Stroke in Systemic Lupus Erythematosus

Yasuhisa Kitagawa, MD, Fumio Gotoh, MD, Atsuo Koto, MD, and Hiroyuki Okayasu, MD

We investigated the clinical and pathologic characteristics of stroke in 234 patients with systemic lupus erythematosus. Thirteen patients (5.6%) developed cerebrovascular disease. Cerebral infarction was noted in eight, cerebral hemorrhage in two, and subarachnoid hemorrhage in three. In seven (54%) of these 13 patients, stroke occurred ≤5 years after systemic lupus erythematosus was diagnosed. Among the predisposing risk factors for stroke, hypertension was the most important. Lupus anticoagulant was detected in three (38%) and anticardiolipin antibody in three (43% of seven investigated) of the patients with infarction. Evaluation of the clinical manifestations and autoantibodies indicated that renal involvement and high titers of anti-deoxyribonucleic acid antibody were more frequent in the stroke group than in the non-stroke group. Autopsy studies on six of the patients with stroke revealed small infarcts and hemorrhages in all, but in no case was true angiitis observed. Libman-Sacks endocarditis was found in two of the three patients with infarction. In conclusion, the important contributory factor to the development of stroke in patients with systemic lupus erythematosus is considered to be hypertension mediated by immunologic abnormalities. Antiphospholipid antibodies and Libman-Sacks endocarditis are closely associated with occlusive cerebrovascular disease. (Stroke 1990;21:1533–1539)

Among the various connective tissue diseases, systemic lupus erythematosus (SLE) is frequently associated with neuropsychiatric disorders.1–4 Although considerable knowledge has been accumulated concerning the clinical and serologic abnormalities associated with SLE, the pathogenesis of the cerebrovascular disease (CVD) that is occasionally associated with SLE remains uncertain. Several etiologic factors for CVD such as angiitis, antineuronal antibodies, cardiac diseases, and coagulopathies have been suggested. We analyzed the clinical and pathologic characteristics of the CVD occurring in SLE patients in an attempt to clarify its pathogenesis.

Subjects and Methods

All inpatient and outpatient medical records of 234 consecutive persons with SLE seen from 1972 to 1989 were retrospectively reviewed in detail for evidence of stroke. The diagnosis of SLE was made on the basis of the 1982 revised criteria for the classification of SLE.5 Stroke was diagnosed in SLE patients who had neurologic deficits with a corresponding lesion on a brain computed tomogram (CT scan). Cases in which autopsy revealed a focus of cerebral infarction, cerebral hemorrhage, and/or subarachnoid hemorrhage were also included. Patients with transient ischemic attacks or neurologic signs and symptoms lasting for >24 hours, suggesting clinical stroke, but without corresponding CT lesions were excluded. Patients with asymptomatic infarcts encountered on brain CT scans or at autopsy were also excluded. The follow-up period ranged from 6 months to 15 years, with a mean of 6.7 years.

Particular attention was paid to the presence of risk factors for CVD such as hypertension, diabetes mellitus, hypercholesterolemia, heart disease, antiphospholipid antibodies, and large doses of corticosteroid. The following definitions were formulated for the study: hypertension, blood pressure of >160/95 mm Hg on multiple occasions; diabetes mellitus, fasting blood glucose concentration of >120 mg/dl; hypercholesterolemia, total cholesterol concentration of >250 mg/dl; heart disease, abnormal heart murmurs suggesting the presence of valvular stenosis and/or insufficiency; and large doses of corticosteroid, initial corticosteroid dose of >60 mg/day.

