Baseline Disease Activity, Hyperlipidemia, and Hypertension Are Predictive Factors for Ischemic Stroke and Stroke Severity in Systemic Lupus Erythematosus

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Background and Purpose—To determine factors associated with ischemic stroke and stroke severity in patients with systemic lupus erythematosus.

Methods—Between 1992 and January 2005, 238 consecutive systemic lupus erythematosus patients with no history of stroke were followed-up longitudinally at the Maryland Lupus Clinic. Patients were monitored quarterly for a mean of 8 years after their systemic lupus erythematosus diagnosis, and 44 patients (19%) developed first-ever ischemic stroke. At the end of study, Cox proportional regression analyses were used to determine the effect of baseline clinical variables of systemic lupus erythematosus patients in relation to the subsequent occurrence of ischemic stroke and stroke severity after first-ever ischemic strokes. Severe stroke was defined as having a National Institute of Health Stroke Scale ≥6.

Results—Severe ischemic strokes occurred in 34 of 44 (77%) patients. Baseline predictors of ischemic strokes and severe ischemic strokes included disease activity, hyperlipidemia, and hypertension.

Conclusions—Severe ischemic strokes in systemic lupus erythematosus are not uncommon. Aggressive primary and secondary stroke prevention measures, particularly treatment of hyperlipidemia and hypertension, as well as vigorous treatment of clinical symptoms of active lupus, are needed to prevent serious morbidity and neurological disability. (Stroke. 2007;38:281-285.)

Key Words: ischemic stroke ■ neurological disability ■ risk factors ■ systemic lupus erythematosus

The morbidity and mortality related to atherosclerotic vascular disease in systemic lupus erythematosus (SLE) remain substantial, despite improved survival rates. Despite compelling evidence that risk factors are important contributors to accelerated atherosclerotic vascular disease in SLE, the influence of these risk factors on the occurrence of ischemic strokes is less well-established than with other types of vascular diseases.

The pathogenesis of ischemic strokes in SLE involves more than the traditional Framingham risk factors. Whereas some case-control studies have shown an association of ischemic strokes with different combinations of anti-phospholipid (aPL) antibodies, some have not. Moreover, SLE patients with aPL antibodies have a higher incidence of left-sided cardiac valvular abnormalities and Libman-Sacks endocarditis, conditions that may potentially contribute to thromboembolism and large cerebral vessel strokes. Others have suggested that SLE severity is a strong determinant of atherosclerosis (and strokes), particularly in patients with more aggressive disease who receive large cumulative doses of glucocorticoids. Nonetheless, these previous studies have been heterogeneous, with relative small proportion of SLE patients having ischemic strokes and incomplete follow-up.

Using the revised nomenclature and case definitions of neuropsychiatric SLE, the classification of ischemic strokes according to the Trial of Org 10172 in Acute Stroke Treatment criteria, the National Institutes of Health Stroke Severity Scale (NIHSS), we sought to determine the effect of baseline features associated with the occurrence of ischemic strokes, severe ischemic strokes, and neurological disability in a contemporary SLE cohort. Understanding the factors predictive of ischemic strokes in SLE will provide effective means for developing strategies aimed at preventing morbidity, disability and mortality in patients with SLE.

Methods

Patients
The University of Maryland Lupus cohort consists of 238 patients enrolled between 1992 and January 2005, according to the 1982...
American College of Rheumatology revised criteria as modified in 1997.16 This cohort has been previously described in detail.17 Patients have been monitored quarterly over a mean follow-up period of 8 years (range, 1 to 10 years).

