Predictors of Incident Seizure in Systemic Lupus Erythematosus

XiangYang Huang, Laurence S. Magder, and Michelle Petri

ABSTRACT. ***Objective***. The risk factors for incident seizures in systemic lupus erythematosus (SLE) were prospectively determined in a cohort study.

Methods. A total of 2203 patients with SLE followed longitudinally in the Hopkins Lupus Cohort were analyzed. Demographic variables, clinical manifestations, laboratory tests, and SLE disease activity were recorded at each quarterly visit. Adjusted estimates of association of risk factors for onset of seizure were derived using pooled logistic regression. We examined incident seizures in 3 ways: at the time of diagnosis, more than 45 days after the diagnosis of SLE, and after cohort entry.

Results. Of 2203 patients with no history of seizure prior to SLE diagnosis, 157 (7.13%) had the first seizure occurrence at the time of (37 patients, 1.68%) or after diagnosis (120 patients, 5.45%) of SLE. The risk of seizure occurring around the time of SLE diagnosis was higher in patients with a history of malar rash ($p = 0.002$), proteinuria ($p = 0.004$), and psychosis ($p < 0.001$). Multivariable analysis of the first seizure occurring after the diagnosis of SLE showed that history of low C3 ($p = 0.0078$), psychosis ($p < 0.0001$), cranial or peripheral neuropathy ($p = 0.0043$), anti-Sm antibody ($p = 0.0551$), renal involvement ($p = 0.0177$), and current corticosteroid dose ($p < 0.0001$) were independently associated with a higher incidence of seizure. Disease activity was not predictive after adjusting for corticosteroids.

Conclusion. Risk of seizure after diagnosis of SLE is increased in those patients with prior psychosis, neuropathy, proteinuria, anti-Sm, low C3, and use of corticosteroids. (First Release January 15 2016; J Rheumatol 2016;43:565–75; doi:10.3899/jrheum.150135)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS RISK FACTORS SEIZURES

Seizures occur in many patients with systemic lupus erythematosus (SLE)[1,2,3,4,5] and contribute to damage accrual[2]. The first symptomatic seizure in SLE can occur either around the time of (32%) or after (68%) SLE onset[2]. After the initial seizure, 12% to 43% experience recurrence[3], mostly in the first year.

Seizures can be a primary event resulting from the direct effect of active SLE on the nervous system, but they may also be a secondary event due to stroke, hypertension (HTN), electrolytic disturbance, uremia, infection, or treatment. Studies have found that seizure was associated with early disease onset[2], male sex[3], younger age[2], and African[5] or African American ethnicity[2]. Patients with SLE who develop seizure seem to have shorter disease duration[4], higher SLE disease activity[2,3,5,6], damage accrual[2,3], and a higher frequency of other neuropsychiatric disorders[3], especially psychosis[3,4,6] and stroke[3,4,7]. Certain clinical nonneuropsychiatric features have been found to be associated with seizure, including cutaneous vasculitis[2,3], serositis[4], and renal involvement[2,4]. Mucocutaneous manifestations were also found to be protective (i.e., a longer time-to-seizure occurrence)[2]. Some studies have suggested a high prevalence of antiphospholipid antibodies (aPL)[3,8], anti-Sm antibody[3], autoantibodies to ribosomal P proteins (anti-P)[9,10], antineuronal antibodies[11], or brain reactive autoantibodies[12] in patients with SLE with seizure. A lower risk of seizure was found with anti-La[13]. The current use of oral corticosteroids[2,5] and use of intravenous glucocorticoids[4] or cyclophosphamide[4] have been associated with seizure. Average dose of glucocorticoids and use of cyclophosphamide were associated with a shorter time-to-seizure occurrence[2]. Although chloroquine[14,15,16,17,18,19,20] was associated with seizure in the general population, 2 studies showed a protective effect of hydroxychloroquine (HCQ) against seizure occurrence in SLE[2,5].

To further elucidate the risk factors for seizure in patients with SLE, we determined the clinical and laboratory predictors associated with occurrence of first seizure in a large SLE cohort with longitudinal multivariable regression analysis.

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MATERIALS AND METHODS

Patients and study design. This analysis is based on the Hopkins Lupus Cohort (since 1987). The study was approved on a yearly basis by the Johns Hopkins University School of Medicine Institutional Review Board. All patients gave written informed consent. Data on demographic variables, clinical manifestations, laboratory tests, treatment, and comorbidities were obtained from the medical records of the patient at cohort entry and updated on standard forms at every quarterly visit.

At each quarterly clinic visit, manifestations, treatment, and laboratory measures were comprehensively evaluated. Clinical assessment of disease activity and damage was ascertained using the physician's global assessment (PGA)[21], SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index)[22] and the Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index (SDI)[23]. Comorbidities were also noted [diabetes mellitus (intake of oral hypoglycemic agents and/or insulin) and HTN (recording of 3 abnormal readings and/or use of antihypertensive medications)].

