Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9228-21
Intern Med 61: 3045-3052, 2022
http://internmed.jp

【 ORIGINAL ARTICLE 】

Heterogeneity of Stroke in Patients with Systemic Lupus Erythematosus

Takaya Kitano[1], Toru Hirano[2], Shuhei Okazaki[1], Eri Itotagawa[2], Yoshiki Yagita[3], Yoshitaka Morita[4], Akihiro Watanabe[5], Daisuke Takahashi[5], Manabu Sakaguchi[6], Hiroshi Fujiwara[7], Kenichi Todo[1], Tsutomu Sasaki[1], Atsushi Kumanogoh[2] and Hideki Mochizuki[1]

Abstract:

Objective The underlying pathophysiology varies according to stroke subtype. However, stroke heterogeneity among patients with systemic lupus erythematosus (SLE) remains unstudied. We hypothesized that the contribution of SLE to stroke might vary according to its subtype and investigated the associations of SLE and various stroke subtypes.

Methods Diagnostic codes and electronic medical records were used to identify 70 patients with SLE who developed acute cerebral infarction or intracerebral hemorrhaging at four tertiary referral hospitals between 2008 and 2018. Intracerebral hemorrhaging was classified as lobar or deep, while cerebral infarction was classified according to the SSS-TOAST criteria. Physician notes were used to identify SLE activity, and their prevalences were compared among stroke subtypes. Outcomes were collected from the patients' medical records.

Results The most common stroke subtype in patients with SLE was that of undetermined causes (31%), followed by small artery occlusion (16%), cardioaortic embolism (13%), other causes (11%), lobar hemorrhaging (10%), deep hemorrhaging (10%), and large artery atherosclerosis (9%). Stroke onset occurred during a period of high SLE activity in 21 patients (30%). The proportion of patients with high SLE activity varied according to stroke subtype (p=0.039) and was highest for cerebral infarction with undetermined causes. Stroke recurrence or death was observed in 40% of patients within 5 years after the initial stroke onset.

Conclusion The contributions of SLE to stroke varied significantly according to the stroke subtype. Given the unfavorable prognosis, close stroke subtype-specific observation by rheumatologists and stroke specialists is recommended after stroke events.

Key words: stroke, lupus, cerebrovascular disease, antiphospholipid syndrome, thrombosis, prognosis

(Intern Med 61: 3045-3052, 2022)
(DOI: 10.2169/internalmedicine.9228-21)

Introduction

Approximately 30-40% of patients with systemic lupus erythematosus (SLE) develop neuropsychiatric events during the course of their disease (1-5). Stroke, which includes cerebral infarction and intracerebral hemorrhaging, is a common neuropsychiatric manifestation of SLE (6, 7) and is the cause of up to 15% of deaths among patients with SLE (8). In addition, patients with SLE have an approximately two-fold higher risk of stroke than the general population (9-11). Therefore, stroke prevention and management are critical for

[1]Department of Neurology, Osaka University Graduate School of Medicine, Japan, [2]Department of Respiratory Medicine and Clinical Immunology, Osaka University Graduate School of Medicine, Japan, [3]Department of Stroke Medicine, Kawasaki Medical School, Japan, [4]Department of Rheumatology, Kawasaki Medical School, Japan, [5]Department of Neurology, Osaka Minami Medical Center, Japan, [6]Department of Neurology, Osaka General Medical Center, Japan and [7]Division of Rheumatology and Allergy, Osaka General Medical Center, Japan
Received for publication December 15, 2021; Accepted for publication February 2, 2022
Correspondence to Dr. Shuhei Okazaki, s-okazaki@umin.ac.jp

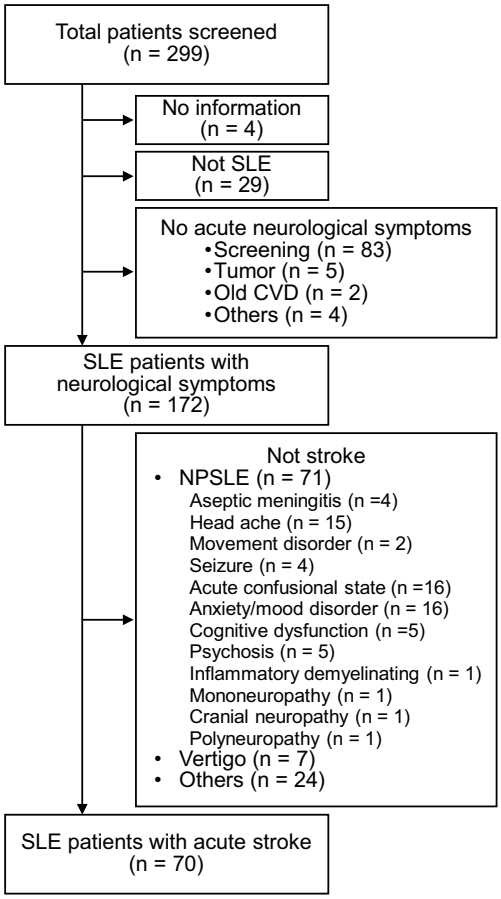

Figure 1. Study flowchart. CVD: cerebrovascular disease, NPSLE: neuropsychiatric systemic SLE, SLE: systemic lupus erythematosus

patients with SLE. However, it is unclear to what extent stroke events are truly attributable to SLE. Furthermore, the pathophysiology of stroke in patients with SLE is not well understood.

