of which are often increased in patients with LA, have also been reported in association with stroke in SLE.19,65 The importance of these antibodies as a predictor of a thrombotic tendency has recently been questioned since many SLE patients without LA or anticardiolipin antibodies have an increased thrombotic tendency38,66 and since anticardiolipin antibodies are relatively frequent in other conditions without a thrombotic tendency.66–72 A false-positive VDRL, which is generally associated with an elevated titer of anticardioli-pin antibodies,73,74 was not significantly associated with stroke in our patients (Table 1). SLE patients have additional abnormalities leading to a hyper-coagulable state, including decreased fibrinolysis75,76 from decreased plasminogen activation75,76 and decreased tissue thromboplastin activation.77

More than half of our patients who had either a TIA or a stroke had one or more strokes following their initial ischemic event. This is supported in the literature by numerous reports of the tendency for multiple cerebral infarcts in patients with SLE.13,19,24,78 In our study the multiple cerebral infarcts had devastating consequences.

Patients with SLE have a 15% stroke incidence based on Group A. This justifies vigorous reduction of stroke risks, including control of hypertension and blood glucose concentration, cessation of smoking, and management of increased cholesterol or lipid concentrations in all patients with SLE. Aspirin's failure to prevent stroke in patients with LA has been reported,79–81 but aspirin has not been well studied in SLE. Since aspirin is relatively benign in low doses and may decrease stroke risk in some patients, we suggest 325 mg/day in all patients with SLE of <5 years' duration and in patients in high-risk groups with contraindications to more aggressive therapy.

Steroids have prevented spontaneous abortion in patients with SLE or LA82,83 and have reduced the elevated PTT in patients with LA.84,85 Steroids have failed to prevent systemic thrombosis41 and are probably not effective in preventing stroke78,80 in patients with SLE or LA. The risks of steroid therapy at the levels proven to be effective against spontaneous abortion (40 mg/day) may be acceptable for the duration of a pregnancy, but not for the years required for stroke prevention. Steroids are indicated in patients with SLE and TIA or stroke.
only if there are signs of sufficient activity of the systemic disease to justify the use of steroids.

Cardiogenic emboli, which are frequent in SLE, are best prevented by anticoagulants.19, 86 Anticoagulation is the preventive therapy of choice in SLE patients, with or without LA, following an episode of systemic thrombosis.87, 88 Several studies have reported stroke patients with SLE who were safely and effectively treated with anticoagulants.81, 89, 90 Although the fibrinolytic defect in SLE would not be corrected by anticoagulant therapy, decreasing the formation of fibrin might bring the balance between fibrinogenesis and fibrinolysis nearer normal. Since heparin and warfarin can be used relatively safely in patients with SLE, even in the presence of LA,89 and since our case histories suggest that anticoagulant therapy may have been effective in our patients, we suggest anticoagulation of patients with SLE who have had a stroke, TIA, or cardiac valvular disease, indicating a very high risk for recurrent cerebral ischemia.

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References


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