Neuropsychiatric (NP) manifestations and seizures attributed to SLE were defined according to the ACR nomenclature and case definitions for NP-SLE syndromes[24]. Seizure related to HTN, uremia, infection, diabetes mellitus, or electrolytic abnormalities was excluded. However, those patients with well- controlled HTN or diabetes were included in the analysis. Data on seizures were obtained from the medical records of each patient at cohort entry. The cohort database did not include the subtype of seizure. All patients were treated with antiseizure medicines after first seizure. Patients with SLE with proteinuria attributed to SLE were included. Renal biopsy was performed in those with ongoing proteinuria > 500 mg.

Statistical analysis. Three analyses of incident seizure were performed.

First, we explored the factors associated with having an incident episode of seizures at about the time of SLE diagnosis. The time of SLE diagnosis was set as the time period within 1 year before or within 45 days after the day of SLE diagnosis. We compared groups defined by clinical history with respect to the proportion with incident seizures at the time of diagnosis. Statistical significance was assessed using chi-square tests.

Second, we investigated factors associated with rates of new incidence of seizure occurring more than 45 days after SLE diagnosis; data were reformatted to consist of 1 record for every month after diagnosis for each patient. Each record contained the clinical history of the patient up until that time based on information from our retrospective history (if the month was before cohort entry) or from prospectively collected information (if the month was after cohort entry). Each person-month record also contained a variable indicating whether new seizure had occurred during that month. To estimate the association between clinical history and rates of seizure, each month was classified into a subgroup based on that predictor (e.g., age 18–39 yrs). Then we estimated the rate of new seizure per month in each subgroup by calculating the number of events of seizure divided by the number of person-months observed in that subgroup. Results were converted to rates per person-year. To assess whether associations between risk factors and rates of seizure persisted after controlling for potential confounding variable, we applied pooled logistic regression to the monthly data[25].

Third, we performed an analysis of predictors of incident seizures similar to the above analysis but restricting the analysis to followup that occurred during cohort participation. This restriction enabled us to look at predictors that were available only during cohort participation (e.g., SLE disease activity).

RESULTS

Demographic and clinical characteristics of included patients. There were 213 patients with a history of seizure among the total 2259 patients with SLE recruited in the cohort from June 1987 to June 2013. Fifty-six patients who had a history of seizure more than 1 year before diagnosis of SLE were excluded from our analysis. Among the 2203 patients included in our analysis, patients were most frequently women (92.5%), with 82.5% less than 45 years old, and of multiple ethnicities (white 55% and African American 37.6%). Forty-six percent were followed up for more than 5 years. The SDI indicated minimal cumulative organ damage in patients, with 0 in 58%, 1 in 22%, 2–3 in 15%, and 4 or more in 5%, at cohort entry. The demographic characteristics, clinical manifestations, and laboratory tests are shown in Table 1.

Frequency of incident seizure. Among the 2203 patients with SLE without prior history of seizure, 157 patients (7.13%) had a first seizure occurrence at, or after, diagnosis. Of these, 37 patients (1.68%) had their first seizure at about the same time as diagnosis (within 1 yr before or 45 days after), while 120 patients (5.45%) had their first seizure more than 45 days after SLE diagnosis.

Predictors of seizure occurring around the time of SLE diagnosis. Considering the 37 patients who had the first seizure of SLE, we found that the likelihood of incident seizure at about the time of diagnosis was higher among patients with a history of malar rash ($p = 0.002$), proteinuria ($p = 0.004$), and psychosis ($p < 0.000$). Seizure at about the time of diagnosis was more likely among those with a history of serositis ($p = 0.037$; Table 1). The risk was somewhat higher among those with anti-Sm antibody, but not statistically significantly ($p = 0.097$; Table 1).

Demographic predictors of incident seizure occurring after SLE diagnosis. A total of 120 patients developed the first occurrence of seizure more than 45 days after diagnosis of SLE. As noted in Table 2, seizure onset was less likely in patients with higher income (RR = 0.549, $p = 0.046$), longer disease duration (RR = 0.283, $p = 0.002$), and recent calendar year (RR = 0.524, $p = 0.013$). Age, sex, ethnicity, education, smoking, and alcohol abuse history were not associated with seizure onset.

Clinical predictors of incident seizure after SLE diagnosis. A history of proteinuria was associated with new seizure onset (RR = 1.61, $p = 0.0092$; Table 2). As noted in Table 2, a history of many other neuropsychiatric manifestations was associated with a higher risk of seizures: specifically, psychosis (RR = 3.688, $p < 0.0001$), organic brain syndrome (RR = 2.962, $p = 0.0006$), aseptic meningitis (RR = 2.44, $p = 0.0505$), cerebrovascular disease (RR = 1.609, $p < 0.0001$), cranial or peripheral neuropathy (RR = 2.015, $p < 0.0001$), and cognitive impairment (RR = 2.184, $p = 0.0181$). A history of having an abnormal brain computerized tomographic (CT) scan (RR = 2.150, $p = 0.0156$) was associated with new seizure occurrence (Table 2).

