Outcomes of Seizures in Patients with Systemic Lupus Erythematosus in a Tertiary Government Hospital in the Philippines

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ABSTRACT

Background. Seizures in patients with systemic lupus erythematosus (SLE) are uncommon but life-threatening; mortality rate is 25-29%. Seizure in a person with lupus may be due to lupus itself or other conditions. There are no published studies describing the causes and outcomes of seizures in Filipino patients with lupus.

Objective. To describe the causes and outcomes of seizure in a cohort of patients with lupus seen at Philippine General Hospital.

Methodology. We reviewed the medical records of patients with SLE) with a documented seizure and admitted between January 2016 and April 2019. History, physical examination and laboratory findings, and clinical course were obtained.

Results. We included 29 patients with 31 seizure events. They were all women, mostly single, of low socio-economic status, and had poor functional capacity. Lupus was active in 77.4% (24/31), commonly with mucocutaneous or hematologic manifestations.

Seizures were generalized in 87 % (27/31). Prior to seizure, one-third had headache, fever, and vomiting. There were no neurologic localizing signs. Twenty-four seizure events (77%) occurred among patients with active lupus; 16 (67%) was attributed to neuropsychiatric systemic lupus erythematosus (NPSLE) and eight (33%) to other causes: infection (tuberculous meningitis and septic encephalopathy), posterior reversible encephalopathy syndrome (PRES), uremia, arrhythmia, and eclampsia. Seven seizures in inactive lupus were not SLE-related.

Mortality rate was 28%; infection was the most common cause. Seizure resolved in 97%. Mean duration of hospitalization was 26.7 days. Patients were discharged improved from 19 seizure events (18 patients); 14 had follow-up consultations, three were readmitted. There was no seizure recurrence within 30 days of discharge. There was improvement in functional capacity.

Conclusion. The most common cause of seizure was NPSLE, followed by infection. Despite high rates of complete seizure resolution, poor outcomes were noted in almost half of the patients. Prolonged hospitalization was common. A high rate of mortality was observed. Infection was the most common cause of mortality.

Key Words: central nervous system syndromes, neuropsychiatric systemic lupus erythematosus, SLE

Top 7 Finalist for Original Studies in the 2019 UP-PGH Department of Medicine Research Forum on October 2019 at the UP-PGH, Ermita, Manila.

Poster presented in the 2019 Annual Philippine Rheumatology Association Convention on February 20-22, 2019 at the EDSA Shangri-La Hotel, Mandaluyong.

Poster presented in the 2020 Asia Pacific League of Associations in Rheumatology (APLAR) Annual Virtual Convention on October 24-29, 2020.

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INTRODUCTION

Seizure is a life-threatening neuropsychiatric systemic lupus erythematosus (NPSLE) manifestation. Clinical studies of Filipino patients with lupus showed that NPSLE is present in 13-18% of the study population.[1,2] In 2018, a review of 100 patients with lupus in the Philippine General Hospital (PGH) found seizure occurrence in 7%.[2]

Seizures may be due to lupus disease activity or non-lupus related conditions. Prompt identification of the cause/s of seizure is important for immediate treatment and prevention of mortality, permanent neurologic damage, and poor health-related quality of life.[3-6] However, there are no local published studies on the causes of seizure and its impact on the prognosis of lupus patients.

The objective of the study was to describe the causes and the outcomes of seizure in a cohort of patients with systemic lupus erythematosus (SLE) seen at the PGH.

MATERIALS AND METHODS

We conducted a retrospective study of medical charts of all patients diagnosed with SLE, who fulfilled the 1997 American College of Rheumatology (ACR) or 2012 Systemic Lupus International Clinic Collaboration (SLICC) classification criteria for SLE, and who were documented to have had seizure occurrence prior to or during confinement at PGH between January 2016 to April 2019.

We extracted the following data: demographics, SLE manifestation at time of index seizure event, physical examination findings, laboratory results, physician assessments, treatment, and outcomes. The Mexican SLE disease activity index was used to measure lupus activity.[7] This is a validated simplified version of a lupus activity index not requiring immunologic tests. It is advantageous for settings with limited availability of immunologic tests.

