

Clinical characteristics and outcomes of neuropsychiatric involvement in juvenile systemic lupus erythematosus

¹Şeyma Erdem Torun¹, ²Merve Cansu Polat², ³Emine Özçelik¹, ⁴Zahide Ekici Tekin^{1,3}, ⁵Elif Çelikel¹,
⁶Cüneyt Karagöl¹, ⁷Şeyma Ertem¹, ⁸Merve Gülyüz⁴, ⁹Didem Öztürk¹, ¹⁰Yasemin Uğur Es¹, ¹¹Sultan Nilay Yoğun¹,
¹²Esra Nur Şener¹, ¹³Mehveş Işıklar Ekici¹, ¹⁴Esra Esen¹, ¹⁵Ayşegül Neşe Çıtak Kurt⁴, ¹⁶Banu Çelikel Acar¹

¹Department of Pediatric Rheumatology, Ankara Bilkent City Hospital, Ankara, Türkiye, ²Department of Pediatric Rheumatology, Gaziantep City Hospital, Gaziantep, Türkiye, ³Department of Pediatric Rheumatology, Ankara Yıldırım Beyazıt University, Ankara, Türkiye, ⁴Department of Pediatric Neurology, Ankara Bilkent City Hospital, Ankara, Türkiye

Corresponding Author: **Şeyma Erdem Torun**

e-mail: seymaerdemtorun@gmail.com

Received : 02.06.2026, Accepted : 16.09.2026

DOI: 10.12956/TJPD.2026.1379

ABSTRACT

Objective: Neuropsychiatric (NP) involvement in juvenile onset systemic lupus erythematosus (jSLE) is associated with increased morbidity and diagnostic challenges. Data regarding pediatric populations remain limited. This study aimed to determine the prevalence, clinical features, imaging findings, and treatment outcomes of neuropsychiatric SLE (NPSLE) at a tertiary pediatric rheumatology center.

Materials and Methods: This retrospective study included 46 jSLE patients followed between 2015 and 2025. Patients were classified as NPSLE or non-NPSLE. Demographic, clinical, laboratory, imaging, and treatment data were analyzed.

Results: NPSLE was identified in 14 (30.4%) patients, and it was predominantly observed at disease onset. Patients with NPSLE had significantly higher disease activity at the time of diagnosis ($p=0.001$). Seizures ($n=5$, 10.8%) and depression ($n=2$, 4.3%) were the most common symptoms. Anti-ribosomal P antibody positivity was more common in NPSLE patients ($p=0.019$). Macrophage activation syndrome was observed in 3 (6.5%) patients, all of whom were in the NPSLE group. All patients received corticosteroids and hydroxychloroquine, and most were treated with cyclophosphamide. At the final follow-up, disease activity had significantly decreased, and most patients achieved low disease activity without neurological sequelae.

Conclusion: NPSLE is a common and severe manifestation of jSLE and is associated with high disease activity. Early and aggressive immunosuppressive therapy may play a critical role in controlling disease activity and improving prognosis.

Keywords: Child, cyclophosphamide, lupus erythematosus systemic, neurologic manifestations, remission induction

Introduction

Juvenile-onset systemic lupus erythematosus (jSLE) is a serious multisystemic autoimmune disease that can lead to significant organ damage, morbidity, and mortality; it represents approximately 15-20% of all SLE cases (1). It is classified as a rare disease with an incidence of 0.3 to 0.9 per 100.000 children and a prevalence of 1.89 to 25.7 per 100.000 children (2,3). Compared to adult-onset SLE, jSLE patients have higher morbidity and mortality rates (4). Neuropsychiatric (NP) and renal involvement tend to be more severe in pediatric patients and are associated with a poorer prognosis (5). The reported prevalence of neuropsychiatric SLE (NPSLE) ranges from 37% to 95% in adults and from 20% to 95% in pediatric patients (6). NP manifestations may present with a wide spectrum of clinical features such as seizures, psychosis, headache, cognitive dysfunction, mood disorders, cerebrovascular events, peripheral neuropathy, and transverse myelitis (7). NPSLE may be directly related to primary disease activity; however, it may also arise due to treatment-related factors, metabolic disorders, or infections

(8). Therefore, early diagnosis of NP involvement is not always possible; early recognition of clinical symptoms is crucial for the timely initiation of targeted treatment for organ involvement, prevention of permanent neurological sequelae, and improvement of patients' quality of life (QoL). However, data on NP involvement in children with SLE are limited (9).