We found that the onset of new seizure was associated with a history of anti-Sm antibody (RR = 1.802, $p = 0.0048$), low C3 (RR = 1.958, $p = 0.0011$), and low C4 (RR = 1.676, $p = 0.0064$).

Table 1. Risk of seizure occurring around the time of SLE diagnosis, by patient characteristic.

Patient Characteristic	No. with Each Characteristic	No. (%) with Seizures	p
Patients, n	2203	37 (1.69)	
Sex			
Female	2038	32 (1.57)	0.164
Male	165	5 (3.03)	
Ethnicity			
White	1211	23 (1.9)	0.351
African American	830	10 (1.2)	
Asian	162	4 (2.27)	
Age, yrs			
< 29	1081	24 (2.22)	0.085
30–44	730	12 (1.64)	
45–59	305	1 (0.33)	
60+	78	0 (0.00)	
Single/married/other			
Divorced	242	2 (0.83)	0.451
Married	1215	21 (1.73)	
Single	672	14 (2.08)	
Widowed	51	0 (0.00)	
Income, US $			
< 25,000	561	17 (3.03)	0.011*
25–60,000	616	8 (1.30)	
60–100,000	417	4 (0.96)	
100,000+	355	2 (0.56)	
Education			
< High school	200	2 (1.00)	0.763
High school	536	11 (2.05)	
Some college	587	11 (1.87)	
College +	768	12 (1.56)	
Alcohol abuse			
No	2037	35 (1.67)	0.664
Yes	159	2 (1.71)	
Smoking history			
No	1375	23 (1.67)	0.951
Yes	820	14 (1.71)	
History of SLE — manifestations			
Malar rash			
No	1355	14 (1.03)	0.002*
Yes	848	23 (2.71)	
Discoid rash			
No	1907	35 (1.84)	0.149
Yes	296	2 (0.68)	
Photosensitivity			
No	1297	19 (1.46)	0.349
Yes	906	18 (1.99)	
Oral ulcers			
No	1477	23 (1.56)	0.524
Yes	726	14 (1.93)	
Serositis			
No	1586	21 (1.32)	0.037*
Yes	617	16 (2.59)	
Arthritis			
No	995	16 (1.61)	0.813
Yes	1205	21 (1.74)	
Renal disorder (urine protein +++)			
No	1862	21 (1.25)	0.004*
Yes	521	16 (3.07)	
Neurologic criterion (including seizure and psychosis)			
No	2123	1 (0.05)	< 0.001*
Yes	80	36 (45)	
Hematology disorder			
No	1325	24 (1.81)	0.550
Yes	878	13 (1.48)	
ANA			
No	70	0 (0)	0.270
Yes	2118	37 (1.70)	
Immunologic disorder			
No	1099	20 (1.82)	0.609
Yes	1104	17 (1.54)	
Anti-Sm			
No	1711	25 (1.46)	0.097
Yes	419	11 (2.63)	
Anti-dsDNA			
No	829	16 (1.93)	0.485
Yes	1368	21 (1.54)	
Anti-RNP			
No	1528	22 (1.44)	0.143
Yes	595	14 (2.35)	
Anti-Ro			
No	1465	25 (1.71)	0.930
Yes	665	11 (1.65)	
Anti-La			
No	1848	33 (1.79)	0.394
Yes	278	3 (1.08)	
Low C3			
No	996	19 (1.91)	0.451
Yes	1204	18 (1.50)	
Low C4			
No	1152	19 (1.65)	0.894
Yes	1045	18 (1.72)	

* Statistically significant. SLE: systemic lupus erythematosus; ANA: antinuclear antibodies.

Predictors of incident seizure after the diagnosis of SLE in multivariable analysis. Based on the univariate results for the predictors in the 120 patients with seizure that occurred after SLE diagnosis, preliminary models were fit to assess which variables were most important. We found that low C4 was not significant after controlling for low C3. Anti-RNP and anti-Ro were not significant after controlling for anti-Sm antibody. Proteinuria and hematologic lupus were not statistically significant after adjustment for the other variables in the final model. Calendar year appeared important even after adjusting for other variables. We found that psychosis appeared by far to be the most important neurologic variable. Other neurologic manifestations, such as cognitive impairment, organic brain syndrome, lupus headache, aseptic meningitis, or abnormal brain CT scan were not statistically significant after controlling for psychosis.

Therefore, the final multivariable analysis included calendar year 2004 or later, low C3, anti-Sm antibody, psychosis, and cranial or peripheral neuropathy. After adjusting for all other variables in the model, we found that patients with anti-Sm antibody had a borderline higher rate

Table 2. The rate of having a first seizure more than 45 days after the time of SLE diagnosis, by patient characteristic.