The main study outcomes were: causes of seizure and outcomes of seizure. We defined "NPSLE-seizure" as attributable to lupus disease activity, in the absence of other causes such as infection, metabolic abnormalities, arrhythmia, or medications. "Non-NPSLE seizure" was defined as a seizure directly attributable to any one of the aforementioned other cause/s, in the absence or presence of lupus disease activity. We identified outcomes of seizure in terms of: seizure resolution, 30-day seizure recurrence, mortality, and functional capacity (prior to seizure, at 6- and12-month follow-up). The ACR classification criteria of functional status in rheumatoid arthritis was adapted.[8] These classified patients from Class I through IV, wherein Class I referred to full ability to perform all activities of daily living (self-care, vocational, and avocational) and Class IV as limited in all these activities.

We used means, standard deviations, and proportions to summarize the data.

This study has been approved by the University of the Philippines-Manila Research Ethics Board. The authors declare no conflicts of interest.

RESULTS

There were 41 documented seizure events out of 764 admissions among patients with lupus during the 40-month study period. Thirty-one seizure events (29 patients) had full documentation and were included in the study. There were two patients who each had two seizure events.

Patient characteristics

The mean age of patients was 28.2 (SD 8.3) years. All were women, including two who were pregnant, mostly single, of low socio-economic status, and had poor functional capacity (Table 1). Nine patients had other NPSLE syndromes (psychosis, cerebrovascular disease, and transverse myelitis) close to the seizure occurrence. There were five patients who had previous neuropsychiatric lupus events-seizure in three and cerebrovascular disease in two.

Seven of 29 patients had concurrent autoimmune diseases (AID); the most common was antiphospholipid syndrome. Six of 29 patients had organ damage, which is a non-reversible change and unrelated to disease activity, in at least one of the following domains: renal, ocular, musculoskeletal, and neurologic. Co-morbidities, aside from organ damage and concurrent AID, were seen in ten of 29 patients; chronic renal disease and pulmonary infections were common. (Tables 2 and 3)

Description and causes of seizures

Most of the seizures were generalized (27/31, 87%). There was progression to status epilepticus in four; three started as generalized and one as a focal seizure. While nine patients presented with concomitant neuropsychiatric syndromes, 25 presented only with nonspecific syndromes such as headache (13, 42%), vomiting (6, 19%), and fever (6, 19%). Nuchal rigidity and lateralizing signs were absent in all patients, even among four patients who were later diagnosed with meningitis.

Table 1. Demographic characteristics of patients with lupus presenting with seizure admitted in UP-PGH from 2016–2019, N=29 patients

Characteristic	n	(%)
Female	29	(100)
Married	9	(31)
Completed secondary or higher education	26	(90)
Employed	10	(35)
With known diagnosis of lupus	20	(69)
Mean current age, in years (SD)	28.2	(8)
Mean duration of lupus in years* (SD)	2.9	(3)

**Duration applies to patients with previous diagnosis of lupus prior to seizure event*

Overall, the most common cause of seizure was NPSLE (16, 52%). Infection was the most common cause of non-NPSLE seizure (Table 4).

Among patients with active lupus, 16/24 (67%) were attributed to NPSLE; most (13/16, 81%) occurred within a year of the diagnosis (mean duration of diagnosis, 2.0 years; range 0.25–9). The eight non-NPSLE seizure events in patients with active lupus were due to varied conditions (Table IV). Half of these seizure events (4/8 events) occurred also within a year of diagnosis (mean 3.1 years, range 0.3–9).

Seven seizures occurred among patients with inactive lupus. All but one (6/7) seizure event occurred more than a year after diagnosis (mean 2.8 years, range 0.6–6).

Table 2. Clinical characteristics of lupus patients with seizure admitted in UP-PGH from 2016–2019, N=29 patients (31 events)

Characteristic	n	(%)
ACR functional capacity prior to seizure		
I	6	(19)
II	5	(16)
III	10	(32)
IV	10	(32)
Disease activity*		
Inactive	7	(23)
Probable	5	(16)
Active	19	(61)
Comorbidities		
Antiphospholipid antibody syndrome	6	(19)
Organ damage	6	(19)
Infection	5	(16)
Previous neuropsychiatric lupus	5	(16)

**Based on Mexican SLE disease activity index*

Table 3. Disease activity among of lupus patients with seizure admitted in UP-PGH from 2016–2019, N=24 seizure events