The aim of this study was to determine the prevalence of NPSLE at our center and to examine the clinical findings, imaging features, and treatment outcomes of these patients in detail.

Materials and Methods

Study Design and Patient Population: In this study, the electronic and paper medical records of 46 patients with jSLE who were regularly followed up at a tertiary referral hospital between 2015 and 2025 were retrospectively reviewed. The diagnosis of SLE was confirmed according to the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (10). The patients

were divided into two groups: NPSLE and non-NPSLE. NP manifestations were evaluated in accordance with the 1999 American College of Rheumatology (ACR) case definitions for NPSLE (7). NP manifestations were classified as SLE-related if they occurred at disease onset or during an active disease phase, fulfilled the 1999 ACR case definitions for neuropsychiatric syndromes, and could not be attributed to a more probable alternative etiology. Patients were excluded from the NPSLE classification if NP symptoms were attributable to central nervous system infection, metabolic disturbances, uncontrolled hypertension, renal impairment or uraemia, thrombotic or structural central nervous system pathology, or medication-related adverse effects, including corticosteroid exposure. Manifestations with inherently low diagnostic specificity such as headache, depression, and mood disturbances were accepted as NPSLE only when corroborated by objective clinical, laboratory, neuroimaging, or specialist evaluation findings. Demographic characteristics, age of disease onset, disease duration, follow-up duration, symptoms, clinical characteristics, laboratory findings, treatments and neuroimaging data were recorded.

Laboratory Evaluation: Laboratory parameters including complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), anti-double-stranded DNA (anti-dsDNA), and antiphospholipid antibodies [(APA); anti-cardiolipin IgG and IgM levels, Beta-2 glycoprotein IgM and G levels, and lupus anticoagulant] were recorded. ANA, anti-dsDNA and extractable nuclear antigen (ENA) antibodies were measured using indirect immunofluorescence or enzyme-linked immunosorbent assay techniques. Serum complement levels (C3 and C4) were determined using immunodiffusion or turbidimetric immunoassay methods. Urinalysis abnormalities were defined according to the following criteria: hematuria was defined when more than five erythrocytes were detected microscopically; proteinuria was defined as a spot urine protein-to-creatinine ratio greater than 0.2 in children over two years of age and greater than 0.5 in children under two years of age, while nephrotic range proteinuria was defined as a ratio exceeding 2. Kidney biopsy specimens were histopathologically classified according to the 2003 International Society of Nephrology/Renal Pathology Society classification criteria (11).

Disease Activity Assessment: Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), which was routinely calculated at each clinical visit (12). SLEDAI-2K scores were calculated based on patients' clinical findings at admission and during the preceding 10 days. Within this scoring system, 8 points were assigned for each of the following manifestations when present: seizures, psychosis, organic brain syndrome, visual disturbances, cranial nerve involvement, lupus headache, cerebrovascular events, and vasculitis. A score of 4 points was given for arthritis, myositis, urinary casts, hematuria, proteinuria, and pyuria. Findings such as rash, alopecia, mucosal ulcers, pleuritis, pericarditis, hypocomplementemia, and elevated anti-dsDNA levels were each scored as 2 points. Additionally, fever, thrombocytopenia, and leukopenia were assigned 1 point each when present. SLEDAI-2K scores

were calculated at diagnosis and at the final follow-up visit (13, 14). Suboptimal control was defined as active disease with an SLEDAI-2K score >4 (14).