A standardized protocol was applied to all SLE patients with ischemic strokes, including SLE disease activity index, standardized laboratory tests, and diagnostic studies performed at baseline and at time of stroke, as well as types of ischemic strokes defined according to the Trial of Org 10172 in Acute Stroke Treatment classification. Hypertension was defined when blood pressure is >140/80 at entry into the cohort and confirmed to be elevated 3 months later or if the patient was using antihypertensive medications. Diabetes mellitus was defined at time of entry to the cohort when fasting blood sugar was >110 mg/dL, or if the patient was using blood sugar lowering agents. Cholesterol levels were considered to be normal at levels ≥200 mg/dL, whereas triglycerides ≤150 mg/dL, high-density lipoprotein cholesterol ≥50 mg/dL, and low-density lipoprotein cholesterol ≤130 mg/dL were considered to be normal. The aPL antibodies, including the anti-cardiolipin (aCL) IgG and IgM auto-antibodies were measured with an enzyme immunoassay,18 with reference ranges being: <12 GPL units/mL = negative, 12 to 19 GPL units/mL = low positive, 20 to 80 GPL units/mL = moderately positive, and >80 GPL units/mL = high positive.

The severity of the neurological deficits at 1 month from the admission to the hospital for the stroke was determined using the NIHSS scale. Severe ischemic stroke was defined as a NIHSS score ≥6. For patients admitted to another hospital at the time of the stroke event, the NIHSS score was determined at time of the discharge through data abstraction from medical records (6 patients); this process has an established high degree of reliability and validity.19 Patients with strokes before diagnosis of SLE, patients with transient ischemic attacks, as well as patients with nonischemic strokes including cerebral hemorrhage, subarachnoid hemorrhage (even with secondary cerebral ischemia caused by spasm), cerebral venous thrombosis, cerebral vascular malformation, and migraine strokes, were excluded.

This study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Board Office for Research on Human Subjects at the University of Maryland School of Medicine.

Statistical Methods
The baseline features of those patients with stroke (severe strokes [NIHSS ≥6, n=34] and minor strokes [NIHSS ≤6, n=10]) and those without strokes (n=188) were examined. Comparisons were done by χ² for categorical variables and by analyses of variance (ANOVA) for continuous variables. Demographic features, clinical manifestations frequently occurring in SLE, antibodies to dsDNA, aPL, as well as C-reactive protein, homocysteine level, smoking history, obesity, presence of hypercholesterolemia, hypertension, diabetes mellitus, and medications ever used including aspirin, nonsteroidal anti-inflammatory drugs, statins, and antihypertensive medications, were examined in relation to stroke occurrence, stroke severity, and neurological disability. Cox proportional hazard models were developed to assess the effects of different baseline clinical variables on the risk of occurrence of any stroke and stroke severity. The time to any stroke, the time to severe stroke (NIHSS ≥6), and the time to last visit for those not experiencing a stroke were the end-points in the proportional hazards models. Variables considered for inclusion in these models were age, disease activity, aCL, serum cholesterol, diabetes, and hypertension. The selection of these variables was based on their association with strokes in the univariable analyses and their effect size in the presence of other variables. In all analyses, P<0.05 was considered significant. All analyses were performed using SAS, version 9.1.

Results
Of the 238 SLE patients in the University of Maryland lupus cohort, 232 patients were included in the present analyses; 6 patients were excluded because of having stroke at time of entry, or having a history of hemorrhagic strokes, migraine strokes, subarachnoid hemorrhage, or transient ischemic attack. Of the 232, 209 (90%) were women and 154 (66%) were black. The average age at disease diagnosis was 32.5 years. At the time of these analyses were performed, first-ever ischemic strokes had occurred in 44 of 232 (19%) patients; on the average, these strokes occurred 4 years after patients entered the cohort. Thirty-four of the 44 (77%) SLE patients experienced severe ischemic stroke (NIHSS ≥6). The estimated rates of any and severe stroke were 25.3 and 19.3 per 1000 patient-years, respectively. The types of ischemic strokes included: (1) large-artery/atherothrombotic strokes, the most prevalent strokes (45%); (2) small-vessel/lacunar infarcts (39%); (3) cardioembolic strokes (9%); and (4) stroke of undetermined origin (7%). Recurrence of stroke occurred in 4 patients (9%) within the first year of the initial stroke and in 3 patients (7%) after the first year.

Univariable Analyses of Ischemic Strokes
Baseline demographic and clinical features of SLE patients with ischemic strokes and those without ischemic strokes are shown in Table 1. Older age, cutaneous vasculitis, high disease activity at baseline, and high dose of glucocorticoids used and, not surprisingly, hypercholesterolemia and hypertension were more frequent in those patients with strokes than in those who never had them (Table 1).