Lupus manifestation	n	(%)
Mucocutaneous	16	(52)
New rash	13	(42)
Oral ulcers	9	(29)
Alopecia	8	(26)
Vasculitis	5	(16)
Hematologic	11	(36)
Lymphopenia	6	(19)
Hemolytic anemia	5	(16)
Thrombocytopenia	5	(16)
Leukopenia	3	(10)
Musculoskeletal	10	(32)
Arthritis	8	(26)
Myositis	2	(7)
Nephritis	10	(32)
Neuropsychiatric	9	(29)
Psychosis	4	(13)
Cerebrovascular disease	4	(13)
Myelitis	1	(3)
Serositis	2	(7)
Retinopathy	1	(3)

Two patients had more than 1 seizure event. The first patient had two separate seizure episodes, more than 30 days apart, during the same hospital admission. The first was due to NPSLE; the second to hypokalemia. The second patient's seizures were three years apart. The first was due to NPSLE (cerebrovascular disease); the second to post-gliotic seizure.

Management of seizures

All patients with NPSLE-related seizures (16 events) were given high-dose glucocorticoids; methylprednisolone pulse therapy in 11. Cyclophosphamide was given as additional immunosuppressant to two patients (13%). All patients were given anticonvulsants, which were discontinued for all patients within a year of discharge. Patients with non-NPSLE seizures were treated according to the underlying cause.

Outcome of seizure

Seizure resolved in 97% of events (30/31). One patient had recurrent seizures for three days and died from sepsis. There were seven other deaths, due to infections (nosocomial pneumonia and bacteremia, in four) and arrhythmias (in three). Most of them (6/8) were confined for lupus activity but two had meningitis and one had sepsis on entry to the hospital. Two patients died within three days of the seizure event and while six patients died more than 30 days after the seizure. The mean hospital stay of the deceased patients was 44 days (SD 44.3; range 3–140).

Three patients with poor prognosis were brought home against medical advice. Seizure resolved but there was deterioration in status due to massive intracranial hemorrhage (1), and infection (2).

Eighteen patients (19 events, 61%) were discharged improved. The mean duration of hospitalization for these patients was 20.1 (SD 13.7) days. Most (16/19, 84%) stayed in the hospital for thirty days or less. Altogether, the mean

Table 4. Causes of seizures in lupus patients admitted in UP-PGH from 2016-2019, N=31 seizures

Cause of Seizure	Active Lupus	Inactive Lupus	Total
Neuropsychiatric lupus	16	0	16
Non-neuropsychiatric lupus	8	7	15
Posterior reversible encephalopathy syndrome	3	0	3
Infection			
TB meningitis	1	2	3
Sepsis	1	1	2
Suppurative meningitis	0	1	1
Uremia	1	1	2
Arrhythmia	1	0	1
Hypokalemia	0	1	1
Post-gliotic seizure	0	1	1
Eclampsia	1	0	1
Total	24	7	31

duration of hospitalization for the 31 seizure events was 26.7 (SD 27.1) days, ranging from 2–140.

Fourteen patients had follow-up consultations. There was no seizure recurrence within 30 days of discharge. However, three patients were readmitted within 30 days for other disease conditions: infections (disseminated TB, complicated urinary tract infection, sacral decubitus ulcer) and fluid overload. All readmitted patients were discharged improved.

We assessed the functional capacity of those who were able to follow-up. Four patients who had good (ACR I-II) baseline functional capacity sustained this status on follow up. Ten patients had poor (ACR III-IV) baseline poor baseline capacity but nine improved to ACR I-II status.

Active lupus patients had a higher proportion of discharge and a lower proportion of poor outcome compared with the inactive patients (Table 5). Of note, the latter group had a higher proportion of patients with co-morbidities.

The proportion of patients with co-morbidities was higher in the non-NPSLE group compared with NPSLE group (Table 6). In most cases, the co-morbidity was related to the cause of the seizure: uremic seizures in two chronic renal insufficiency patients, central nervous system infection in two tuberculosis patients, and PRES and eclampsia in two pregnant patients. Participants with co-morbidities, regardless of disease activity and cause of seizure, had lesser proportion of discharged patients (7/12 [58%] vs 12/18 [67%]) and a higher proportion of patients with poor outcome (6/12 [46%] vs 7/18 [39%]).