Stroke is a heterogeneous disease that includes several underlying mechanisms. Because patients with SLE develop various types of stroke (12-16), the pathophysiology of stroke is not likely to be uniform in patients with SLE, although there is limited information regarding this heterogeneity. We hypothesized that the contribution of SLE to stroke, which is clinically important in determining the optimal treatment (1, 17), may vary according to stroke subtype.

Thus, the present study evaluated the associations of SLE with each stroke subtype, the contribution of SLE, and the outcomes after stroke in this patient population.

Materials and Methods

Data that support the findings of this study are available from the corresponding author upon reasonable request. The study complied with the Declaration of Helsinki, and the retrospective study protocol was approved by the institutional ethics committees of Osaka University Hospital, Osaka General Medical Center, Osaka Minami Medical Center, and Kawasaki Medical School Hospital, which waived the requirement for written informed consent. Patients were allowed to opt out of the research use of their data.

Patients

This multicenter retrospective study included patients who were treated at four tertiary referral hospitals in Japan. Patients with SLE and stroke were identified by searching the electronic medical records for relevant diagnostic codes from the International Classification of Diseases-10th revision (ICD-10). Patients were considered eligible if they were diagnosed with SLE (ICD-10: M32) and had undergone brain magnetic resonance imaging (MRI) during their admission between January 1, 2008, and December 31, 2018. Patients were also considered eligible if they were diagnosed with SLE (ICD-10: M32) and either intracerebral hemorrhaging (ICD-10: I61) or cerebral infarction (ICD-10: I63) during the same period. If a patient experienced more than one stroke event, only the initial event was considered for case selection. This process identified a total of 299 eligible patients.

The eligible patients' medical records and brain images were thoroughly reviewed by a trained neurologist (TK), who excluded patients with incomplete medical records (n= 4) or an incorrect diagnosis of SLE (n=29). Stroke was defined as a new neurological deficit with corresponding radiological evidence of hyperdense hematoma from intracerebral hemorrhaging detected using non-contrast computed tomography (CT) or a hyperintense lesion with restricted diffusion caused by cerebral infarction detected using diffusion-weighted MRI. Patients were also excluded if they did not have acute neurological symptoms (n=94), if they had non-stroke neuropsychiatric SLE manifestations based on the American College of Rheumatology nomenclature (n =71), or if they had other diseases (n=31).

The study ultimately included 70 patients with SLE who developed acute cerebral infarction or intracerebral hemorrhaging (Fig. 1).

Data collection

Data regarding age, sex, medical history, smoking status, stroke severity based on the National Institutes of Health Stroke Scale score, and cumulative manifestations based on the American College of Rheumatology definitions (18) were extracted from the patients' medical records. Laboratory data at admission, including complete blood counts, antibodies to double-stranded DNA (ds-DNA), complement components, and urine parameters, were also collected. Renal impairment was defined as a serum creatinine concentration of >1.5 mg/dL (>132.6 μmol/L). Outcomes regarding stroke recurrence and death were collected from each hospital's medical records, and cases were censored at the last follow-up or on December 31, 2019.

Classification of stroke

Intracerebral hemorrhaging was classified as lobar or deep hemorrhaging (19). Deep hemorrhaging included putaminal,

Table. **Patient Characteristics.**

	N=70	Missing
Age, years	55 (41-67)	0
Female sex	55 (79%)	0
Duration of SLE, years	14 (5-27)	5
Hypertension	44 (63%)	0
Diabetes	11 (16%)	0
Dyslipidemia	17 (24%)	0
Atrial fibrillation	6 (9%)	0
Renal impairment	13 (19%)	0
Previous stroke	23 (33%)	0
Previous ischemic heart disease	5 (7%)	0
Smoking	11 (16%)	0
Antiplatelet use	21 (30%)	0
Anticoagulant use	18 (26%)	0
Prednisone dose, mg	6.5 (3.3-10)	2
Immunosuppressive agents	3 (4%)	3
Modified Rankin scale score	0 (0-2)	6
NIHSS score	2 (1-6)	11
Manifestations*		
Malar rash	18 (38%)	23
Discoid rash	14 (30%)	23
Photosensitivity	13 (28%)	23
Oral ulcer	10 (21%)	23
Arthritis	30 (64%)	23
Serositis	14 (30%)	23
Renal disease	24 (51%)	23
Neurological disorders	11 (23%)	23
Hematological disorders	27 (57%)	23
Immunological disorders	42 (89%)	23
Positive ANA test result	42 (89%)	23

Data are presented as number (%) or median (interquartile range).
SLE: systemic lupus erythematosus, NIHSS: National Institutes of Health Stroke Scale, ANA: antinuclear antibody
* Manifestations based on the 1997 criteria from the American College of Rheumatology.

thalamic, brainstem, and cerebellar hemorrhaging. Ischemic stroke was classified according to the SSS-TOAST criteria (20). This system classifies the stroke event based on the patient's risk factors, medical history, and imaging findings (especially lesion size and distribution) as large artery atherosclerosis, cardioaortic embolism, small artery occlusion, other causes, or undetermined causes. This system has high inter-examiner agreement (20). In this study, subtyping without considering SLE as a cause of stroke was performed.