Statistical analysis

The research data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 23 (IBM Corp. Armonk, NY, USA). In the descriptive statistics section, categorical variables were presented as frequencies and percentages in tables and graphs, while continuous variables were reported as medians (IQR). The normality of distribution for continuous variables was evaluated using both visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The Mann-Whitney U test was used to compare non-normally distributed continuous variables between two groups. The chi-square test was employed for comparisons of categorical variables. A p-value of <0.050 was considered statistically significant in this study.

Results

Characteristics of the overall cohort: A total of 46 jSLE patients were included in the study. Forty-one (89.1%) were female and 5 (10.8%) were male. The median age at diagnosis, age at symptom onset, and median follow-up duration were 17.3 (14.5–20) years, 12.1 (10.6–15) years, and 25 (6–72) months, respectively. The most common finding was constitutional symptoms ($n=37$, 80.4%), followed by hematologic involvement ($n=27$, 58.6%) and mucocutaneous involvement ($n=26$, 56.5%) (Table I). All patients were ANA positive. Hypocomplementemia was detected in 34 (73.9%) patients. Anti-dsDNA antibodies were identified in 86.9% of patients ($n=40$), while extractable nuclear antigen (ENA) positivity was observed in 65.2% ($n=30$). On ENA screening, anti-nucleosome was the most frequently detected antibody ($n=20$, 43.4%), followed by anti-histone ($n=13$, 28.2%), anti-ribosomal P ($n=10$, 21.7%), and anti-Smith antibodies ($n=9$, 19.5%).

All patients received hydroxychloroquine (HCQ). Corticosteroids were administered to 43 (93.5%) patients. The median duration of corticosteroid therapy with tapering was 23 (8–45.5) months and corticosteroid treatment was discontinued in 6 (13%) patients. The other treatments received by the patients are presented in Table I. The median SLEDAI-2K score at diagnosis was 12 (7–20) and decreased to 1 (0–4) at the last follow-up visit.

Characteristics of NPSLE patients: NPSLE was present in 14 (30.4%) patients. It was observed at diagnosis in 13 (28.6%) patients and developed during the 9-month follow-up in one (2.1%) patient. Seizures developed in this patient during follow-up. Sex, age at diagnosis, diagnostic delay, and follow-up duration were similar between patients with and without NPSLE ($p>0.050$) (Table I). Constitutional symptoms were the most common findings in both groups; however, constitutional symptoms and musculoskeletal involvement were more prevalent in the non-NPSLE group ($p=0.025$ and $p=0.005$) (Table I). Three (6.5%) patients had a history of macrophage activation syndrome (MAS), and all of these patients had NP involvement. All patients with NPSLE were

Table I: Demographic and clinical characteristics, disease activity, and treatments according to NPSLE status

	Total	NPSLE	Non-NPSLE	p
Total number of patients	46	14	32	-
Sex*				
Female	41 (89.1)	12 (29.3)	29 (70.7)	0.486
Age at diagnosis (years) [†]	17.3 (14.5–20)	17 (14.9–18.5)	16.7 (13.9–20)	0.376
Age at symptom onset (years) [†]	12.1 (10.6–15)	12.9 (11–15.2)	12 (9.2–15.1)	0.256
Diagnostic delay (months) [†]	1 (0–6)	0 (0–6)	2 (0–5.5)	0.231
Follow-up duration (months) [†]	25 (12–48)	22.5 (11–34.5)	26.5 (12.5–48)	0.117
Duration of steroid use (months) [†]	23 (8–45.5)	25 (9–38)	23 (8–51.5)	0.945
Systems involvement*				
Constitutional manifestations	37 (80.4)	14 (37.8)	23 (62.2)	0.025
Hematological	27 (58.6)	11 (40.7)	16 (59.2)	0.430
Mucocutaneous	26 (56.5)	10 (38.5)	16 (61.5)	0.153
Renal	25 (54.3)	11 (44)	14 (56)	0.430
Musculoskeletal	19 (41.3)	5 (26.3)	14 (73.7)	0.005
Respiratory	14 (30.4)	6 (42.9)	8 (57.1)	0.193
Cardiac	11 (23.9)	4 (36.3)	7 (63.6)	0.056
Gastrointestinal	4 (8.6)	0	4 (100)	0.646
SLEDAI-2K (at diagnosis) [†]	12 (7–20)	20.5 (16.7–26)	10 (6–16)	0.001
SLEDAI-2K (at last visit) [†]	1 (0–4)	2 (0–5)	0 (0–4)	0.258
Treatments*				
NSAIDs	3 (6.5)	1 (33.3)	2 (66.7)	0.673
Steroids	43 (93.5)	14 (32.6)	29 (67.4)	0.327
Cyclophosphamide	19 (41.3)	13 (68.4)	6 (31.5)	0.001
Metotrexate	3 (6.5)	0	3 (100)	0.327
Azathioprine	3 (6.5)	0	3 (100)	0.327
Siklosporin A	2 (4.3)	2 (100)	0	0.088
Mycophenolate mofetil	23 (50)	14 (60.9)	9 (39.1)	0.168
Rituximab	7 (15.2)	3 (42.8)	4 (57.1)	0.113
IVIG	14 (30.4)	7 (50)	7 (50)	0.061