The presence of lupus anticoagulant was inferred if the partial thromboplastin time exceeded the upper limit of the normal range for the laboratory by at least 5 seconds and if the prolonged partial thromboplastin time failed to be corrected following 1:1 dilution of the patient’s plasma with normal plasma. Concentrations of anticardiolipin IgG and IgM antibodies were measured by an enzyme-linked immuno-
which was characterized by the formation of verrucae on the mitral valve. This could have caused the
hemorrhage. Autopsy revealed Libman-Sacks endocarditis, and hypertension were considered probable contrib-
ting factors to the occurrence of cerebral hemorrhage in two, and subarachnoid hemorrhage in three. Among the eight patients with occlusive CVD, five had hemiparesis or dysarthria at onset, two had altered levels of consciousness, and one had convulsions. Among the five patients with hemorrhagic CVD, headache and/or disturbance of consciousness appeared as an initial neurologic manifestation. The mean duration of steroid treatment for the subgroups with occlusive and hemorrhagic CVD were 4.9 and 6.6 years, respectively; for the entire CVD group the mean duration was 5.6 years. There was no significant difference between the subgroups with occlusive and hemorrhagic CVD.

The location of the lesions was demonstrated by CT in eight patients (cases 1, 2, 4, 5, 6, 8, 12, and 13) and at autopsy in six (cases 3, 7, 8, 9, 10, and 11). Multiple cerebral infarcts were detected in five of the eight patients with infarction. Concerning the location of the infarct, the cerebral cortex and subcortical white matter were more common than the basal ganglia. Regarding the location of cerebral hemorrhage, massive lobar hemorrhage was noted in each of the two patients. Cerebral aneurysms were located at the anterior communicating artery in two patients and at the trifurcation of the middle cerebral artery in one.

Case 8 followed an atypical clinical course. The serial CT findings are illustrated in Figure 1. This 37-year-old woman suffered cerebral infarction in the distribution of the left middle cerebral artery at onset and in the distribution of the right occipital cerebral artery 2 years later and massive cerebral hemorrhage 5 years after onset. She had a long history of uncontrol-
rollable hypertension and the antiphospholipid antibody syndrome. In this patient, thrombocytopenia and hypertension were considered probable contrib-
uting factors to the occurrence of cerebral hemorrhage. Autopsy revealed Libman-Sacks endocarditis, which was characterized by the formation of verrucae on the mitral valve. This could have caused the cerebral embolism in the distribution of the middle and posterior cerebral arteries.

The laboratory data for the 13 patients indicated the presence of immunologic and hematologic abnor-
malities. Lupus anticoagulant was detected in three of the eight patients (38%) and antiphospholipid anti-
bodies in three of seven patients (43%) with occlusive CVD. These antiphospholipid antibodies were not detected in the five patients with hemorrhagic CVD.

We examined the chronologic relation between the initial cerebrovascular events and establishment of the diagnosis of SLE (Table 2). In seven of the 13 patients (54%), CVD occurred ≤5 years after SLE was diagnosed. This suggests that CVD appeared mostly during an early stage of SLE.

We examined the relation between the onset of CVD and lupus activities. Positive evidence for lupus activity such as fever, a decrease in the concentration of complement, and elevation of the anti-deoxyribo-
nucleic acid (DNA) antibody titer was noted at the time of CVD in 80% (four) of the five patients with hemorrhagic lesions compared with 50% (four) of the eight with infarction.

We then compared the incidence of various pre-
disposing risk factors for CVD (hypertension, dia-
tes mellitus, hypercholesterolemia, heart disease, and steroid therapy) in the CVD group with that in the non-CVD group (Table 3). Hypertension was signif-
ically more frequent in the CVD group than in the non-CVD group. The incidence of hypertension was 63% among the eight patients with occlusive CVD and 60% among the five with hemorrhagic CVD, as opposed to 25% in the non-CVD patients. However, there was no significant difference in the incidence of other risk factors for CVD between the groups.

The mean duration of steroid treatment was 3 years in the eight hypertensive patients and 8 years in the five normotensive patients. It appeared, therefore, that there was no relation between steroid administration and hypertension.

We examined whether the clinical symptoms and various antibodies differed between the CVD and non-CVD groups. Concerning the clinical manifesta-
tions (Table 4), renal involvement was significantly more frequent in the CVD group than in the non-
CVD group. High titers of anti-DNA antibody were significantly more frequent in the CVD group than in the non-CVD group (Table 5).