Stroke association with SLE activity

We evaluated whether or not a stroke event was attributable to SLE via two approaches. First, a high SLE activity around the time of stroke onset was defined by either a physician's note indicating a clinical assessment or concern regarding uncontrolled disease activity (this was assessed during admission due to stroke by the attending physician) or by the need for new or increased therapy (e.g. prednisone or immunosuppressants) to control active disease (21). SLE activity was evaluated in a categorical manner as either high or not high. Second, for a more objective evaluation, we used a previously reported algorithm to determine the contribution of SLE to a neuropsychiatric event (22), based on the interval between the event onset and the clinical SLE onset, event type, confounding factors (e.g. diabetes mellitus), and predisposing factors (e.g., SLE activity and heart valve disease). A higher prediction score indicates a greater likelihood that SLE contributed to the neuropsychiatric event. However, we omitted the SLE disease activity index because we could not retrospectively calculate that score.

Statistical analyses

Continuous variables were reported as the median [interquartile range (IQR)] and analyzed using Wilcoxon's rank-sum test. Categorical variables were reported as number (percentage) and analyzed using Fisher's exact test, unless otherwise specified. A complete case analysis was performed for items that included missing values. Kaplan-Meier curves and the log-rank test were used to evaluate the intervals between the stroke onset and stroke recurrence alone or along with death as a composite outcome.

Results were considered significant at p values <0.05, and all analyses were performed using the SAS OnDemand for Academics software program (version 9.4; SAS Institute Inc., Cary, USA).

Results

Patient characteristics

The patients' baseline characteristics are shown in Table. The median age was 55 (IQR 41-67) years old, and 79% of the patients were women. Minor neurological deficits were common (median National Institutes of Health Stroke Scale score: 2), although the stroke scale score was missing in 11 (16%) patients, and 3 of these patients were in a coma. The median duration of SLE at the stroke onset was 14 (IQR 5-27) years, although 9 (14%) patients experienced a stroke within 1 year after their SLE diagnosis, and 8 of these patients had a high SLE activity. Five patients had an unknown disease duration that was at least 10 years. The SLE clinical manifestations and laboratory disorders based on the American College of Rheumatology criteria are shown in Table. Stroke was accompanied by other neuropsychiatric manifestations in some patients: cognitive dysfunction (n=2), headache (n=1), seizure (n=1), aseptic meningitis (n=1), mood disorder (n=1), and psychosis (n=1).

Stroke subtypes

Among the analyzed patients, 14 (20%) patients had intracerebral hemorrhaging, 56 (80%) patients had cerebral infarction, and none had coexisting intracerebral hemorrhaging and cerebral infarction. The stroke subtypes were classified as undetermined causes (31%), small artery occlusion (16%), cardioaortic embolism (13%), other causes (11%), lobar hemorrhaging (10%), deep hemorrhaging (10%), and