*: *n*(%) (chi-square test), †: median (IQR) (Mann-Whitney U test), **NPSLE**: Neuropsychiatric systemic lupus erythematosus, **SLEDAI**: Systemic Lupus Erythematosus Disease Activity Index, **NSAIDs**: nonsteroidal anti-inflammatory drugs, **IVIG**: intravenous immunoglobulin

anti-dsDNA positive and had hypocomplementemia (Table II). Anti-ribosomal P antibody positivity was more common in the NPSLE group ($p=0.019$). APA positivity was present in 3 (6.5%) patients in the NPSLE group, and there was no significant difference between the groups ($p=0.533$). However, leukopenia and lymphopenia were more frequently observed in NPSLE patients ($p=0.024$ and $p=0.001$, respectively) (Table II).

Assessment of neuropsychiatric manifestations: There were different clinical presentations of NP involvement. Seizures were observed in five (10.8%) patients and depression in two (4.3%) patients. In addition, NP manifestations such as headache, psychosis, altered consciousness, mood changes, sensorimotor neuropathy, chorea, and transverse myelitis were observed in one (2.1%) patient each. The patient who presented with seizure symptoms tested positive for APA, and an intracardiac thrombus was detected in this patient. In patients with transverse myelitis and chorea, however, APA was negative. Additionally, anti-ribosomal-P antibodies were positive in two patients diagnosed with depression.

All patients underwent cranial magnetic resonance imaging (MRI). Among the patients with seizures, cranial MRI findings in 2 (4.3%) were compatible with posterior reversible encephalopathy syndrome (PRES). Magnetic resonance angiography/venography (MRA/MRV) was performed in twelve (26%) patients. MRA/MRV findings were normal in all patients, whereas cranial MRI was normal in only 4 (8.6%)

patients. Detailed patient-level cranial MRI findings are presented in Table III.

Additionally, electroencephalography (EEG) was performed in 12 (26%) patients, and all EEG findings were normal. Electromyography (EMG) was performed in 4 (8.6%) patients; sensorimotor polyneuropathy was detected in 1 (2.1%) patient, while the remaining results were normal.

Treatment of NPSLE patients: All patients with NPSLE were treated with pulse methylprednisolone (PMP) and HCQ, and all but one patient received cyclophosphamide (CYC). CYC was used more frequently in the NPSLE group compared to the non-NPSLE group ($p=0.001$) (Table I). Additionally, therapeutic plasma exchange (TPE) was administered to 3 (6.5%) patients, rituximab (RTX) to 3 (6.5%) patients, and cyclosporine-A (CSA) to 2 (4.3%) patients. Additionally, antiepileptic treatment was initiated in 4 (8.6%) patients with seizures; selective serotonin reuptake inhibitors were started in 3 patients with depression and mood changes; haloperidol was administered to 1 (2.1%) patient with chorea; a thrombopoietin receptor agonist (eltrombopag) was initiated in 1 (2.1%) patient with thrombocytopenia; and acetylsalicylic acid was started in 3 patients with APA positivity.