DISCUSSION AND CONCLUSION

Seizure is one of the 19 syndromes under the 1999 ACR classification for NPSLE. These are seen among 6.2–14% of lupus patients.[9-12]

The association of demographic and disease characteristics with seizure in lupus patients has been studied. The LUMINA multi-ethnic cohort study showed a correlation between employment and married status to longer time-to-seizure occurrence. Younger age, disease activity, early organ damage, psychosis, renal involvement, renal damage at baseline, anti-phospholipid antibodies, glucocorticoid and cyclophosphamide use are factors associated with earlier time-to-seizure occurrence.[10] Another large cohort study of Caucasian and African American lupus patients showed that the risk for seizure around the time of diagnosis was higher in patients with malar rash.[11] Another factor shown to increase the risk for seizure is a history of prior and current NPSLE manifestations.[11,13] Studies in 1997 and 2008 revealed concurrent NPSLE manifestation in 27.5-58.6% of their participants.[13,14]

Many of our patients with seizure were young, unemployed, unmarried, and with apparent active lupus disease. Many of them had cutaneous lesions and renal disease. A few had psychoses and previous NPSLE, and comorbidities like organ damage or anti-phospholipid antibody syndrome. These features made our patients prone to the development of seizures. The same features should prompt us, physicians, to aim for rapid disease control and be mindful of higher risk for seizures.

A few of our patients had APAS; a condition inconsistently linked with seizures.[9,11,12,14-16] It has been theorized that antiphospholipid antibodies can cause seizure through cerebral microinfarctions, increased neuronal excitability, and accelerated atherosclerosis.[10] However, it is not known if these mechanisms are true for both active and inactive lupus, and for primary and secondary APAS.

Most studies, including ours, agree that the majority of seizure events (80% in our study) occur within the first year of diagnosis.[9,11,12] Moreover, we observed that seizures

Table 5. Outcome of patients presenting with seizure admitted in UP-PGH from 2016–2019 according to disease activity, N=31 seizure events

Disease activity	Number of seizure events	Presence of co-morbidities n (%)	Seizure resolution n (%)	Discharged improved n (%)	Poor outcome n (%)
Active	24	8 (33)	23 (96)	15 (63)	8 (33) 6* + 2†
Inactive	7	4 (57)	7 (100)	4 (57)	3 (43) 2* + 1†

**Mortality; †Patients with poor prognosis brought home against medical advice*

Table 6. Outcome of patients presenting with seizure admitted in UP-PGH from 2016–2019 according to cause of seizure, N=31 seizure events

Cause of seizure	Number of seizure events	Presence of co-morbidities n (%)	Seizure resolution n (%)	Discharged improved n (%)	Poor outcome n (%)
NPSLE	16	3 (19)	15 (94)	10 (63)	6 (38) 4* + 1†
Non-NPSLE	15	9 (60)	15 (100)	9 (60)	6 (40) 4* + 2†

**Mortality; †Patients with poor prognosis brought home against medical advice*
NPSLE, Neuropsychiatric systemic lupus erythematosus

in patients with active disease occurring during the first-year post-diagnosis were more likely to be from NPSLE (13/16 patients). On the contrary, seizures in those with inactive disease occurring more than a year post-diagnosis were more likely to be non-lupus related (6/7 patients).

The most common cause of seizure in our population was NPSLE. Other etiologic factors were infection, PRES, uremia, and eclampsia. Previous studies often focused on NPSLE seizures, and rarely on non-NPSLE conditions. However, an estimated 11-35 % of seizures in different study populations were non-lupus related.[10,14,16] These results emphasize the need for thorough investigation in lupus patients presenting with seizures, irrespective of the presence or absence of extra-neurologic disease activity. It is of note that, in our study, co-morbidities were important considerations in the cause of seizure.