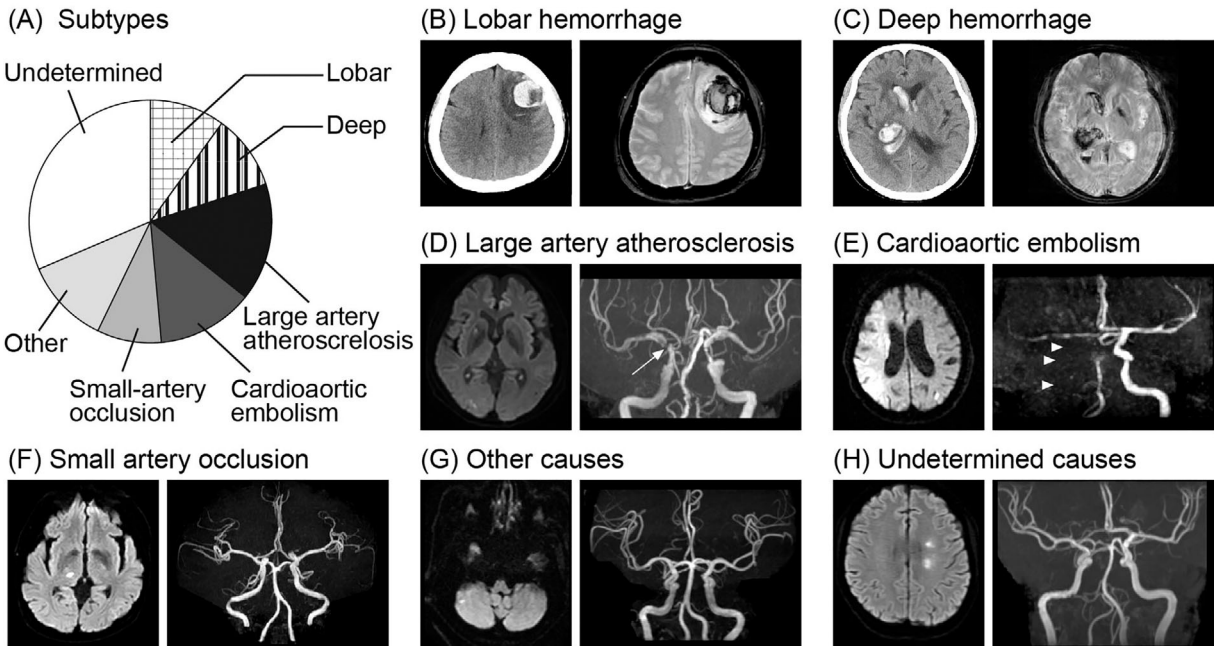

Figure 2. **Representative images of each stroke subtype in patients with systemic lupus erythematosus. (A) Proportions of each subtype. (B) Lobar hemorrhaging observed using non-contrast computed tomography (CT) and T2* images in a man with a history of antiphospholipid syndrome. (C) Deep hemorrhaging observed using non-contrast CT and T2* images in a woman with hypertension. (D-H) Cerebral infarction observed using diffusion-weighted images and magnetic resonance angiography. (D) The right internal carotid artery terminal branch was severely stenosed (arrow), and infarcts were located in the watershed area. (E) The right internal carotid was occluded and not visible (arrowheads). (F) Small artery occlusion in a man with diabetes mellitus. (G) Cerebral infarction after coronary angiography. (H) Scattered subcortical cerebral infarctions were observed without large-artery lesions.**

large artery atherosclerosis (9%). Representative images of each stroke subtype are shown in Fig. 2. All six patients with large artery atherosclerosis had intracranial artery stenosis, although none had extracranial carotid artery stenosis proximal to the lesion. One patient with lobar hemorrhaging had cortical venous thrombosis. Another patient was diagnosed with non-bacterial thrombotic endocarditis.

Baseline characteristics according to stroke subtype

The baseline characteristics according to stroke subtype are shown in Supplementary material 1. A significant difference in age was found among the stroke subtypes (p=0.015), and their distributions according to age group (≤50 years old vs. >50 years old) are shown in Supplementary material 2. Cardioaortic embolism was observed only in patients who were >50 years old (0% vs. 22%, p=0.008), and lobar hemorrhaging tended to be more common in younger patients than in older ones (17% vs. 5%, p=0.118). The prevalence of renal impairment was high among patients with cerebral hemorrhaging (57%). The proportions of patients with antiphospholipid syndrome were comparable between patients with intracerebral hemorrhaging and patients with cerebral infarction (36% vs. 27%, p=0.52), and there was no significant difference in the proportions of patients with antiphospholipid syndrome according to stroke subtype (p=0.95, Supplementary material 3). Furthermore, there was no significant difference in the proportions of patients who received antiplatelet or anticoagulant therapy according to stroke subtype (p=0.26 and p=0.26, respectively; Supplementary material 4).

Stroke subtypes, SLE activity, and contribution of SLE

The stroke onset occurred during high SLE activity in 21 (30%) patients, and the numbers of patients with high SLE activity according to stroke subtype are shown in Fig. 3A. A significant difference in the proportion of patients with high SLE activity was observed between the subtypes (p=0.039), with low prevalences observed for deep hemorrhaging (0%), small artery occlusion (9%), and cardioaortic embolism (11%), while high prevalences were observed for large artery atherosclerosis (50%) and undetermined causes (50%).

The median scores for predicting the contribution of SLE to stroke events were higher in patients with a high SLE activity than in those without [7.5 (IQR 4.5-6.5) vs. 5.5 (IQR 4.5-6.5), p<0.001]. In agreement with the analysis wherein SLE activity was used, a significant difference in the prediction scores was observed between the subtypes (p=0.039, Fig. 3B), with a low median score observed for cardioaortic embolism (4.5) and relatively high scores observed for lobar

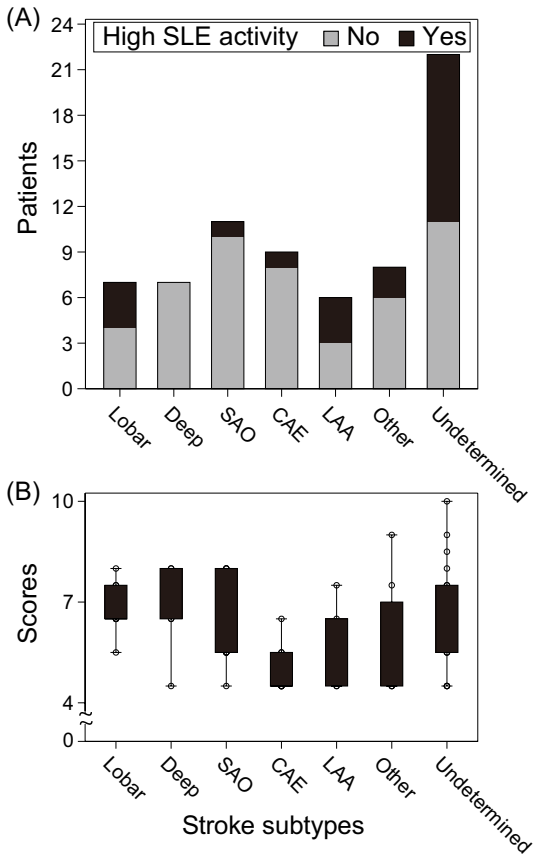

Figure 3. Patients with high systemic lupus erythematosus activity and prediction scores according to stroke subtype. (A) The number of patients with and without high SLE activity according to stroke subtype (21). (B) The prediction scores according to stroke subtype, with the boxes indicating the interquartile ranges. SLE: systemic lupus erythematosus, SAO: small artery occlusion, CAE: cardioaortic embolism, LAA: large artery atherosclerosis

