# Clinical features and predictive factors in neuro-psychiatric lupus

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## Summary

***Background*: Neuropsychiatric lupus (NPL) can present with a wide variety of clinical manifestations secondary to major organ involvement. These are often difficult to diagnose and treat with a high mortality.**

***Objective*: This study aims to describe the prevalence, clinical features and predictive factors for NPL patients.**

***Methods*: Patients with SLE were retrospectively reviewed for 5 years, between January 2000 and August 2005. The prevalence, clinical features and predictive factors for NPL patients were studied. Neuropsychiatric (NP) syndromes were defined using the American College of Rheumatology (ACR) nomenclature and case definitions.**

***Results*: 750 patients with SLE were studied; 13 patients were excluded due to incomplete data. The mean age was 35± 11.7 years and 95.2% were female. The mean SLE disease duration was 6.9± 5.6 years. Eleven of the 19 ACR NP syndromes were identified and NP manifestations occurred in 97 patients (13%) with a total of 103 NP events. Central nervous system (CNS) manifestations accounted for 87% (84 patients), while involvement of the peripheral nervous system (PNS) 13% (13 patients). The three most frequent manifestation were seizures (31.1%), followed by psychoses (22.3%), and cerebrovascular disease (22.3%). CNS involvement was strongly associated with hematologic and gastrointestinal involvements. The mortality rate in patients with NPSLE was 18.8%.**

***Conclusion*: seizures, psychoses and cerebrovascular disease were the three most common NP features in SLE patients. CNS involvement was strongly associated with hematologic and gastrointestinal involvement. *(Asian Pac J Allergy Immunol 2012;30:55-60)***


***Key words:*** *neuropsychiatric, systemic lupus erythematosus, predictive factors, clinical features*

## Introduction

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease affecting multiple organ systems. Neuropsychiatric SLE (NPSLE) or neuropsychiatric lupus (NPL) is the main manifestation that may affect patients physically and mentally, and also lower their quality of life.[1]

NPSLE occurs in between 20 and 80% of SLE patients. The central nervous system (CNS) involvement usually causes severe illness and or death. There are several specific autoantibodies associated with NPSLE. The presence of antiphospholipid antibodies is significantly associated with cerebrovascular disease and cognitive dysfunction, whereas anti-ribosomal *P* antibodies are strongly associated with psychosis and depression in SLE.[2-4] However, other clinical predictors for NPSLE are limited. Here, we did a large retrospective review to find predictive factors for neuropsychiatric syndromes, particularly CNS involvement in SLE patients.

## Methods

We enrolled 750 patients who were age over 15 years and met the diagnostic criteria of SLE[5] in Srinagarind hospital, Khon Kaen, Thailand between January 2000 and August 2005. Charts were retrospectively reviewed by a rheumatologist. Each patient was evaluated and baseline characteristics, age of disease onset, duration of diseases, previous organ involvement,[5] neuropsychiatric manifestations, laboratory results, treatment, and treatment outcome were recorded. Neuropsychiatric manifestations[6] were recorded using the ACR NPSLE nomenclature

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**Table 1.** Neuropsychiatric syndromes observed in systemic lupus erythematosus (NPSLE)[a]

| |
|---|
| **NPSLE syndromes associated with central nervous system involvement** |
| 1. Aseptic meningitis |
| 2. Cerebrovascular disease (stroke, transient ischemic attack, venous sinus thrombosis) |
| 3. Demyelinating syndrome |
| 4. Headache (tension, migraine) |
| 5. Movement disorder (chorea) |
| 6. Myelopathy |
| 7. Seizure disorders |
| 8. Acute confusional state (delirium) |
| 9. Anxiety disorders |
| 10. Cognitive dysfunction (mild to severe cognitive disorder, dementia) |
| 11. Mood disorders |
| 12. Psychoses |
| **NPSLE syndromes associated with peripheral nervous system** |
| 13. Acute inflammatory demyelinating polyradiculopathy (Guillain Barre syndrome) |
| 14. Autonomic disorders |
| 15. Mononeuropathy (single/multiple) |
| 16. Myasthenia gravis |
| 17. Neuropathy (cranial) |
| 18. Plexopathy |
| 19. Polyneuropathy |

[a]Adapted from the 1999 American College of Rheumatology Case Definition (1999, Arthritis & Rheumatism 42: 599-608) with permission. Reprinted by permission of Wiley-Liss, Inc, a subsidiary of John Wiley & Sons, Inc.

and case definitions (1999) as shown on Table 1. NPSLE was diagnosed clinically by the neurologist.