Subgroup	Observed No. Seizures	Person-years of Followup	Rate of Events per 1000 Person-years	Rate Ratios Based on a Model that Adjusts for Age (95% CI)	p
All patients	120	24,444	4.9		
Age, yrs					
< 29	69	13,518	5.1	1.0 (reference group)	
30–44	32	7586	4.2	0.826 (0.54, 1.25)	0.3727
45–59	18	2810	6.4	1.255 (0.74, 1.25)	0.3907
60+	1	529	1.9	0.371 (0.05, 2.66)	0.3240
Sex					
F	112	22,831	4.9	1.0 (reference group)	
M	8	1613	5.0	1.011 (0.49, 2.07)	0.9759
Ethnicity					
African American	49	9586	5.1	1.139 (0.78, 1.66)	0.4986
Asian	11	1485	7.4	1.651 (0.87, 3.14)	0.1265
White	60	13,372	4.5	1.0 (reference group)	
Education					
< high school	15	2479	6.1	1.0 (reference group)	
High school	27	6420	4.2	0.695 (0.37, 1.31)	0.2585
Some college	37	6358	5.8	0.962 (0.52, 1.75)	0.8987
College+	32	8424	3.8	0.628 (0.34, 1.15)	0.1367
Income, US $					
< 25,000	43	7094	6.1	1.0 (reference group)	
25–60,000	33	7088	4.7	0.768 (0.48, 1.21)	0.2539
60–100,000	15	4505	3.3	0.549 (0.30, 0.98)	0.0456*
100,000+	13	3766	3.5	0.569 (0.31, 1.06)	0.0752
Smoking history					
No	78	14,648	5.3	1.0 (reference group)	
Yes	42	9796	4.3	0.805 (0.55, 1.17)	0.2574
Alcohol abuse					
No	113	22,671	5.0	1.0 (reference group)	
Yes	7	1772	3.9	0.792 (0.36, 1.70)	0.5503
Duration of SLE, yrs					
0–3	50	5913	8.5	1.0 (reference group)	
3–6	25	4864	5.1	0.607 (0.37, 0.98)	0.0419*
6–10	22	4996	4.4	0.521 (0.31, 0.85)	0.0107*
10–15	12	4083	2.9	0.347 (0.18, 0.65)	0.0010*
15+	11	4586	2.4	0.283 (0.14, 0.54)	0.0002*
Calendar year					
1987–1995	33	5124	6.4	1.0 (reference group)	
1996–2004	49	8828	5.5	0.862 (0.55, 1.34)	0.5089
2004–2013	27	7994	3.4	0.524 (0.31, 0.87)	0.0129*
History of SLE manifestation					
Malar rash					
No	57	11,889	4.8	1.0 (reference group)	
Yes	63	12,554	5.0	1.047 (0.73, 1.49)	0.8028
Discoid rash					
No	92	20,009	4.6	1.0 (reference group)	
Yes	28	4434	6.3	1.374 (0.90, 2.09)	0.1407
Photosensitivity					
No	59	12,155	4.9	1.0 (reference group)	
Yes	61	12,289	5.0	1.023 (0.71, 1.46)	0.9024
Mucosal-ulcer					
No	78	14,424	5.4	1.0 (reference group)	
Yes	42	10,020	4.2	0.775 (0.53, 1.12)	0.1832
Arthritis					
No	41	7649	5.4	1.0 (reference group)	
Yes	79	16,794	4.7	0.878 (0.60, 1.28)	0.4975
Serositis					
No	65	14,479	4.5	1.0 (reference group)	
Yes	55	9965	5.5	1.230 (0.85, 1.76)	0.2593

Table 2. Continued.