Among the three patients who developed MAS, 2 had seizures and 1 had psychosis, hallucinations, and impaired consciousness. All of these patients were treated with PMP and monthly CYC induction followed by mycophenolate mofetil (MMF). In addition, 2 of these patients required TPE and CSA.

Table II: Immunological and laboratory characteristics according to NPSLE status

	NPSLE	Non-NPSLE	Total	p
Hypocomplementemia*	14 (41.1)	20 (58.8)	34 (73.9)	0.203
Direct Coombs positivity*	12 (37.5)	20 (62.5)	32 (69.6)	0.281
Anti-dsDNA positivity*	14 (35.9)	25 (64.1)	40 (86.9)	0.090
ENA positivity*	12 (40)	18 (60)	30 (65.2)	0.039
Nucleosome	7 (35)	13 (65)	20 (43.4)	0.423
Histone	7 (53.8)	6 (46.2)	13 (28.2)	0.137
PM-Scl	0	2 (100)	2 (4.3)	0.368
RNP	4 (50)	4 (50)	8 (17.3)	0.362
Anti-Sm	3 (33.3)	6 (66.7)	9 (19.5)	0.511
SS-A	1 (50)	1 (50)	2 (4.3)	0.632
Anti-Ku	0	3 (100)	3 (6.5)	0.216
Anti-ribosomal P	7 (70)	3 (30)	10 (21.7)	0.019
SS-B	0	2 (100)	2 (4.3)	0.368
Ro-52	1 (25)	3 (75)	4 (8.6)	0.493
DFS70	2 (50)	2 (50)	4 (8.6)	0.507
AMA 2	2 (66.7)	1 (33.3)	3 (6.5)	0.347
APA positivity*	3 (27.3)	8 (72.7)	11 (23.9)	0.533
Anticardiolipin IgM (U/ml)	2 (33.3)	4 (66.7)	6 (13)	0.618
Anticardiolipin IgG (U/ml)	0	4 (100)	4 (8.7)	0.211
Beta-2 glycoprotein IgM (RU/ml)	4 (50)	4 (50)	8 (17.4)	0.373
Beta-2 glycoprotein IgG (RU/ml)	1 (50)	1 (50)	2 (4.3)	0.675
Lupus anticoagulant (sec)	0	5 (100)	5 (10.9)	0.209
Leukocyte ($\times 10^9/L$)†	3.3(2.2-6)	5.1 (4.2-6.8)	5 (3.4-6.6)	0.024
Lymphocyte ($\times 10^9/L$)†	1 (0.75-1.3)	1.6 (1.3-2)	1.5 (1-2)	0.001
Platelet ($\times 10^9/L$)†	159.5 (49-212)	234 (132-318)	192 (99-303)	0.111
ESR (mm/h)†	50 (15.2-77.5)	28 (7-54)	30 (8-63)	0.113
CRP (mg/L)†	4.9 (0.87-10.4)	5 (1-20)	5.5 (0.1-22)	0.714

*: n(%) (chi-square test), †: median (IQR) (Mann-Whitney U test), **NPSLE**: Neuropsychiatric systemic lupus erythematosus, **ESR (mm/h)**: erythrocyte sedimentation rate, **CRP (mg/L)**: C-reactive protein, **ENA**: extractable nuclear antigen, **anti-dsDNA**: anti-double-stranded DNA, **PM-Scl**: polymyositis-scleroderma antibody, **RNP**: ribonucleoprotein, **anti-Sm**: anti-Smith, **SS A/Ro and SS-B/La**: Sjögren's syndrome-related antibodies, **DFS70**: dense fine speckled 70, **AMA2**: anti-mitochondrial antibody type 2, **APA**: Antiphospholipid antibodies

At diagnosis, the median SLEDAI-2K score was higher in NPSLE patients, but at the last visit, SLEDAI-2K scores were similar between the two groups ($p=0.001$ and $p=0.235$). The detailed clinical characteristics of the patients are presented in Table III and the main clinical, laboratory, and outcome-related findings of patients with NP involvement are summarized in Figure 1.