Active disease was defined as active organ involvement according to the ACR criteria.[5] Major disease exacerbation was defined as organ involvement that needed high-dose steroid treatment. Pulmonary involvement was defined as any pulmonary diseases associated with SLE, such as pulmonary haemorrhage, pneumonitis and interstitial lung disease. Gastrointestinal involvement was defined as any gastrointestinal diseases associated with SLE, such as gastrointestinal vasculitis or serositis. Hematologic involvement was defined as any hematologic problems associated with SLE, such as lymphopenia, haemolytic anemia, and thrombocytopenia. Skin involvement was defined as any dermatologic problems associated with SLE, such as malar rash, oral ulcer, discoid lupus and photosensitivity rash.

### *Ethical Approval*

This study was approved by the Human Ethics Committee of the Faculty of Medicine, Khon Kaen University.

### *Statistical Analysis*

Categorical data were reported as percentages and continuous data as the mean $\pm$ SD. The Student *t* test was used to assess normally distributed continuous data and Wilcoxon rank sum test for non-normally distributed continuous data outcome. The Chi-squared test or Fisher's exact test were used to compare categorical data outcomes. All of the statistical tests were two-tailed and a p-value of $<0.05$ was required for statistical significance.

Univariate logistic regression analyses were applied to calculate the crude odds ratios (ORs) for individual variables for the development of CNS NPSLE. All variables with $P<0.20$ in univariate analysis were included in subsequent multivariate logistic regression analyses. All variables with $P>0.20$ in the multivariate model were excluded with the stepwise approach, whereas those with $P<0.10$ were retained in the final model. Analytical results were presented as adjusted ORs and 95% confidence intervals (CIs). Statistical analyses were done using Stata version 11.0 (StataCorp Inc., College Station, TX, US).

## Results

### *Participants*

Seven hundred and fifty patients (95.2% female) with SLE were studied. Twelve patients were excluded due to incomplete data. The mean age of the patients was 35.1$\pm$11.7 years, while the mean age of disease onset was 28.4 $\pm$ 10.6 years. The mean SLE disease duration was 6.9 $\pm$ 5.6 years.

Eleven of the 19 ACR NPSLE syndromes were identified and 97 of the patients (13%) had a total of 103 NPSLE events. CNS manifestations accounted for 87% (84/97 patients), while involvement of the PNS was 13% (13/97 patients). The three most frequent manifestations included seizures (33%), psychoses (22.7%), and cerebrovascular disease (22.3%), composed of 82.6% cerebral infarction, 8.7% transient ischemic attack and 8.7% venous sinus thrombosis.

**Table 2.** NP manifestations in SLE from this study and selected series

| Neuropsychiatric syndromes | Ainiala et al.[7] (2001) | Mok CC et al.[9] (2001) | Brey et al. [8] (2002) | Kasitanon et al.[10] (2002) | Present Study (2012) |
|---|---|---|---|---|---|
| Number of NPSLE episodes/ number of patients | 122/42 | 113/96 | 239/128 | 98/91 | 103/97 |
| Incidence of NPSLE | 91% (42/46) | 19% (96/518) | 80% (102/128) | 23% (91/390) | 13% (97/738) |
| Category of neurophychiatric episodes | per total patients | per total episodes | per total patients | per total episodes | per total episodes |
| 1. Aseptic meningitis | 1 (2%) | 1% | - | - | 1 (1.0%) |
| 2. Cerebrovascular disease | 7 (15%) | 19% | 2 (2%) | 2 (2.0%) | 23 (22.3%) |
| 3. Demyelinating syndrome | 1 (2%) | 1.5% | - | - | - |
| 4. Headache | 25 (54%) | 4% | 73 (57%) | - | 2 (1.9%) |
| 5. Movement disorder (chorea) | 1 (2%) | 2% | 1 (1%) | - | - |
| 6. Myelopathy | - | 8% | - | 6 (6.1%) | 8 (7.8%) |
| 7. Seizure disorders | 4 (9%) | 28% | 21 (16%) | 53 (54.1%) | 32 (31.1%) |
| 8. Acute confusional state | 3 (7%) | 14% | - | 11 (11.2%) | - |
| 9. Anxiety disorders | 6 (13%) | 1.5% | 27 (24%) | - | - |
| 10. Cognitive dysfunction | 37 (80%) | - | 53 (79%) | - | - |
| 11. Mood disorders | 20 (44%) | 6% | 25 (23%) | - | 1 (1.0%) |
| 12. Psychoses | - | 11% | 6 (5%) | 13 (13.3%) | 23 (22.3%) |
| 13. Guillain Barre syndrome | - | - | - | - | 1 (1.0%) |
| 14. Autonomic disorder | - | - | - | - | - |
| 15. Mononeuropathy, single/multiple | - | 1.5% | 9 (8%) | - | 1 (1.0%) |
| 16. Myasthenia gravis | 1 (2%) | - | - | - | - |
| 17. Neuropathy, cranial | 3 (7%) | 3% | 2 (2%) | - | 1 (1.0%) |
| 18. Plexopathy | - | - | - | - | - |
| 19. Polyneuropathy | 13 (28%) | 1% | 20 (22%) | 5 (5.1) | 10 (9.7%) |

