Disease Activity, Organ Damage, and Treatment Exposure in Systemic Lupus Erythematosus With Neuropsychiatric Involvement: Insights From the Lupus Federated Data Network (LupusNet)

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Key Takeaways

- This analysis identified 122 patients with severe NPSLE (based on SLEDAI-2K criteria) who were enrolled in LupusNet
- Patients with severe NPSLE had higher levels of physician-rated disease activity, including non-neuropsychiatric features, than the full cohort of patients with SLE, although findings are limited by the low prevalence of patients with severe NPSLE
- Treatment intensity was greater for patients with severe NPSLE than the full cohort
- Overall and NPSLE-related organ damage was more frequent in patients with severe NPSLE, which highlights the need for additional research to enable prevention of neuropsychiatric complications in SLE

Background

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is characterized by a heterogeneous clinical presentation[1]
- SLE is commonly accompanied by neuropsychiatric comorbidities, such as headache, anxiety, mood disorders, and cognitive dysfunction[2,3]
- Specific severe neuropsychiatric manifestations of SLE (NPSLE), such as seizure, cranial neuropathy, and acute confusional state, are less common[2,3]
- The Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) captures severe NPSLE of seizure, psychosis, organic brain syndrome, or cranial nerve disorder, which are all scored as 8 points (highest-scoring items on the index)[4]
  - These symptoms represent severe and currently active NPSLE, as the SLEDAI-2K measures SLE activities within a 10-day recall period[4]
- NPSLE are associated with increased morbidity and mortality and can affect domains of health-related quality of life outside of mental health[5,6]
- The real-world burden of SLE with neuropsychiatric involvement remains uncertain
  - Severe NPSLE symptoms are relatively uncommon, and robust large-scale registry data are limited
- The Lupus Federated Data Network (LupusNet) harmonizes data from existing longitudinal SLE registries across multiple geographic regions, which enables consistent analyses of clinical characteristics and outcomes while data remain within the participating networks[7]
  - LupusNet currently aggregates data from 5 major, longitudinal, observational registries of patients with SLE that are located in the Asia-Pacific region, North America, Europe, and Latin America
  - The registries include the Asia Pacific Lupus Collaboration (APLC), the National Databank for Rheumatic Diseases (FORWARD), the Lupus Register of the Spanish Society of Rheumatology (RELESSER), the Grupo Latino Americano De Estudio de Lupus (GLADEL 2.0), and the Almenara Lupus Cohort (Almenara)

Objective

Using harmonized data from participating LupusNet registries, this analysis assessed the frequency of severe NPSLE by using SLEDAI-2K–defined neuropsychiatric involvement in a large international cohort of patients with SLE and compared disease activity, organ damage, and treatment exposure between patients with severe NPSLE and the full SLE population

Methods

- Data from 4 SLE registries mapped in LupusNet were included: APLC (Asia Pacific), RELESSER (Europe), Almenara and GLADEL (Central and South America)
  - Disease activity was assessed using the SLEDAI-2K
    - Patients were categorized into no activity (score of 0), mild activity (score >0 to ≤4), moderate activity (score >4 to <10), and high activity (score ≥10) groups
  - Organ damage was assessed using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) score
  - Overall disease activity was rated using the physician global assessment (PGA)
- Inclusion criteria were as follows:
  - Presence of severe NPSLE: defined for this analysis as ≥1 SLEDAI-2K neuropsychiatric manifestation at any time from registry enrollment (registration)
    - Includes: seizure, psychosis, organic brain syndrome, or cranial nerve disorder
      - All items are scored as 8 points on the SLEDAI-2K
    - This was an operational definition and may not represent clinically attributable NPSLE
- Disease activity, organ damage, and treatment exposure were compared between patients with severe NPSLE and the full cohort
  - Treatments were classified as glucocorticoids, immunosuppressants (cyclophosphamide, cyclosporine, mycophenolate mofetil, mycophenolic acid, tacrolimus, voclosporin), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; azathioprine, leflunomide, methotrexate, penicillamine), biologics (abatacept, anifrolumab, belimumab, obinutuzumab, rituximab, tocilizumab), and therapies for cardiovascular (antihypertensive agents [angiotensin II receptor blockers, other renin-angiotensin-aldosterone system (RAAS) inhibitors, diuretics], anithrombotic agents [acenocoumarol, heparin, warfarin], statins) and musculoskeletal (nonsteroidal anti-inflammatory drugs [NSAIDs; celecoxib, diclofenac, ibuprofen, meloxicam, nabumetone, naproxen, oxaprozin, rofecoxib], asprin) manifestations