Four of the five patients with hemorrhagic CVD died, as did five of the eight with occlusive CVD. Among the nine deaths, postmortem examinations of the central nervous system (CNS) were performed in six patients (Table 6). Macroscopically, multiple large and small areas with encephalomalacia were found in two cases and intracerebral hemorrhage was noted in two. In case 8, multiple large infarcts and massive cerebral hemorrhage were observed. Primary subarach-
chondial hemorrhage was encountered in two cases. In all six cases, microscopic examinations revealed small infarcts and hemorrhages in addition to those observed grossly, but in no case was true angitis detected. In addition, no evidence of focal healed vasculitis, which is
<table>
<thead>
<tr>
<th>Pt/age/sex</th>
<th>Presenting symptoms</th>
<th>Neurologic findings</th>
<th>Location of lesion (by computed tomography or at autopsy)</th>
<th>Duration of steroid treatment (years)</th>
<th>High titer of anti-DNA antibodies</th>
<th>Low C3 concentration</th>
<th>Lupus erythematosus cells</th>
<th>Biologic false-positive for syphilis</th>
<th>Lupus anticoagulant</th>
<th>Anti-cardiolipin antibodies</th>
<th>Anemia</th>
<th>Leukopenia</th>
<th>Thrombocytopenia</th>
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<td>1/15/F</td>
<td>Convulsions</td>
<td>R hemiparesis</td>
<td>Multiple</td>
<td>1.0</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>2/40/M</td>
<td>Disturbance of consciousness</td>
<td>R hemiparesis stupor</td>
<td>R frontal</td>
<td>4.8</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3/62/F</td>
<td>R hemiparesis</td>
<td>R hemiparesis, depression</td>
<td>L basal ganglia</td>
<td>0.4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4/39/M</td>
<td>Dysarthria</td>
<td>R hemiparesis</td>
<td>L basal ganglia</td>
<td>14.0</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5/59/F</td>
<td>Dysarthria</td>
<td>R hemiparesis</td>
<td>Multiple</td>
<td>6.2</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6/59/F</td>
<td>L hemiparesis</td>
<td>L hemiparesis, dysarthria</td>
<td>Multiple</td>
<td>2.0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7/39/F</td>
<td>Disturbance of consciousness, headache</td>
<td>Coma</td>
<td>Multiple</td>
<td>11.0</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8/37/F*</td>
<td>R hemiparesis</td>
<td>R hemiparesis, aphasia</td>
<td>Multiple</td>
<td>...†</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</table>

**Occlusive CVD**

**Hemorrhagic CVD**

Cerebral hemorrhage

9/53/M Headache | L hemiplegia, coma | L temporo-occipital hemorrhage | 4.8 | + | + | + | - | - | ... | ... | - | - | + | + | -

10/41/F Disturbance of consciousness | Coma | R massive cerebral hemorrhage | 1.3 | + | + | + | - | - | - | - | + | + | + | + | +

Subarachnoid hemorrhage

11/38/F Headache | Disturbance of consciousness, stiff neck | ACoA aneurysm | 11.0 | + | - | - | - | - | - | - | - | - | - | - | -

12/49/F Disturbance of consciousness, headache | Stiff neck | R middle cerebral artery aneurysm | 9.2 | + | - | - | - | - | - | - | - | - | - | - | -

13/26/F Disturbance of consciousness, headache | Stiff neck | ACoA aneurysm | 6.8 | - | - | - | + | - | - | - | - | - | - | + | -

CVD, cerebrovascular disease; Pt, patient; F, female; M, male; R, right; L, left; ACoA, anterior communicating artery.

*The patient suffered massive cerebral hemorrhage in R hemisphere 5 years after onset.

†No corticosteroid administration before ictus.
characterized by disruption of the elastic lamina and mild intimal proliferation in medium-sized arteries, was found in any case. Libman-Sacks endocarditis was demonstrated in two of the three patients with infarction, but no cardiopathy was detected in any of the three patients with hemorrhagic CVD.

**Discussion**

Among the neuropsychiatric disorders encountered in patients with SLE, seizures and psychosis are most common, but CVD has been a relatively rare complication, estimated to occur in 5–20%.7-10 This range of incidence might partly reflect the recent advances in neuroradiologic techniques, such as CT and magnetic resonance imaging (MRI), as well as the actual duration of observation.