The prevalence of total NPSLE and each NP manifestation in our study and other studies are presented in Table 2. The mortality rate in patients with NPSLE was 18.8%. One-fourth of deaths were related to CNS involvement, 16.7% were related to CNS infection, and the others were related to metabolic disorders, other organ involvement, or other organ infection. Subjects in the CNS involvement group were significantly more likely to have an onset of disease before the age of 35 years, acute exacerbations involing major organs (hematologic and nephritis), and dermatologic involvement and had a longer duration of disease (Table 3).

Multiple logistic regression analysis (Table 4) showed that the predictors of CNS exacerbations were hematologic involvement (adjusted OR, 1.18; 95%CI, 1.04-1.34) and gastrointestinal involvement (adjusted OR, 1.78; 95%CI, 1.24-2.55).

## Discussion

The clinical data were retrospectively reviewed for better understanding and management of this complex, multi-system disease. Patients with SLE may present with a wide range of NP clinical features, which may be related to the disease itself or to non-SLE causes such as infection, metabolic disorder, reactions to medications and stress. As there is no single diagnostic gold standard for the group of NPSLE

**Table 3.** Comparisons of clinical features between patients with and without central nervous system (CNS) SLE

| Variables | Without CNS SLE (n=654) | With CNS SLE (n=84) | *p*-value |
|---|---|---|---|
| Female | 612 (93.7) | 80 (95.2) | 0.554 |
| Age at onset < 35 yr | 490 (74.9) | 74 (88.1) | 0.005 |
| Mean duration of disease | 6.7 (5.7) | 8.1 (5.4) | 0.005 |
| Major organ flares[1] | 286 (43.7) | 56 (66.7) | <0.0001 |
| Hematologic | 104 (15.9) | 34 (40.5) | <0.001 |
| Nephritis | 215 (32.9) | 43 (51.2) | 0.001 |
| Gastrointestinal | 6 (0.9) | 3 (3.6) | 0.072 |
| Cutaneous vasculitis | 30 (4.6) | 8 (9.5) | 0.065 |
| Cardiopulmonary | 19 (2.9) | 2 (2.4) | 0.786 |
| Serositis | 19 (2.9) | 5 (6.0) | 0.140 |
| Minor organ flares[1] | 204 (31.2) | 34 (40.5) | 0.088 |
| Arthritis | 100 (15.3) | 13 (15.5) | 0.969 |
| Dermatologic | 146 (22.3) | 28 (33.3) | 0.026 |
| Hypoalbuminemia | 238 (36.4) | 32 (38.1) | 0.236 |
| Antibodies | | | |
| Antinuclear antibodies (ANA) | 68 (10.4) | 14 (16.7) | 0.785 |
| Antibody to dsDNA | 119 (18.2) | 10 (11.9) | 0.076 |

**Note.** [1]patients might have more than one organ involvement.

**Table 4.** Multiple logistic regression analysis showed factors significantly associated with central nervous system (CNS) SLE

| Variables | OR (95% CI) | *p*-value |
|---|---|---|
| Hematologic involvement | 1.18 (1.04-1.34) | 0.010 |
| Gastrointestinal involvement | 1.78 (1.24-2.55) | 0.002 |

syndromes, the diagnostic assessment of individual patients is determined by use of clinical assessment, auto-antibodies and neuroimaging data.

The 13% prevalence of NPSLE found in our study is less than that reported in previous studies.[7, 8] This finding may be because the prevalence varies with different population groups and regions (including the age of SLE onset, race, ethnicity and socioeconomic status) and study methodology. Our findings (Table 2) regarding the prevalence of NPSLE and each NP manifestation are similar to those reported by Mok et al.[9] on Chinese patients, but different than the reports from Ainiala et al.,[7] Brey et al.[8] and Kasitanon et al.[10]

Five previous SLE cohort studies[7-9, 11, 12] showed that the most common of the 19 NP syndromes were cognitive function (55-80%), headache (24-72%), mood disorder (14-57%), cerebrovascular disease (5-18%), seizures (6-51%), polyneuropathy (3-28%), anxiety (7-24%) and psychoses (0-8%), whereas in our study, seizures, psychoses and cerebrovascular disease were the most common NP features. In our study, none of the patients had any cognitive dysfunction, anxiety disorders, mood disorders, acute confusional states, demyelinating syndromes, movement disorders, autonomic disorders, cranial neuropathy, plexopathy or myasthenia gravis. Possible explanations for the difference follow.