Results

Cohort Characteristics

- A total of 122 patients with SLEDAI-2K–defined severe NPSLE were identified, which represented 1.7% of the full cohort (n=7298; **Table 1**)
  - Compared with the full cohort, patients with severe NPSLE were similar in age and time from diagnosis to registration

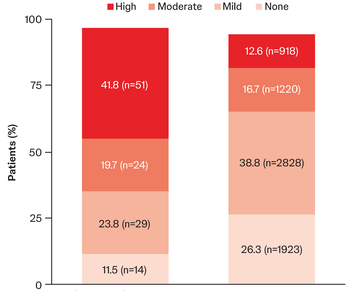
TABLE 1: Demographic and clinical characteristics at registration and 3-year follow-up

	Severe NPSLE cohort	Full cohort
N at registration (%)	122 (100)	7298 (100)
N at 3-year follow-up (%)	62 (50.8)	3736 (51.2)
Mean (SD) follow-up, years	3.5 (2.3)	3.5 (2.5)
Mean (SD) age, y	41.6 (13.2)	44.4 (13.1)
Mean (SD) time from diagnosis to registration, y	7.9 (7.7)	10.3 (8.3)
Source database, n (%)		
APLC	57 (46.7)	3907 (53.5)
RELESSER	21 (17.2)	1803 (24.7)
GLADEL 2.0	34 (27.9)	1083 (14.8)
Almenara	10 (8.2)	505 (6.9)
LN at registration, n (%)	25 (20.5)	1275 (17.5)
Mean (SD) SLEDAI-2K score at registration[a]	9.7 (8.8)	4.1 (4.5)
Mean (SD) SLEDAI-2K score at Year 3[a]	4.3 (4.5)	2.9 (3.2)
Mean (SD) PGA score at registration	1.4 (1.0)	0.82 (0.77)
Mean (SD) PGA score at Year 3	0.70 (0.72)	0.57 (0.64)
Mean (SD) SDI score at registration	0.98 (1.40)	0.70 (1.22)
Mean (SD) SDI score at Year 3	2.1 (1.9)	1.2 (1.6)
No SDI damage at the end of follow-up, n (%)	37 (30.3)	3680 (50.4)
SDI neuropsychiatric damage at the end of follow-up, n (%)	101 (82.8)	803 (11.0)
SDI features ever, n (%)		
Cerebrovascular accident	35 (28.7)	182 (4.9)
Cognitive impairment or major psychosis	9 (7.4)	171 (4.6)
Cranial or peripheral neuropathy (excluding optic)	22 (18.0)	98 (2.6)
Seizures requiring therapy for 6 months	22 (18.0)	98 (2.6)
Transverse myelitis	2 (1.6)	27 (0.7)

[a]All items used to define severe NPSLE are scored as 8 points on the SLEDAI-2K.
Almenara=Almenara Lupus Cohort; **APLC**=Asia Pacific Lupus Collaboration; **GLADEL**=Grupo Latino Americano De Estudio de Lupus; **LN**=lupus nephritis; **NPSLE**=neuropsychiatric manifestations of systemic lupus erythematosus; **PGA**=physician global assessment; **RELESSER**=Lupus Register of the Spanish Society of Rheumatology; **SD**=standard deviation; **SDI**=Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index; **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.