Musculoskeletal, renal, cardiac, and pulmonary SLE manifestations, obesity, and smoking history and anti-cardiolipin IgG antibodies were more frequent in the group of patients with ischemic strokes than in the group without them, but the difference was not statistically significant.

In patients who had ischemic strokes, there was a trend toward higher baseline serum total cholesterol levels. Likewise, the proportion of patients with raised non–high-density lipoprotein cholesterol and triglycerides were higher in those who had ischemic strokes than in those who did not. Other serum lipoproteins examined were comparable between the groups.

Severe Ischemic Strokes
As shown in Table 1, baseline clinical factors including disease activity, cutaneous vasculitis, higher doses of prednisone use, hypercholesterolemia, raised non–high-density lipoprotein cholesterol and triglycerides, and hypertension were more frequent in SLE patients with severe stroke compared with those with minor stroke. Baseline SLE manifestations (musculoskeletal, renal, and pulmonary), cardiac disease (coronary artery syndrome, and valvular heart disease), carotid stenosis, and smoking history were more frequent in those patients who had severe stroke compared with those with minor stroke, although the difference was not statistically significant.

Baseline high aCL antibodies were comparable among patients with severe and minor strokes; there was no association between aCL antibodies and types of ischemic strokes. As expected, the large-vessel strokes were more frequent in patients with severe stroke compared with those with minor stroke (58.8% versus 0%), and the small-vessel strokes were
more frequent in patients with minor stroke compared with those patients with severe stroke (90.0% vs 23.5%).

**Cox Proportional Hazard Multivariable Regression Analyses**

The results of the multivariable analyses are shown in Table 2. Baseline variables significantly and independently associated with the subsequent occurrence of ischemic stroke and severe ischemic stroke were disease activity, hypercholesterolemia, and hypertension. The associations of disease activity and the subsequent occurrence of ischemic stroke or severe stroke were emphasized when we dichotomized the patients according with their baseline disease activity to minor (SLE disease activity index $<6$) versus moderate to severe score (SLE disease activity index $\geq 6$). The logrank survival analyses revealed a hazard ratio for any stroke of 2.09 (95% confidence interval, 1.0 to 4.6), and for severe stroke a hazard ratio of 2.56 (95% confidence interval, 1.0 to 6.4). Of importance, and as depicted in Table 2, there was no linear relationship between baseline disease activity and the occurrence of ischemic stroke or severe stroke.

The baseline aCL was not predictive of subsequent occurrence of any ischemic stroke or severe stroke. When we dichotomized patients according with their baseline aCL titers to negative versus positive aCL, the association of aCL and ischemic stroke revealed a hazard ratio of 1.1 (95% confidence interval, 0.55 to 2.18), whereas the association with severe stroke revealed a hazard ratio of 0.8 (95% confidence interval, 0.35 to 1.81). As shown in Table 2, no linear relationship was verified.

**Discussion**

Although certain clinical features have been associated with an increased risk of SLE-related strokes, the predictive factors associated with ischemic strokes are not well-understood. We assessed the baseline factors associated with the subsequent occurrence of ischemic stroke in the Maryland lupus cohort and ascertained that severe ischemic strokes are common. Though the incidence of ischemic stroke in this SLE cohort is comparable with data reported in the literature,4,11 we emphasize that the incidence of ischemic stroke in SLE is higher than in the general population,20 and that severe ischemic stroke in SLE is not uncommon. It is important to note, however, that the use of NIHSS $\geq 6$ indicating severe stroke in our population is not conventional, but that may be related to the nature of ischemic stroke in SLE patients.