Concerning the onset of CVD, Futrell and Millikan11 reported that most SLE patients who developed stroke had their first episode during the first 5 years of SLE, the incidence of CVD being highest during the first year. In these patients, the risk of recurrence remained high throughout the follow-up period. Our data are consistent with the above report in the case of occlusive CVD. However, a similar tendency was not prevalent in SLE patients with hemorrhagic CVD.

As regards the pathogenesis of CVD in SLE patients, primary and secondary causes have been suggested.12,13 The primary causes include vasculitis, specific antineuronal antibodies, and lupus anticoagulant. As secondary causes, renal disorders, hypertension, and steroid administration have been suggested. In our experience, hypertension was the most important factor contributing to the development of CVD. Hypertension was closely associated with renal involvement mediated by immunologic abnormalities, characterized by high titers of anti-DNA antibody, in the patients with SLE. We examined the histologic findings in the kidneys of seven patients; there was a significant correlation between the severity of renal involvement and the degree of hypertension.

Corticosteroid may accelerate atherosclerosis in the coronary arteries in patients with SLE,14 but its effect on the cerebral vessels remains uncertain. In our study, there were no differences in the dosage of corticosteroid and the incidence of hypercholesterolemia between the CVD and non-CVD groups.

Antiphospholipid antibodies such as lupus anticoagulant and anticardiolipin antibody may play an important role in the development of occlusive CVD. In our series, lupus anticoagulant was detected in 38% of the SLE patients with infarction. It has been said that approximately 5–10% of SLE patients with lupus anticoagulant develop CVD.15,16 This antibody may inhibit the formation of prostacyclin in the intimal vessels.17,18 It may cross-react with phospholipid in the endothelial cell membrane and prevent the release of arachidonic acid, which in turn lowers the production of prostacyclin and causes platelet aggregation. Several other potential mechanisms (such as prekallikrein inhibition, alterations of anti-thrombin III, decreased fibrinolysis, decreased release of plasminogen activator, and inhibition of protein C activation) have been proposed.19,20 Recent studies of anticardiolipin antibodies also suggest

**TABLE 2.** Chronologic Relation Between Initial Episodes of Cerebrovascular Disease and Diagnosis of Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Years after diagnosis of SLE</th>
<th>Occlusive</th>
<th>Hemorrhagic</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>0–5</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>5–10</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10+</td>
<td>2</td>
<td>1</td>
<td>3</td>
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SLE, systemic lupus erythematosus. Data are number of patients.

**FIGURE 1.** Serial computed tomograms in case 8. Cerebral infarction occurred in left middle cerebral artery at onset, followed 5 years later by massive cerebral hemorrhage.

**TABLE 3.** Incidence of Predisposing Risk Factors for CVD Among Patients With Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>CVD group (n=13)</th>
<th>Non-CVD group (n=221)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
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<tr>
<td>Hypertension</td>
<td>8</td>
<td>61.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>15.4</td>
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<tr>
<td>Hypercholesterolemia</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1</td>
<td>7.7</td>
</tr>
<tr>
<td>Large doses of steroid</td>
<td>3</td>
<td>23.1</td>
</tr>
</tbody>
</table>

CVD, cerebrovascular disease.

*p<0.01 different from CVD group by \( \chi^2 \) test.
other mechanisms that could induce endothelial cell injury. These antibodies have been associated with systemic thrombotic problems including major arterial occlusions, deep-vein thrombosis, and pulmonary hypertension, as well as with thrombocytopenia and recurrent fetal abortion. Asherson et al reported a relation between CVD and antiphospholipid antibodies in patients with SLE and related disorders. Multiple episodes of cerebral infarction are common in patients with antiphospholipid antibodies, and some patients develop multi-infarct dementia during the course of their illness.

Lupus anticoagulant and anticardiolipin antibody share the same or closely related antigenic specifications, and approximately 50% of patients with anticardiolipin antibody also have lupus anticoagulant. These antibodies have recently been reported to contribute to the occurrence of cerebral thrombosis not only in SLE but also possibly in some SLE-related or other diseases in which these antibodies are present.