It is notable that seizure due to PRES was found in 9.7% of our study population. Among our patients, it is uncertain whether PRES is a result of active lupus disease, hypertension, immunosuppressive therapies, or renal disease. Intuitively, since endothelial dysfunction and vasogenic edema occur both in PRES and lupus, it is not surprising to find these conditions co-existing. A 2017 Thai study noted that, in Asia, the prevalence of PRES in lupus range from 0.69-2.02%.[17]

The European League Against Rheumatism (EULAR) recommends glucocorticoid and/or immunosuppressive therapy for patients with seizures in the presence of generalized lupus activity.[13,18] In our study, 11 out of the sixteen NPSLE patients were given the 3-day intravenous methylprednisolone pulse therapy; two patients received additional monthly cyclophosphamide for six months. All but one seizure event was well controlled with anticonvulsants. However, the negative impact of seizure on prognosis was evident from the high mortality rate (28 % documented in-hospital mortality; 38% mortality if three patients who went home against medical advice in poor condition are added). The mortality rate from two studies done in France and Malaysia was 14.5% and 25%.[3,14]

Deaths in our study were commonly due to hospital-acquired infections although the predominant reason for hospital confinement was lupus disease activity. A Malaysian study with mortality of 15/ 58 patients with lupus, similarly observed that the cause of death in half was infection.[14]

Our patients with seizures had prolonged hospital stay (mean hospitalization 26.7 days). Those who died had significantly longer stays than those who survived (26.7 ± 27.1 days vs 44.0 ± 44.3, $p<0.05$). This points to the need to aggressively implement measures to prevent and treat nosocomial infections among these patients.

Complete resolution of seizures was seen in more than 90% of the patients in the study. Those who survived rarely had a seizure recurrence and prolonged use of anticonvulsant was unnecessary. Our cohort had better outcomes compared to previous reports where resolution rate was 76%, seizure recurrence in 21.3–53%, and discontinuation of anticonvulsants only in 26%.[9,14] There was maintained or improved functional status (ACR I-II) in the majority of patients after a year. Interventions that hasten recovery after discharge, such as nutritional counseling and physical therapy, may contribute to these favorable outcomes.

In our study, we observed that the presence of co-morbidities may portend a worse outcome. Several large retrospective studies have similar findings. A 2017 study showed that SLE was associated not only with a high risk of pre-existing conditions but also with developing new co-morbidities most frequently seen in the first two years after lupus diagnosis.[19] A nine-year study done in the United Kingdom involving 1,605 lupus participants determined the burden of co-morbidities and its impact on mortality on lupus patients compared with healthy controls. The authors concluded that co-morbidities contribute significantly (27.6%) to all-cause mortality in lupus patients.[20] Another study done in Taiwan with 427 in-patients with SLE compared mortality among those who had septicemia, non-septicemia infection, and non-infection hospital admissions. The risk of mortality was higher in patients with septicemia who had previous admissions for septicemia compared to those who were admitted due to non-septicemia infection and non-infection condition. The authors found that fewer previous septicemia admissions decreased the risk of septicemia mortality.[21] Experts including the EULAR guidelines recommend proactive defense against infections, concentrating both on primary prevention, as well as timely recognition and treatment.[4,5,22] Monitoring for the presence and treatment of comorbidities is important in the management of patients with lupus due to its prognostic implications.[4,5]

Since the study was retrospective in design, there was the possibility of some missing data. Long-term prospective cohort studies with a much larger study population are needed to confirm observations made in this study. This study method will minimize recall bias and decrease the amount of missing data.

In conclusion, the most common cause of seizure was NPSLE. Metabolic and infectious causes of seizure occurred similarly in patients with both active and inactive lupus. These results emphasize the need for thorough investigation in patients with lupus presenting with seizures, with or without extra-neurologic disease activity. In this study seizures were well-controlled with medications and the recurrence was low. Mortality occurred in 28%; infection being the most common cause. The duration of hospitalization was prolonged and was significantly longer for those who died. There was good functional capacity in the majority of the survivors. Effective implementation of programs for infection control, nutritional build-up, physical therapy, and adherence to outpatient consults are suggested measures for faster recovery and prevent unfavorable outcomes in these young patients.[4,5,22-25]

Statement of Authorship

All authors participated in data collection and analysis, and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

This paper was funded by the authors.

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APPENDIX

The American College of Rheumatology 1991 revised criteria for the classification of the global function status in patients with rheumatoid arthritis*

Class I Completely able to perform usual activities of daily living (self-care**, vocational, and avocational)
Class II Able to perform usual self-care and vocational activities, but limited in avocational activities
Class III Able to perform usual self-care activities, but limited in vocational and avocational activities
Class IV Limited in usual self-care, vocational, and avocational activities

* *Hochberg MA, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of the global function status in patients with rheumatoid arthritis. Arthritis & Rheumatism. 1992; 35(5): 498-502.*

** *Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient desired and age-sex-specific*