Several clinical studies2,3 have identified that conventional risk factors predict an increased risk of stroke and coronary artery disease in SLE. They do not, however, fully explain the high risk of cardiovascular disease in SLE. This suggests that
SLE patients may possess other characteristics that render them at greater risk for ischemic strokes. In our study, high SLE disease activity at baseline contributed significantly and independently to the subsequent occurrence of ischemic stroke and severe ischemic stroke. An association has also been suggested between disease activity and carotid IMT and the presence of carotid plaques. Although disease activity was not found to be an independent contributor to the occurrence of vascular events including strokes in the LUMINA (Lupus in Minori ties: Nature versus nurture) patients, there was a trend for blacks (our lupus cohort is predominantly black) to have more vascular events compared with other ethnic groups. Further controlled studies are likely to distinguish the importance of the underlying disease activity versus the treatment in predicting cardiovascular and cerebrovascular outcomes.

Our study demonstrates that hypercholesterolemia is more common in SLE patients with ischemic strokes, and that non–high-density lipoprotein cholesterol is an independent predictor associated with the subsequent occurrence of ischemic stroke and severe ischemic strokes. Although epidemiological and observational studies have shown a clear association between cholesterol levels and all-cause strokes in the general population, less information is available in the SLE literature. Hyperlipidemia is proatherogenic, and is associated with endothelial dysfunction and increased intima media thickness of the carotid arteries, surrogate measures of subclinical atherosclerosis.

Subanalyses of the use of statin therapy at baseline in this SLE cohort was associated with reduced risk of ischemic strokes and the occurrence of minor strokes. Further research should validate our findings in long-term randomized interventional clinical trials in patients with SLE.

Similar to our study, others have determined that in the general population, hypertension is an independent predictor of poor outcome after first-ever ischemic stroke, in particular, in the elderly. Hypertension is associated with lacunar and thromboembolic strokes and is considered an important risk factor predictive of severe ischemic strokes in this SLE cohort. Whether adequate blood pressure control in SLE hypertensive patients would prevent first-ever strokes and stroke severity requires further investigation. Certainly, careful attention to blood pressure control is critical in SLE patients, to prevent organ damage (be it renal, cardiovascular, or other).

Similar to other studies, we found that cardiac valvular abnormalities in SLE patients are more frequent in patients with ischemic strokes. Hypercoagulability associated with aPL, and in particular lupus anticoagulant appeared to be an important cofactor in these other studies. Our univariable analyses supported the importance of aPL antibodies in the occurrence of ischemic stroke in SLE. However, an association between aPL antibodies and stroke severity was not observed. Similar observation has been described where aPL antibodies do not seem to be a strong risk factor for recurrent stroke in patients with recent ischemic strokes.

Unlike other investigators, we have not been able to find that age, smoking, glucocorticoid use, baseline C-reactive protein levels, and diabetes mellitus are risk factors for the occurrence of stroke and severe ischemic strokes in SLE once disease activity, hyperlipidemia, and hypertension were controlled. These factors may be important in the nonhypertensive, nonhyperlipidemic patients with relatively low levels of baseline disease activity. It is also possible that glucocorticoids used early in the disease may prove to be protective by modulating the immune response and decreasing the inflammatory process characteristic of this disease.

There are several limitations to this study that warrant consideration. First, we have ascertained risk factors at the time patients entered the cohort and not at the time preceding stroke; thus, we excluded patients who developed events before time of entry to the cohort. Second, we examined ischemic strokes with different pathophysiologic mechanisms, including thromboembolic, atherosclerotic, vascular inflammation, and hypercoagulable states without distinguishing these possible different mechanisms. Lacking histopathological evidence, it is impossible to state with any degree of certainty the contribution of each of these pathophysiologic components (which at times may occur concomitantly) to the vascular events. Third, given our interest in neuropsychiatric lupus, our study may suffer from potential selection bias, as patients referred to us may be enriched with neuropsychiatric events, stroke included.

In summary, despite their relative young age and low rates of stroke recurrence, strokes of variable severity are not uncommon in SLE patients. Baseline high disease activity, hyperlipidemia, and hypertension are independent predictors of ischemic strokes and stroke severity. Further studies will determine whether treating hyperlipidemia and other traditional risk factors in SLE patients may substantially reduce or prevent the development of severe stroke and whether such measures will have impact on mortality, disability, and quality of life in SLE.

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Disclosures
None.

References