Subgroup	Observed No. Seizures	Person-years of Followup	Rate of Events per 1000 Person-years	Rate Ratios Based on a Model that Adjusts for Age (95% CI)	p
Urine protein					
No	65	16,028	4.1	1.0 (reference group)	
Yes	55	8417	6.5	1.610 (1.12, 2.31)	0.0092*
Hematology disorder					
No	48	11,675	4.1	1.0 (reference group)	
Yes	72	12,768	5.6	1.372 (0.95, 1.97)	0.0899
Immunology disorder					
No	41	9534	4.3	1.0 (reference group)	
Yes	79	14,909	5.3	1.232 (0.84, 1.79)	0.2780
ANA					
No	26	4542	5.7	1.0 (reference group)	
Yes	94	19,901	4.7	0.825 (0.53, 1.27)	0.3859
Organic brain syndrome					
No	109	23,638	4.6	1.0 (reference group)	
Yes	11	806	13.6	2.962 (1.59, 5.5)	0.0006*
Aseptic meningitis					
No	115	24,016	4.8	1.0 (reference group)	
Yes	5	427	11.7	2.440 (0.99, 5.9)	0.0505*
Stroke					
No	115	23,806	4.8	1.0 (reference group)	
Yes	5	638	7.8	1.622 (0.62, 3.97)	0.2896
Cerebrovascular disease					
No	112	23,404	4.8	1.0 (reference group)	
Yes	8	1039	7.7	1.609 (0.78, 3.29)	< 0.0001*
Headache (lupus)					
No	106	22,620	4.7	1.0 (reference group)	
Yes	14	1824	7.7	1.638 (0.93, 2.86)	0.0826
Mononeuritis multiplex					
No	118	24,243	4.9	1.0 (reference group)	
Yes	2	201	9.9	2.045 (0.50, 8.27)	0.3158
Cranial or peripheral neuropathy					
No	108	23,165	4.7	1.0 (reference group)	
Yes	12	1278	9.4	2.015 (1.11, 3.65)	< 0.0001*
Cognitive impairment					
No	110	23,467	4.7	1.0 (reference group)	
Yes	10	977	10.2	2.184 (1.14, 4.17)	0.0181*
Longitudinal myelitis					
No	120	24,306	4.9	1.0 (reference group)	
Yes	0	138	0.0	< 0.001 (< 0.001, < 999.9)	0.9805
Psychosis					
No	109	23,792	4.6	1.0 (reference group)	
Yes	11	651	16.9	3.688 (1.98, 6.86)	< 0.0001*
Abnormal CT brain					
No	109	23,348	4.7	1.0 (reference group)	
Yes	11	1096	10.0	2.150 (1.15, 3.99)	0.0156*
Abnormal MRI brain					
No	104	21,502	4.8	1.0 (reference group)	
Yes	16	2941	5.4	1.125 (0.66, 1.90)	0.6617
Fever					
No	72	16,101	4.5	1.0 (reference group)	
Yes	48	8343	5.8	1.287 (0.89, 1.85)	0.1760
Raynaud phenomenon					
No	65	13,380	4.9	1.0 (reference group)	
Yes	55	11,064	5.0	1.023 (0.73, 1.47)	0.9001
Vasculitis					
No	109	21,702	5.0	1.0 (reference group)	
Yes	11	2742	4.0	0.799 (0.43, 1.48)	0.4774

Table 2. Continued.

Subgroup	Observed No. Seizures	Person-years of Followup	Rate of Events per 1000 Person-years	Rate Ratios Based on a Model that Adjusts for Age (95% CI)	p
Sjögren syndrome					
No	105	21,386	4.9	1.0 (reference group)	
Yes	15	3057	4.9	1.000 (0.58, 1.71)	1.0000
Anti-dsDNA					
No	34	8151	4.2	1.0 (reference group)	
Yes	86	16,293	5.3	1.265 (0.85, 1.88)	0.2453
Anti-Sm					
No	89	20,484	4.3	1.0 (reference group)	
Yes	31	3960	7.8	1.802 (1.19, 2.71)	0.0048*
Anti-Ro					
No	77	17,451	4.4	1.0 (reference group)	
Yes	43	6992	6.1	1.394 (0.96, 2.02)	0.0807
Anti-La					
No	105	21,643	4.9	1.0 (reference group)	
Yes	15	2800	5.4	1.104 (0.64, 1.89)	0.7199
Anti-RNP					
No	83	18,491	4.5	1.0 (reference group)	
Yes	37	5952	6.2	1.386 (0.94, 2.04)	0.0990
Anticardiolipin					
No	57	11,578	4.9	1.0 (reference group)	
Yes	63	12,866	4.9	0.995 (0.69, 1.42)	0.9765
Lupus anticoagulant					
No	101	21,048	4.8	1.0 (reference group)	
Yes	19	3396	5.6	1.600 (0.80, 3.10)	0.5421
Low C3					
No	32	10,164	3.1	1.0 (reference group)	
Yes	88	14,280	6.2	1.958 (1.30, 2.93)	0.0011*
Low C4					
No	44	12,038	3.7	1.0 (reference group)	
Yes	76	12,406	6.1	1.676 (1.15, 2.43)	0.0064

** Statistically significant; SLE: systemic lupus erythematosus; CT: computed tomography; MRI: magnetic resonance imaging; ANA: antinuclear antibody.

of seizure (RR = 1.518, p = 0.0551). Incidence of seizure declined within recent cohort years (RR = 0.680, p = 0.0826). Notably, history of low C3 (RR = 1.763, p = 0.0078), psychosis (RR = 2.432, p < 0.0001), and cranial or peripheral neuropathy (RR = 2.212, p = 0.0043) were independently associated with a higher risk of incident seizure (Table 3).

Predictors of incident seizure after cohort entry in univariate analysis. Of the 120 patients with seizures starting more than 45 days after SLE diagnosis, 56 occurred during cohort participation. As noted in Table 4, the incidence of seizure onset significantly increased when the urine dipstick protein at the most recent visit was 3+ (RR = 7.4, p < 0.0001). The rate of incident seizure was 3.3 times higher in patients with SLE with higher current SLE disease activity as measured by a SELENA-SLEDAI score ≥ 5 versus 0 (RR = 3.349, p = 0.0004). The rate of incident seizure was 3.9 times higher in patients with SLE with a PGA score of 1.5 or more versus 0 (RR = 3.927, p < 0.0001; Table 4).

Table 3. Predictors of first seizure after SLE diagnosis based on a multivariate model.