In some cases, it is difficult to determine whether occasional NP manifestations in SLE patients, particularly the minor or softer NP manifestations (*e.g.*, headache, mild cognitive dysfunction, anxiety and some mood disorders) reflect organic damage caused by SLE, or are simply psychological reactions to the stress or having a major chronic systemic illness or an unrelated condition. Second, we did not detect any cognitive dysfunction because a simple screening test for cognitive dysfunction is not currently available for routine clinical use, due to the lack of a single standard neuropsychological test for every presentation of SLE. Third, characteristics of NPSLE are also present in asymptomatic patients and some abnormalities may be detected using available diagnostic tools, so there are unexpected and widespread NPSLE involvements in a wider than expected population. Lastly, in clinical settings, consultation with other specialists may require experts in rheumatology and psychology. An interesting finding was the association of a high mortality in SLE patients with seizures. Although there was a high prevalence of seizures in our study, seizures can occur, either in the setting of active generalized multisystem lupus or as isolated neurological events that may be related to old structural lesions, or acute inflammation from a variety of causes.

Psychosis is also a common NP feature in our findings. It should be stressed that these patients may have acute psychoses as a primary manifestation of CNS system involvement, corticosteroid induced psychosis or a primary psychotic disorder not related to SLE. Psychosis is, however, most probably related to a direct SLE-mediated organ dysfunction in the CNS if the onset of psychosis is accompanied by other evidence of exacerbation of

SLE-related disease activity or the presence of anti-ribosomal P antibody.

Cerebrovascular disease occurred in 19.6% of the group we studied and ischemic stroke was the most common manifestation, as reported in previous studies.[2,3] Cerebrovascular disease, particularly that related to SLE, is probably due to multifactorial processes such as accelerated atherosclerosis and the prothrombotic state as a consequence of anti-phospholipid antibodies,[13] which provides a therapeutic rationale for the use of anticoagulants in selected cases.

Headaches in our SLE patients occurred less frequently than expected. Headaches, however, may be related to the disease itself or other disorders such as stress, medication or co-morbid illnesses. Lupus headaches most likely are multifactorial and probably only a small proportion of them truly represent active lupus. Importantly, no NPSLE manifestation is specific to lupus and each NP manifestation is also common in healthy individuals or patients with other chronic disorders.

Our findings showed that the presence of ANA and antibodies to dsDNA did not correlate with NP manifestations. This result is in accord with previous finding that some patients with active NPSLE may lack serum ANA and antibody to dsDNA.[14] Additionally, antiphospholipid antibody is associated with focal CNS involvement in SLE, while antiribosomal P antibody is associated with diffuse CNS involvement by SLE[2-4]. In our study, tests for autoantibodies for neurological involvement in SLE patients—*particularly antiphospholipid antibody and anti-ribosomal P antibody*—were impractical for routine testing.

Our results showed that exacerbations in major organs, particularly renal and hematologic involvement, were strongly correlated with active CNS involvement in SLE patients.

Additionally, active dermatologic involvement of minor systems was also significantly associated with active CNS involvement in these patients. Cutaneous vasculitis and gastrointestinal involvement was only marginally related to active CNS involvement.

However, after adjustment for other factors, only hematologic and gastrointestinal involvements were significantly predictive of CNS involvement. Even though a previous study in Thailand showed that cutaneous vasculitis may be associated with neuropsychiatric manifestations, the analysis was not adjusted for other factors[10]. Information on these findings may have important consequences for disease management and for future study of patient subtypes.

The strengths of our study is that it includes a large number of SLE patients and rigorous baseline data collection. The limitations to our study were as follows:firstly, the data collection was retrospective; therefore, patient assessment might have been incomplete so details of NPSLE syndromes could not be analyzed; secondly, minor NPSLE manifest-tations, particularly headaches, anxiety, mood disorders, cognitive dysfunction and autonomic disorders may not always have been identified, so the prevalence of NPSLE was less reported elsewhere in the literature; thirdly, our study may have underestimated the number of deaths because some of the patients may have died in other hospitals or at home. Finally, no autopsy was performed to establish the cause of death for every case; thus, it is not possible to conclude whether the cause of death was related to SLE-mediated organ dysfunction or other diseases.

The mortality of NPSLE patients in our study was high (18.8%); thus, early diagnosis and a proper therapeutic approach are needed to improve the outcome of NPSLE. Further detailed study of patients with NPSLE should be done to gather the clinical information needed to prepare a practical guide for both recognition and management of this difficult illness in individual patients with NPSLE.

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