hemorrhaging (6.5), deep hemorrhaging (6.5), other causes (6.5), and undetermined causes (6.5).

The concentrations of complement, antibodies ds-DNA, and C-reactive protein (CRP) were also compared according to stroke subtype (Fig. 4). No significant differences were found according to stroke subtype in terms of the C3 concentration (p=0.86), C4 concentration (p=0.31), CH50 level (p=0.25), antibodies to ds-DNA (p=0.157), and CRP concentration (0.69). Detailed data regarding the age, laboratory test results, prediction scores, and SLE activity for all patients are provided in Supplementary material 5.

The prognosis after stroke

The Kaplan-Meier curves for post-stroke outcomes are shown in Fig. 5. Stroke recurrence or death occurred in 27% of the patients within 2 years and in 40% of the patients within 5 years. Stroke recurrence was observed within 3 months in 5 (7%) patients, within 2 years in 13 (19%) patients, and within 5 years in 21 (30%) patients. The subtype of recurrent stroke was confirmed in 12 patients, and 7 patients had the same type of recurrent stroke as the first event. Death was observed within 2 years in 11 (16%) patients, including 2 patients who died because of initial stroke, 3 patients who died because of stroke recurrence, 3 patients who died because of sepsis, 2 patients who died because of other causes, and 1 patient without a documented cause of death. Death occurred during admission for eight patients. No significant difference was found in the prognosis after stroke between patients with and without high SLE activity (p=0.48, Supplementary material 6).

Discussion

This study revealed that patients with SLE developed various subtypes of stroke and that the contribution of SLE varied according to stroke subtype. These results suggest that the underlying pathophysiology of stroke is not uniform in patients with SLE. The stroke onset occurred during a period of high SLE activity in 30% of the patients, while 40% of the patients experienced stroke recurrence or death within 5 years after the initial stroke. These findings highlight the heterogeneity of stroke in patients with SLE, suggesting that measures to prevent stroke recurrence should be customized for each stroke subtype.

Only a few studies have evaluated stroke subtypes among patients with SLE. Mikdashi et al. evaluated 44 patients with ischemic stroke and classified the subtypes as large artery (45%), small vessel (39%), cardioembolic (9%), and undetermined origin (7%) (16). Those proportions are different from our results, although the classification criteria were similar (20, 23). The mean age was approximately 40 years old in the study by Mikdashi et al. (16), which was younger than the median age in our study (55 years old). Thus, the differences in stroke subtype may be partially related to differences in the patient age.

This study also evaluated the relative contribution of SLE to stroke using two approaches, which revealed that the contribution of SLE varied significantly according to stroke subtype. Interestingly, only 30% of stroke events occurred during a period of high SLE activity, although the estimation of SLE activity can be subjective, and the absence of concomitant high SLE activity does not preclude SLE involvement in the underlying pathophysiology. Thus, risk factor management should be customized for each stroke subtype, such as atrial fibrillation treatment in cases with cardioaortic embolism. Furthermore, aggressive intervention may be warranted for stroke risk factors, as prednisone use may accelerate atherosclerosis in patients with SLE (24). Moreover, given the unfavorable prognosis after stroke, close follow-up by rheumatologists and stroke specialists would be desirable in patients with SLE, even if their disease activity is not high.

Several studies have reported on the pathology underlying SLE-related ischemic stroke. Vasculitis is a known cause of cerebrovascular involvement in patients with SLE, although autopsy studies have indicated that vasculitis is a relatively rare cause of stroke in patients with SLE (15, 25, 26). Inter-