Variable	Comparison	Adjusted Rate Ratio (95% CI)	p
After 2004	Yes vs no	0.680 (0.440, 1.051)	0.0826
History of anti–Sm	Yes vs no	1.518 (0.991, 2.327)	0.0551
History of low C3	Yes vs no	1.763 (1.161, 2.676)	0.0078
History of psychosis	Yes vs no	2.432 (1.321, 4.477)	< 0.0001
History of cranial or peripheral neuropathy	Yes vs no	2.212 (1.208, 4.051)	0.0043
History of positive ANA	Yes vs no	0.904 (0.578, 1.414)	0.6585
Year since SLE diagnosis	Per year	0.923 (0.891, 0.956)	< 0.0001

ANA: antinuclear antibody; SLE: systemic lupus erythematosus.

Table 4. Rate of having a first seizure more than 45 days after time of SLE diagnosis during cohort participation, by time-varying risk factors.

Subgroup	Observed No. Seizures	Person-years of Followup	Rate of Events per 1000 Person-years	Rate Ratios Based on Model that Adjusts for Age (95% CI)	p
Everyone	56	13,747			
Age group, yrs					
< 30	27	6707	4.0	1.0 (reference group)	
30–44	17	4651	3.7	0.908 (0.495, 1.666)	0.7552
45–59	11	2017	5.5	1.354 (0.672, 2.731)	0.3965
60+	1	370	2.7	0.671 (0.091, 4.938)	0.6951
Duration of SLE, yrs					
0–3	14	2251	6.2	1.0 (reference group)	
3–6	14	2520	5.6	0.893 (0.426, 1.874)	0.7656
6–10	15	3000	5.0	0.804 (0.388, 1.666)	0.5572
10–15	6	2686	2.2	0.356 (0.138, 0.935)	0.0359*
15+	7	3288	2.1	0.342 (0.138, 0.848)	0.0206*
Most recent (without seizure) SLEDAI					
None	16	5093	3.1	1.0 (reference group)	
< 2	1	264	3.8	1.204 (0.160, 9.080)	0.8573
2–5	19	5173	3.7	1.169 (0.601, 2.274)	0.6449
5+	19	1807	10.5	3.349 (1.722, 6.513)	0.0004*
Unknown	1	1407	0.7	0.226 (0.030, 1.705)	0.1493
Mean SLEDAI (without seizure) in last 12 mos					
None	6	1906	3.1	1.0 (reference group)	
< 2	7	3129	2.2	0.711 (0.239, 2.114)	0.5391
2–5	10	3681	2.7	0.863 (0.314, 2.375)	0.7754
5+	13	1208	10.8	3.420 (1.300, 8.999)	0.0127*
Most recent physician's global assessment					
None	13	4194	3.1	1.0 (reference group)	
0–1	7	3821	1.8	0.591 (0.236, 1.482)	0.2620
1–1.5	12	2436	4.9	1.589 (0.725, 3.484)	0.2472
1.5+	23	1891	12.2	3.927 (1.989, 7.753)	< 0.0001*
Current prednisone, mg/day					
None	9	6421	1.4	1.0 (reference group)	
0–9	10	3328	3.0	2.144 (0.871, 5.276)	0.0970
10–19	14	1793	7.8	5.572 (2.411, 12.876)	< 0.0001*
20	22	761	28.9	20.668 (9.514, 44.899)	< 0.0001*
Mean prednisone in last 12 mos, mg/day					
None	7	4598	1.5	1.0 (reference group)	
1–9	11	3576	3.1	2.021 (0.783, 5.214)	0.1457
10–19	15	1348	11.1	7.312 (2.981, 17.936)	< 0.0001*
20+	6	326	18.4	12.108 (4.067, 36.045)	< 0.0001*
Current hydroxychloroquine					
No	27	4143	6.5	1.0 (reference group)	
Yes	28	8200	3.4	0.524 (0.309, 0.889)	0.0166*
Mean current hydroxychloroquine in last 12 mos					
None	14	2533	5.5	1.0 (reference group)	
Some	9	1468	6.1	1.109 (0.480, 2.563)	0.8087
Always	16	5880	2.7	0.492 (0.240, 1.009)	0.0528*
Current immunosuppressant					
No	34	8769	3.9	1.0 (reference group)	
Yes	21	3575	5.9	1.515 (0.879, 2.611)	0.1344
Most recent urine protein dipstick					
< 3	41	11,693	3.5	1.0 (reference group)	
3+	13	500	26.0	7.4 (4.0, 13.9)	< 0.0001

* Statistically significant; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.

The rate of incident seizure increased significantly as the dose of current prednisone increased. Among those taking 10–19 mg/day, the rate of incident seizure was 5.6 times higher than the rate among those not taking prednisone (RR = 5.572, $p < 0.0001$). Among those taking ≥ 20 mg per day, the rate was increased by a factor of 20.7 (RR = 20.668, $p < 0.0001$). The rate of incident seizure was 0.5 times lower in patients taking HCQ than the rate among those not taking HCQ (Table 4).