Discussion

In this study evaluating 46 patients with jSLE, NP involvement was identified in 30.4% of patients. The clinical spectrum was highly heterogeneous, with seizures and depression being the two most common clinical manifestations. Less frequent but clinically important manifestations were also observed, including PRES, transverse myelitis, chorea, psychosis, altered consciousness, mood changes, headache, and sensorimotor neuropathy. Patients with NPSLE had higher disease activity at diagnosis than those without NP involvement, and all patients who developed MAS were in the NPSLE group. Following treatment, disease activity markedly decreased in patients with NPSLE, and no neurological sequelae were observed at the final follow-up.

This study provides a comprehensive evaluation of clinical characteristics of patients with NPSLE followed at a tertiary pediatric rheumatology center in Türkiye. There is no specific biomarker or imaging finding that is definitive for the diagnosis of NPSLE; therefore, clinicians face major challenges in both the diagnostic and treatment processes

(15). In this study, the prevalence of NPSLE was determined to be 30%. It is observed that the prevalence of NPSLE reported in the literature varies widely, a finding attributed to differences in diagnostic criteria, sample size, and study design. In fact, while the prevalence of NPSLE was reported as 13.5% in a multicenter study involving jSLE patients in Türkiye, another study from Türkiye reported this rate as 24.5%. Similarly, a study conducted in Poland found a prevalence of 23.8%, while a study conducted in Egypt found a prevalence of 46.3%. These findings demonstrate that the prevalence of NPSLE can vary significantly depending on different populations and methodological approaches (16-19). For this reason, there is a need for multicenter studies involving large sample groups from different countries.

For the diagnosis of NPSLE, it is essential to carefully inquire about symptoms such as headaches, depression, and behavioral or mood changes at every visit and to be alert for the presence of neurological involvement (20). Early recognition of symptoms is of critical importance for preventing the development of permanent neurological sequelae and improving patients' QoL. However, clinicians' tendency not to be sufficiently persistent in inquiring about mild and nonspecific NP symptoms may lead to underreporting of NP involvement rates in some centers. Therefore, adopting a standardized and systematic clinical evaluation approach will not only facilitate early diagnosis but also contribute to obtaining more accurate data on the prevalence of NPSLE.

Table III: Clinical features, neuroimaging findings, and treatments of patients with NPSLE

No	Sex	Age*	Presenting complaint	Neuropsychiatric manifestations	Cranial MRI	MRA/ MRV	EEG	EMG	Other organ system involvement*	SLEDAI-2K (at last visit)	Treatments†
1	F	8	Fever MAS	Seizure PRES	Bilateral occipital lobe hyperintensity	-	N	-	LN, Hematological	1	PMP, CYC, TPE MMF, LEV
2	F	17	Fever Agitation MAS	Altered consciousness	Bilateral cerebral hyperintense lesions and corpus callosum hematoma	N	N	N	ACL, Respiratory, LN, Hematological	4	PMP, TPE IVIg, CYC, CSA, MMF
3	M	15	Rash, fever Anxiety	Depression	Bilateral frontotemporal hyperintense signal changes	N	N	-	ACL, MSC, LN	4	PMP, CYC, MMF SSRI
4	M	13	Rash, fatigue Arthritis Mood changes	Mood changes	Bilateral frontotemporal hyperintense signal changes	N	*-	-	ACL, Hematological	0	PMP, CYC, MMF, SSRI, ASA
5	F	12	Rash, fatigue Edema Hematuria	Depression	N	-	-	-	ACL, LN	0	PMP, MMF, SSRI
6	F	10	Fever, fatigue Rash MAS	Seizure	Basal ganglia hyperintense signal changes	N	N	-	ACL, MSC, Respiratory, LN, Hematological	4	PMP, CYC, CSA, LEV, MMF, Insulin
7	F	14	Fever, fatigue Headache Myocarditis	Headache	N	N	N	-	ACL, Respiratory, LN, Hematological, Cardiac	18	PMP, CYC, MMF
8	F	14	Arthralgia, fatigue Alopecia Amenorrhea	Seizure PRES	Bilateral temporo-occipital diffusion restriction and empty sella	N	N	-	ACL, MSC, Hematological	8	PMP, CYC (2 doses) RTX (4 cycles), MMF, IVIG
9	F	13	Dyspnea Seizure Fatigue	Sensorimotor polyneuropathy	Bilateral cerebral cortical atrophy	N	N	Sensorimotor polyneuropathy	Respiratory, LN, Hematological	2	PMP, CYC RTX (4 cycles), MMF, IVIG
10	F	12	Urinary incontinence	Transverse myelitis	Focal right thalamic hyperintensity	N	N	N	MSC, LN, Hematological	2	PMP, CYC RTX (2 cycles), MMF, IVIG, Eltrombopag
11	F	13	Fine motor impairment	Chorea	Diffuse diffusion restriction in the bilateral cerebral hemispheres and signal change in the right caudate nucleus	N	N	-	MSC, LN, Cardiac	0	PMP, CYC MMF, Haloperidol
12	F	11	MIS-C	Psychosis	N	N	N	-	ACL, Hematological	0	PMP, CYC MMF, IVIG
13	F	15	Edema Hemoptysis	Seizure	Prominent bilateral cortical sulci	N	N	-	ACL, LN, Respiratory, Hematological, Cardiac	0	PMP, TPE, IVIG CYC, MMF, Lev, ASA
14	F	13	MIS-C	Seizure	N	N	N	N	ACL, LN, Respiratory, Hematological, Cardiac	0	PMP, TPE, IVIG CYC, MMF, Lev, ASA