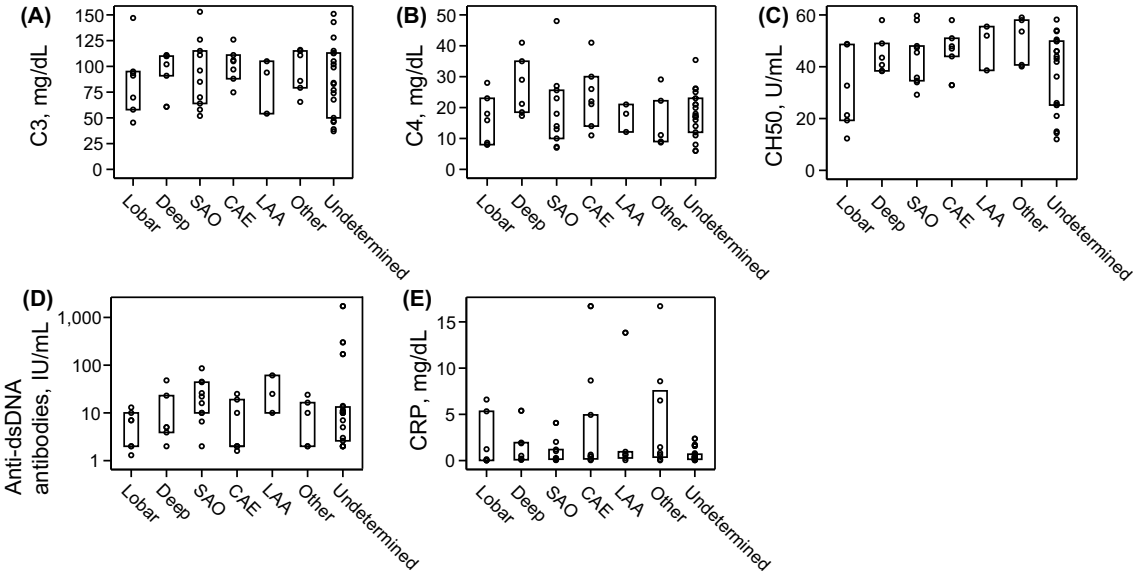

Figure 4. **Serum concentrations of complement C3, C4, CH50, anti-dsDNA antibodies, and CRP according to stroke subtype. The serum concentrations of (A) C3, (B) C4, (C) CH50, (D) anti-dsDNA antibodies, and (E) CRP are shown according to stroke subtype. No significant associations of the marker concentrations with the stroke subtypes (p=0.86, p=0.31, p=0.25, p=0.157, and p=0.69) were found. Twelve values were missing for C3, 13 values were missing for C4, 16 values were missing for CH50, and 16 values were missing for anti-dsDNA antibodies. The boxes indicate the interquartile ranges. CRP: C-reactive protein, SAO: small artery occlusion, CAE: cardioaortic embolism, anti-dsDNA: anti-double stranded DNA, LAA: large artery atherosclerosis**

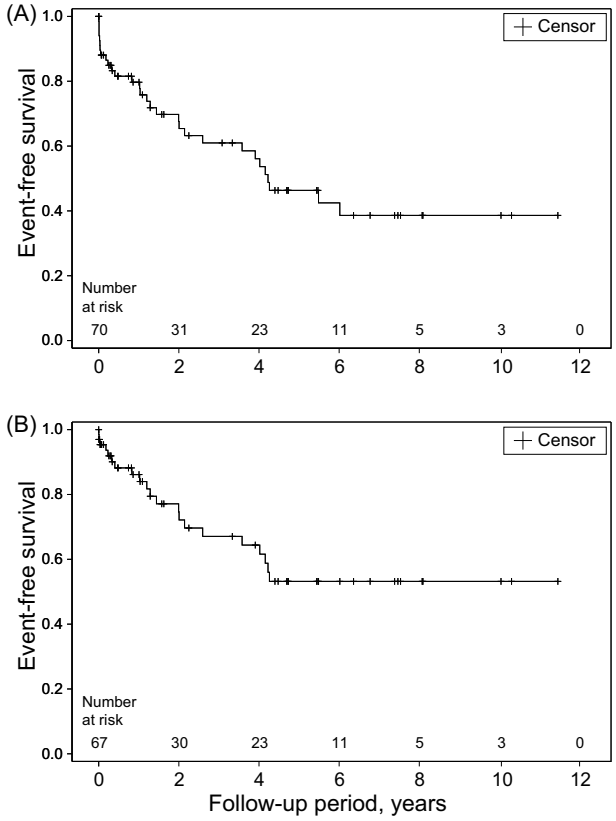

Figure 5. **Kaplan-Meier curves for the cumulative risks of stroke or death (A) and stroke alone (B).**

estingly, we observed low prevalences of diabetes (0%) and dyslipidemia (17%) in patients with large artery atherosclerosis, relative to previously reported prevalence among patients without SLE (27). Thus, some proportion of small artery occlusion and large artery atherosclerosis may be related to vasculitis, especially in young patients without atherosclerotic risk factors. Hypercoagulability and endothelial damage due to antiphospholipid antibodies may be another cause of ischemic stroke (28-31). Furthermore, embolism due to nonbacterial thrombotic endocarditis or Libman-Sacks endocarditis is a possible mechanism for cardioaortic embolism (30, 32, 33).

We identified 7 patients who had lobar hemorrhaging, and 5 of these patients were <50 years old. This is surprising, as the mean age of patients with lobar hemorrhaging is up to 70 years old in the general Japanese population (34, 35). Cerebral amyloid angiopathy is the major etiology of lobar hemorrhaging in elderly patients (36), although it is caused by aging-related β-amyloid deposition in the cortical blood vessels. Therefore, this mechanism is not plausible in patients with SLE. Severe antiphospholipid syndrome itself is another possible cause of cerebral hemorrhaging (37), although we only identified antiphospholipid syndrome in three of our seven patients with lobar hemorrhaging. Thus, the development of lobar hemorrhaging may have been related to other pathologies, such as vasculitis and coagulation disorders (38).