Table 5. Independent association between select predictors* and seizure onset based on those patients with SLE who developed seizure during cohort participation.

Variables	Comparison	Adjusted Rate Ratio (95% CI)	p
Year since SLE diagnosis	Per year	0.96 (0.92, 1.01)	0.080
Urine protein dipstick 3+	Yes vs no	2.74 (1.38, 5.44)	0.0041
Current SLEDAI > 4	Yes vs no	1.21 (0.66, 2.24)	0.54
Current prednisone, mg	0–9 mg/day vs none	1.75 (0.66, 4.60)	0.26
Current prednisone, mg	10–19 mg/day vs none	4.00 (1.61, 9.92)	0.0028
Current prednisone, mg	20+ mg/day vs none	11.77 (4.81, 28.81)	< 0.0001
Current hydroxychloroquine	Yes vs no	0.90 (0.50, 1.59)	0.71

*In addition to predictors in this table, the model included predictors found significant in analysis of all postdiagnosis seizures including history of anti-Sm, low C3, psychosis, and neuropathy. SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index.

Multivariate analysis of the predictors of incident seizure after cohort entry (Table 5). The time-varying variables that appeared important based on analysis of the 56 patients with incident seizure during cohort participation were then combined. These included most recent SLEDAI ≥ 5, current prednisone dose, current HCQ dose (200 mg twice daily), and urine dipstick protein. In multivariate analysis, the rate of incident seizure was 2.9 times higher in patients with urine dipstick protein positive 3+ versus none (RR = 2.74, p = 0.0041). We found that prednisone dose was very strongly associated with incident seizure. The incidence of new onset of seizure increased with the dose of current prednisone. HCQ was not protective after adjusting for the other variables in the model. High SELENA-SLEDAI was not a statistically significant predictor after adjusting for prednisone (RR = 1.2, p = 0.54). When the high mean SELENA-SLEDAI in the last 12 months was substituted in the model for most recent SELENA-SLEDAI, an elevated RR was found (RR = 1.5, 95% CI 0.7, 3.4); however, this finding was not statistically significant (p = 0.27).

DISCUSSION

Seizure affects about 1% of the general population[26]. Seizure was among the most frequent neuropsychiatric syndromes in SLE, besides headache, mood disorders, and cognitive dysfunction[27,29]. Hanly, *et al* found a cumulative frequency of 4.6% over a mean followup of 3.5 years in a cohort of 1631 patients with SLE[5]. Ramsey-Goldman, *et al*[4] and Gonzalez-Duarte, *et al*[28] found that the frequency of incident seizures after SLE diagnosis (incident) was 6.2% in 1295 patients with SLE[4] and 12.5% in 1200 patients with SLE over a mean of 5 years[28]. In our cohort with 46% of patients followed up for more than 5 years, 7.13% had the first seizure occurrence at about the time of diagnosis of SLE (1.68%) or after (5.45%). The rate of incident seizure (among those with no prior seizure experience) was 4.9 per 1000 person-years. We found that 56 (26.3%) of 213 patients with a history of seizures had the first seizure occurrence more than 1 year before diagnosis of SLE. Of the 157 patients in our cohort who developed seizure later, 24% developed seizures about the same time as their SLE diagnosis. Consistent with our findings, Appenzeller, *et al* found epileptic seizures occurred at the onset of SLE symptoms in 19 (31.6%) of SLE patients with seizures[1]. We found that seizure onset was less likely in patients with longer disease duration. Consistently, another study found that 54% of incident seizure occurred within 1 year of SLE diagnosis[29]. Therefore, although seizure can occur at any time — before, at, or after — SLE diagnosis, seizures have been a relatively early event in the disease course of SLE[4].

"Calendar Year" refers to the year during which the followup occurred. We were interested in knowing whether the rates of incident seizure changed over time, so we estimated the rates of seizure over different time periods. We found that the incident rate of seizures in more recent calendar years had decreased. This finding may be the result of increased use of antimalarials. Although we did not find strong evidence that antimalarial use is protective, others have reported such findings[2,5]. Antimalarial use is now virtually universal — and recently, blood levels are being measured to improve adherence.

African[5] or African American ethnicity[2,4], younger age[2], and male sex[3] have been associated with seizure. Both Hanly, *et al* and Ramsey-Goldman, *et al* found a high risk of seizure in African ethnicity[5] and African American ethnicity[4]. However, this association was not confirmed in our larger study.

The incident seizure at about the time of diagnosis was higher among patients with a history of malar rash. In contrast, livedo reticularis and cutaneous vasculitis have been found to be associated with cerebrovascular accident and seizures[28].

We found that urine protein identified by dipstick of 3+ was statistically significantly associated with incident seizure after cohort entry. Several previous studies also found that renal involvement (particularly World Health Organization Class IV glomerulonephritis) was associated with a shorter time to seizure occurrence[2] and nephritis was associated with

seizure[1]. Our findings using time-varying information strengthen the evidence for this association.