- Patients with severe NPSLE at any time during follow-up tended to have higher disease activity at registration (mean SLEDAI-2K score of 9.7 vs 4.1) than the full cohort, partly due to the fact that severe NPSLE captured on the SLEDAI-2K are all scored as 8 points (**Figure 1**)
  - Patients in the severe NPSLE cohort had higher mean SLEDAI and PGA scores than the full cohort at Year 3 (**Table 1**)

FIGURE 1: SLE disease activity category at registration in patients with severe NPSLE and in the full cohort

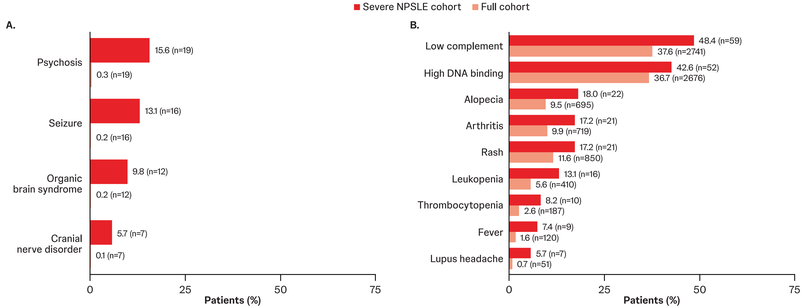


Not all patients in the severe NPSLE cohort had severe NPSLE at registration. Four patients in the severe NPSLE cohort and 409 in the full cohort did not have a SLEDAI-2K score at baseline.
None: SLEDAI-2K score of 0; mild: SLEDAI-2K score >0 to ≤4; moderate: SLEDAI-2K score >4 to <10; high: SLEDAI-2K score ≥10.
NPSLE=neuropsychiatric manifestations of systemic lupus erythematosus; **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000; **SLE**=systemic lupus erythematosus.

SLE Activity Features and Organ Damage

- The most common severe NPSLE feature at registration was psychosis, followed by seizures and organic brain syndrome (**Figure 2A**)
- In addition to NPSLE, SLEDAI-2K features were more common in patients with severe NPSLE versus the full cohort, including low complement, arthritis, proteinuria, alopecia, and rash (**Figure 2B**)
- At the end of follow-up, patients with severe NPSLE had more organ damage on average, which was indicated by higher mean SDI scores compared with the full cohort (**Table 1**)
  - At registration, 53% of patients with severe NPSLE versus 64% of patients in the full cohort had no damage (SDI=0)
  - A greater proportion of patients with severe NPSLE compared with the full cohort had damage items scored under the neuropsychiatric domain, including previous cerebrovascular accident, cognitive impairment/major psychosis, cranial or peripheral neuropathy, seizures requiring therapy, and transverse myelitis at any time

FIGURE 2: (A) SLEDAI-2K severe NPSLE features and (B) other SLEDAI-2K features[a] at registration in patients with NPSLE and in the full cohort

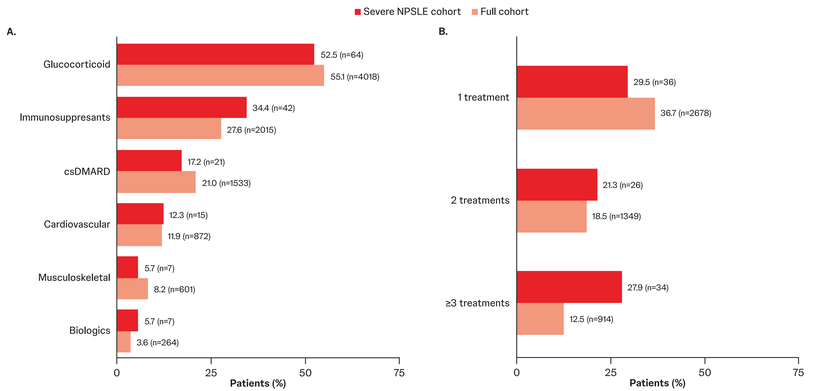


[a]Features were included if there was a ≥5-percentage point difference between the NPSLE cohort and the full cohort.
NPSLE=neuropsychiatric manifestations of systemic lupus erythematosus; **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.

Treatment Exposure

- Use of immunosuppressants, biologics and treatment with ≥2 treatments was higher in the NPSLE cohort compared with the full cohort (**Figure 3**)

FIGURE 3: (A) Treatment exposure from registration to Year 3 and (B) number of treatments of interest[a] from registration to Year 3 in patients with severe NPSLE and in the full cohort



[a]Treatment count excludes glucocorticoids and antimalarials.
csDMARD=conventional synthetic disease-modifying antirheumatic drug; **NPSLE**=neuropsychiatric manifestations of systemic lupus erythematosus.

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