Previous studies have shown that patients have the highest risk of stroke within one year after the SLE diagno-

sis (39, 40). Our cohort included nine patients who developed stroke within one year after their SLE diagnosis, and a high SLE activity was observed for eight of these nine patients. Thus, patients may be especially vulnerable to stroke early after the diagnosis of SLE, which may coincide with a high disease activity and/or insufficient treatment. However, 61 patients developed stroke beyond 1 year after their SLE diagnosis, which highlights the need for careful examinations and follow-up, regardless of the duration of SLE.

In the present study, we investigated the prognosis of SLE patients after stroke and revealed that 40% of patients experienced stroke recurrence or died within 5 years of the initial event. These data highlight the unfavorable prognosis of SLE patients who developed stroke. Among the 12 patients who developed stroke recurrence and whose stroke subtype was confirmed, seven had the same subtype of recurrent stroke as at the first event. Although the data regarding subtype of recurrent stroke are limited by the retrospective nature of the study, the fact that some patients developed the same type while others developed different types suggests the heterogeneity of stroke in SLE patients, i.e., one pathophysiology can explain the occurrence of stroke in some patients, while multiple factors are involved in others. The cause of a high risk of recurrent stroke in SLE patients and the diversity of stroke in this population should be addressed in future studies.

Limitations

Several limitations associated with the present study warrant mention. First, selection bias is possible, as our process for identifying eligible patients might not have captured all patients with SLE who experienced a stroke event. Second, the estimation of the SLE activity by the attending physician may have been partially subjective. Therefore, we adopted another method of analyzing the data using a more objective prediction score and reconfirmed the heterogeneity of stroke in patients with SLE. Third, the outcomes after stroke were determined using the institutional medical records, which might have missed patients who were treated for stroke recurrence at other hospitals. Finally, the retrospective nature of the study resulted in some instances of missing data for different variables (e.g., laboratory test results). Therefore, larger prospective studies are needed to confirm the generalizability of our findings.

Conclusion

This study revealed that the contribution of SLE significantly varied according to stroke subtype, suggesting that customized interventions are needed. Future studies of stroke in patients with SLE should also consider the underlying heterogeneity of stroke in this patient population. Given the unfavorable prognosis, close observation according to stroke subtype by rheumatologists and stroke specialists would be desirable after patients with SLE experience stroke events.

The authors state that they have no Conflict of Interest (COI).

Acknowledgements

The authors thank M. Okamoto for data collection.

References

1. Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. Nature Rev Rheumatol **6**: 358-367, 2010.
2. Hanly JG, Su L, Farewell V, McCurdy G, Fougere L, Thompson K. Prospective study of neuropsychiatric events in systemic lupus erythematosus. J Rheumatol **36**: 1449-1459, 2009.
3. Mok CC, To CH, Mak A. Neuropsychiatric damage in Southern Chinese patients with systemic lupus erythematosus. Medicine **85**: 221-228, 2006.
4. Zhou HQ, Zhang FC, Tian XP, et al. Clinical features and outcome of neuropsychiatric lupus in Chinese: analysis of 240 hospitalized patients. Lupus **17**: 93-99, 2008.
5. Hanly JG, Urowitz MB, Su L, et al. Prospective analysis of neuropsychiatric events in an international disease inception cohort of patients with systemic lupus erythematosus. Ann Rheum Dis **69**: 529-535, 2010.
6. Brey RL, Holliday SL, Saklad AR, et al. Neuropsychiatric syndromes in lupus: prevalence using standardized definitions. Neurology **58**: 1214-1220, 2002.
7. Hanly JG, Li Q, Su L, et al. Cerebrovascular events in systemic lupus erythematosus: results from an international inception cohort study. Arthritis Care Res (Hoboken) **70**: 1478-1487, 2018.
8. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine **82**: 299-308, 2003.
9. Arkema EV, Svenungsson E, Von Euler M, Sjöwall C, Simard JF. Stroke in systemic lupus erythematosus: a Swedish population-based cohort study. Ann Rheum Dis **76**: 1544-1549, 2017.
10. Wiseman SJ, Ralston SH, Wardlaw JM. Cerebrovascular disease in rheumatic diseases. Stroke **47**: 943-950, 2016.
11. Holmqvist M, Simard JF, Asplund K, Arkema EV. Stroke in systemic lupus erythematosus: a meta-analysis of population-based cohort studies. RMD Open **1**: e000168, 2015.
12. Conen KL, Jeanneret C, Hecker B, Cathomas G, Biedermann BC. Acute occlusive large vessel disease leading to fatal stroke in a patient with systemic lupus erythematosus: arteritis or atherosclerosis? Arthritis Rheum **54**: 908-913, 2006.
13. Kitano T, Sengoku K, Itotagawa E, Todo K. Dynamic morphological changes in Libman-Sacks endocarditis under different anticoagulation regimens. BMJ Case Rep **12**: e229909, 2019.
14. Mitsias P, Levine SR. Large cerebral vessel occlusive disease in systemic lupus erythematosus. Neurology **44**: 385-393, 1994.
15. Kitagawa Y, Gotoh F, Koto A, Okayasu H. Stroke in systemic lupus erythematosus. Stroke **21**: 1533-1539, 1990.
16. Mikdashi J, Handwerger B, Langenberg P, Miller M, Kittner S. Baseline disease activity, hyperlipidemia, and hypertension are predictive factors for ischemic stroke and stroke severity in systemic lupus erythematosus. Stroke **38**: 281-285, 2007.
17. Nikolopoulos D, Fanouriakis A, Boumpas DT. Cerebrovascular events in systemic lupus erythematosus: diagnosis and management. Mediterr J Rheumatol **30**: 7-15, 2019.
18. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum **40**: 1725, 1997.
19. Rannikmäe K, Woodfield R, Anderson CS, et al. Reliability of intracerebral hemorrhage classification systems: a systematic review. Int J Stroke **11**: 626-636, 2016.
20. Ay H, Furie KL, Singhal A, Smith WS, Sorensen AG, Koroshetz