Other possible predisposing factors include some of cardiac origin. Although echocardiography did not reveal abnormal findings, autopsy studies demonstrated Libman-Sacks endocarditis in two patients with infarction. Libman-Sacks endocarditis can sometimes be diagnosed with certainty only at autopsy. It has been said that Libman-Sacks endocarditis rarely produces hemodynamic changes, but according to the recent reports of Devinsky et al and Futrell and Millikan, this disease can contribute to the occurrence of emboli. Moreover, significant valvular lesions have been found to be associated with antiphospholipid antibodies in patients with stroke and complicating SLE.

Cerebral hemorrhage has been reported to occur in 0.4–7% of SLE patients. In our series, hypertension was the predominant contributory factor for hemorrhagic CVD. However, no atherosclerotic changes or angiogenesis were detected in the cerebral vessels on pathologic study. Thrombocytopenia was not specific in the patients with hemorrhagic CVD. However, no atherosclerotic changes or angiogenesis were detected in the cerebral vessels on pathologic study. Thrombocytopenia was not specific in the patients with hemorrhagic CVD. In case 8, however, cerebral hemorrhage was caused by intractable hypertension and thrombocytopenia. This patient developed cerebral infarction due to lupus anticoagulant at onset and later showed massive cerebral hemorrhage. Early reports of patients with lupus anticoagulant tended to emphasize hemorrhagic disorders, but subsequent studies have shown that bleeding is rare. When bleeding does occur, it can often be attributed to associated thrombocytopenia or clotting factor deficiency. In case 8, prolonged hypertension and thrombocytopenia contributed to the development of massive hemorrhage.

The incidence of subarachnoid hemorrhage due to berry aneurysm is higher in SLE patients than in the general population. This has been attributed to antiangiitis. In their pathologic study, Ellis and Verity reported that the incidence of subarachnoid hemorrhage in 57 cases with CNS lupus was 30%, but in almost all cases the subarachnoid hemorrhage was related to intracerebral hemorrhage. Hashimoto et al described two cases of cerebral aneurysms associated with SLE. On reviewing the literature, these authors found vasculitis in only two of nine cases and showed that the aneurysms accompanied by vasculitis tended to occur at unusual sites and to be of the fusiform type. Aneurysms in the usual location re-
revealed no evidence of vasculitis. In our study, berry aneurysms were found at the anterior communicating artery in two cases and at the trifurcation of the middle cerebral artery in one. Angiitis was not observed in any patient.

Vasculitis of the small vessels has been suggested to cause manifestations of CNS lupus. However, true vasculitis has proved to be a rare pathologic finding in the brain. Johnson and Richardson reported true vasculitis with inflammatory cell infiltrates in the vessel wall in only three of their series of 24 cases. The main pathologic features included vascular lesions such as microinfarct and microhemorrhage. Ellis and Verity performed one of the most comprehensive evaluations; among 57 autopsy cases, vasculitis was observed in only 7%. Recently, Devinsky et al examined the detailed neuropathologic findings of 50 SLE patients, but in no case was true angiitis found. There is no reliable serologic or neuroradiologic procedure that can verify the presence of cerebral angiitis. Neither CT nor MRI can resolve this problem. A diagnosis of angiitis is made only at autopsy. In our study postmortem examinations failed to reveal the presence of angiitis, and there was no evidence of healed vasculitis modified by corticosteroid in any case examined.

In summary, the important factor contributing to the development of stroke in SLE patients is considered to be hypertension. Antiphospholipid antibodies and Libman-Sacks endocarditis are closely associated with occlusive CVD. Angiitis was not related to the development of stroke in our patients.

Acknowledgments

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References


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<th>Table 6. Autopsy Findings in Six Patients With Cerebrovascular Disease and Systemic Lupus Erythematosus</th>
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KEY WORDS • anticoagulants, antiphospholipid antibodies • endocarditis • hypertension • lupus erythematosus, systemic