Seizure in SLE may occur in isolation or accompany other neurologic manifestations[30,31]. Psychosis was noted to be associated with occurrence of seizure[3,4,6] in several other SLE studies. Notably, we confirmed that history of psychosis was independently associated with a higher risk of incident seizure 45 days after the diagnosis of SLE. Antibodies against murine neuronal membrane proteins correlated with psychosis and/or seizures in 1 study of 100 patients with SLE[12], which might explain the association of psychosis with seizures. We also found an association of cranial or peripheral neuropathy with seizure in SLE. In the general population, a relationship between seizure and neuropathy has been recognized in familial cases[32,33,34].

Some studies have suggested a high prevalence of aPL[3,8], anti-Sm antibody[3], anti-P[9,10], and antineuronal antibodies[11,12] in patients with SLE with seizure. Notably, we found that anti-Sm antibody increased the risk of incident seizure both at the time of diagnosis of SLE and after. Anti-Sm antibody has also been associated with organic brain syndrome (encephalopathy) in patients with SLE[35] and schizophrenia in the general population. Reports have associated aPL with seizure in SLE[1,3,36,37] due to thrombotic events or nonischemic mechanisms[38]. We did not find an association of seizure with aPL in SLE. Consistently, Hanly, *et al*[5], Ramsey-Goldman, *et al* (which included Hopkins patients)[4], and other studies[39,40] reported no association between antiphospholipid positivity and seizures in patients with SLE. In non-SLE studies, it has not been clear whether aPL are[41] or are not[42] associated with seizure. However, a large study of 960 patients with epilepsy found no increase in anticardiolipin in non-SLE seizure patients versus controls[42]. We did not find a lower risk of seizures in patients with anti-La, in contrast to a previous report[43]. We did not have data about anti-P[9,10] or antineuronal antibodies[11,12] because they are not routinely available and were not measured in our cohort.

Previous studies had shown that seizure occurred in patients with higher global SLE disease activity[1,2,3]. However, previous reports did not control for corticosteroid use at the time of seizure onset. In univariate analysis, we found an association between SELENA-SLEDAI and seizure onset, but this association was reduced and not statistically significant after adjusting for corticosteroid dose at the time of seizure onset. This suggests that the association between disease activity and seizures might be due to greater use of corticosteroid dose among those with higher disease activity. However, because of the relatively small number of events in this analysis, the CI for the association between high SLEDAI and risk of seizures are wide and we cannot rule out an independent effect of high SLEDAI.

We found that a history of low C3 was independently associated with a higher risk of incident seizure after diagnosis of SLE. This indicates a role of serologic activity in seizure occurrence. Low complement is included in the SLEDAI.

The current use of corticosteroids has been associated with increased risk of incident seizure[5] and a shorter time-to-seizure[2]. We found that prednisone dose was very strongly associated with incident seizure, and incidence of seizure increased with dose of current prednisone. This result persisted after adjusting for disease activity and was consistent with the studies of both Hanly, *et al*[5] and Ramsey-Goldman, *et al*[4]. The association between prednisone and seizure is consistent with SLE global activity being a risk factor for seizure; but prednisone could also have an independent effect.

Antimalarials are neuroexcitatory and could decrease seizure threshold. In the general population, chloroquine[14,15,16,17,18,19,20] has been associated with seizure. Hanly, *et al* found that antimalarials in the absence of immunosuppressive agents were associated with a reduced seizure risk[5]. The LUMINA cohort also reported that antimalarial therapy was protective for seizure occurrence in patients with SLE[2]. However, we did not obtain strong evidence that HCQ was protective against seizure after adjustment for the other variables in the multiple variable models. This result was consistent with the study of Ramsey-Goldman, *et al*[4], which included some of our patients.

In transgenic mice over-expressing interleukin 6 or tumor necrosis factor-α, a chronic inflammatory state in the brain predisposes to the occurrence of seizures and neuronal cell loss[44]. Our findings on the association of low C3, anti-Sm antibody[3], cutaneous activity (malar rash), lupus nephritis, and psychosis with seizure support an inflammatory mechanism in the onset of seizures in SLE.

Many previous studies were limited by small sample size, short duration of followup or cross-sectional design. The strength of our study is the large number of patients and the availability of clinical data roughly every 3 months during lengthy followup. We recognize the limitations of our study. We have examined only the first occurrence of seizure at or after SLE diagnosis. We did not have information on the subtypes of seizure that occurred or on followup seizures or anti-seizure treatment. We did not have data on anti-P or anti-neuronal antibodies.

Incident seizure at the time of diagnosis of SLE was associated with malar rash, psychosis, nephritis, and anti-Sm antibody. The risk of incident seizure after diagnosis of SLE was increased in those patients with psychosis, neuropathy, proteinuria, anti-Sm antibody, and low C3. Corticosteroid dose was strongly associated with incident seizure in models that included disease activity. These results may help clinicians identify patients at highest risk for seizures and provide useful information for guiding the evaluation of disease and therapy.

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