WJ. An evidence-based causative classification system for acute ischemic stroke. Ann Neurol **58**: 688-697, 2005.

21. Gladman DD, Urowitz MB, Kagal A, Hallett D. Accurately describing changes in disease activity in systemic lupus erythematosus. J Rheumatol **27**: 377-379, 2000.

22. Bortoluzzi A, Scire CA, Bombardieri S, et al. Development and validation of a new algorithm for attribution of neuropsychiatric events in systemic lupus erythematosus. Rheumatology (Oxford) **54**: 891-898, 2015.

23. Adams HP Jr., Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke **24**: 35-41, 1993.

24. Doria A, Shoenfeld Y, Wu R, et al. Risk factors for subclinical atherosclerosis in a prospective cohort of patients with systemic lupus erythematosus. Ann Rheum Dis **62**: 1071-1077, 2003.

25. Devinsky O, Petito CK, Alonso DR. Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli, and thrombotic thrombocytopenic purpura. Ann Neurol **23**: 380-384, 1988.

26. Ellis SG, Verity MA. Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955--1977. Seminars Arthritis Rheum **8**: 212-221, 1979.

27. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. New Engl J Med **365**: 993-1003, 2011.

28. Toloza SM, Uribe AG, McGwin G Jr., et al. Systemic lupus erythematosus in a multiethnic US cohort (LUMINA). XXIII. Baseline predictors of vascular events. Arthritis Rheum **50**: 3947-3957, 2004.

29. Mikdashi J, Handwerger B. Predictors of neuropsychiatric damage in systemic lupus erythematosus: data from the Maryland lupus cohort. Rheumatology (Oxford) **43**: 1555-1560, 2004.

30. Roldan CA, Gelgand EA, Qualls CR, Sibbitt WL Jr. Valvular heart disease as a cause of cerebrovascular disease in patients with systemic lupus erythematosus. Am J Cardiol **95**: 1441-1447, 2005.

31. Fujieda Y, Amengual O. New insights into the pathogenic mechanisms and treatment of arterial thrombosis in antiphospholipid syndrome. Eur J Rheumatol **8**: 93-99, 2020.

32. Roldan CA, Shively BK, Crawford MH. An echocardiographic study of valvular heart disease associated with systemic lupus erythematosus. N Engl J Med **335**: 1424-1430, 1996.

33. Roldan CA, Sibbitt WL Jr., Qualls CR, et al. Libman-Sacks endocarditis and embolic cerebrovascular disease. JACC Cardiovasc Imaging **6**: 973-983, 2013.

34. Roh D, Boehme A, Young C, et al. Hematoma expansion is more frequent in deep than lobar intracerebral hemorrhage. Neurology **95**: e3386-e3393, 2020.

35. Inagawa T, Ohbayashi N, Takechi A, Shibukawa M, Yahara K. Primary intracerebral hemorrhage in Izumo city, Japan: incidence rates and outcome in relation to the site of hemorrhage. Neurosurgery **53**: 1283-1298, 2003.

36. Gross BA, Jankowitz BT, Friedlander RM. Cerebral intraparenchymal hemorrhage: a review. JAMA **321**: 1295-1303, 2019.

37. Boura P, Papadopoulos S, Tselios K, et al. Intracerebral hemorrhage in a patient with SLE and catastrophic antiphospholipid syndrome (CAPS): report of a case. Clin Rheumatol **24**: 420-424, 2005.

38. Arinuma Y, Kikuchi H, Aramaki K, Kyogoku M, Hirohata S. Histopathological analysis of cerebral hemorrhage in systemic lupus erythematosus complicated with antiphospholipid syndrome. Mod Rheumatol **21**: 509-513, 2011.

39. Ramagopalan SV, Pakpoor J, Seminog O, Goldacre R, Graham L, Goldacre MJ. Risk of subarachnoid haemorrhage in people admitted to hospital with selected immune-mediated diseases: record-linkage studies. BMC Neurol **13**: 176, 2013.

40. Zöller B, Li X, Sundquist J, Sundquist K. Risk of subsequent ischemic and hemorrhagic stroke in patients hospitalized for immune-mediated diseases: a nationwide follow-up study from Sweden. BMC Neurol **12**: 41, 2012.