*: Disease onset (years), **N**: Normal, **ACL**: Acute cutaneous lupus, **ASA**: acetylsalicylic acid, **CSA**: cyclosporine, **CYC**: cyclophosphamide (750 mg/m²), **EEG**: electroencephalography, **EMG**: electromyography, **F**: female, **IVIg**: intravenous immunoglobulin, **LEV**: levetiracetam, **LN**: lupus nephritis, **M**: male, **MAS**: macrophage activation syndrome, **MMF**: mycophenolate mofetil, **MSC**: musculoskeletal system, **MRI**: magnetic resonance imaging, **MRA**: magnetic resonance angiography, **MRV**: magnetic resonance venography, **MIS-C**: multisystem inflammatory syndrome in children, **NPSLE**: neuropsychiatric systemic lupus erythematosus, **PMP**: pulse methylprednisolone (30 mg/kg/day), **PRES**: posterior reversible encephalopathy syndrome, **RTX**: rituximab (375 mg/m² weekly for 4 weeks), **SLEDAI-2K**: Systemic Lupus Erythematosus Disease Activity Index 2000, **SSRI**: selective serotonin reuptake inhibitor, **TPE**: therapeutic plasma exchange. Constitutional symptoms were present in all patients. All patients received hydroxychloroquine.

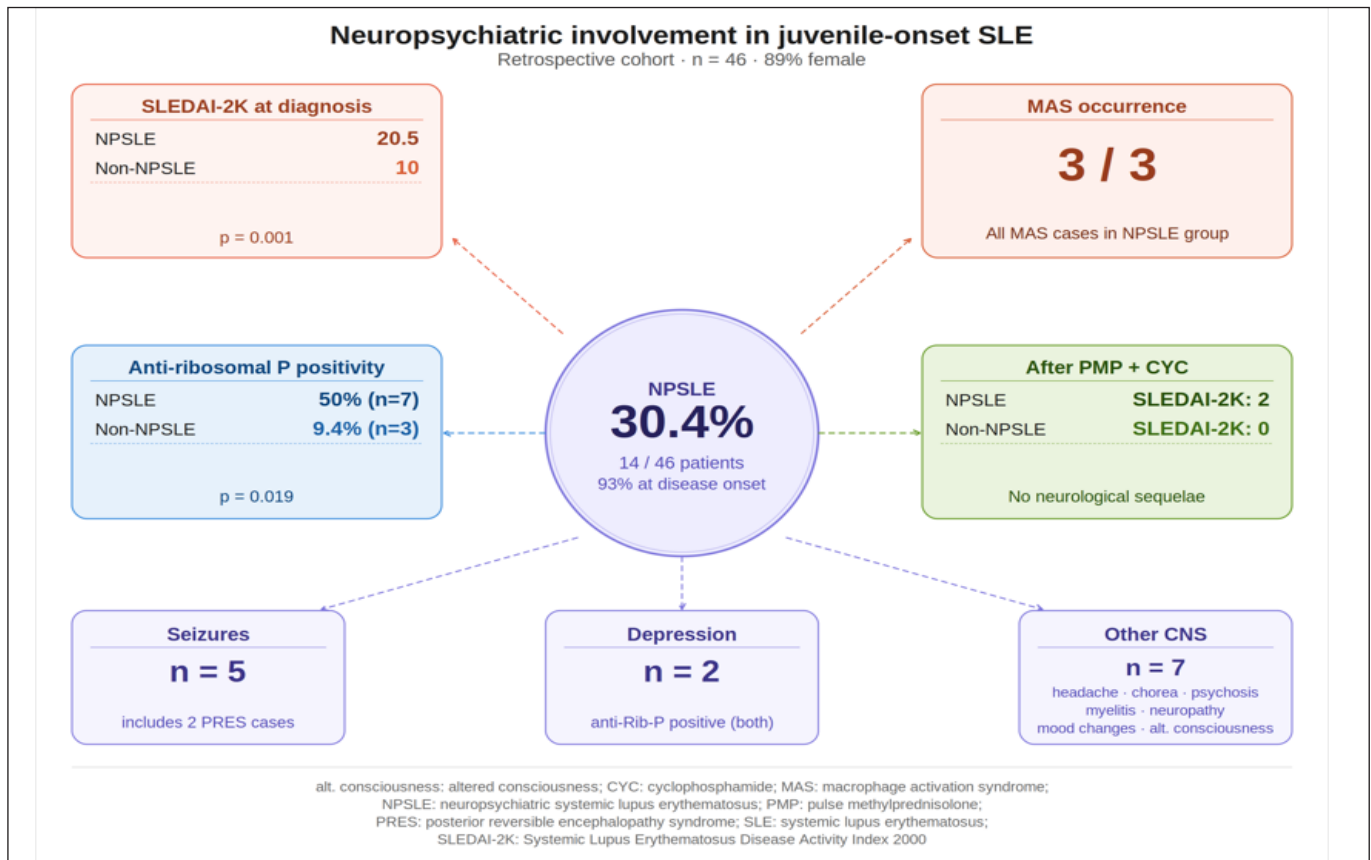


Figure 1: Overview of neuropsychiatric involvement in juvenile-onset SLE.

Symptoms of NP most commonly appear within the first two years following diagnosis; however, they may also develop at any time during the course of the disease (20). Paç Kılıçarslan et al. (17) reported that NP symptoms developed as the first manifestation of SLE in 65% of patients, whereas this rate was 48.5% in the study by Giani et al. (21). In the present study, NP symptoms developed during follow-up in only one patient diagnosed with NPSLE. NP symptoms that develop during follow-up may be related to primary disease activity or may occur as a result of treatment, particularly with corticosteroids. Therefore, a careful etiological evaluation is of paramount importance.

The most common neurological finding in our series was seizures. Seizures are among the common complications of NPSLE and are typically observed as isolated episodes that do not progress to epilepsy (22). Seizures may be associated with primary disease activity; however, they may also result from PRES, cerebral venous sinus thrombosis, or autoantibody-mediated mechanisms (22). PRES has been associated with various clinical conditions, and it has been reported that approximately 45% of patients have an underlying autoimmune disease, with SLE being the most common (23). In fact, in our study, PRES was detected concurrently in two patients who presented with complaints of seizures, and this was considered to be associated with NPSLE.

On the other hand, depression is the most common psychiatric disorder in SLE and was also the most frequently observed psychiatric finding in our study (24). Although it has been shown

that anti-ribosomal P antibodies have low sensitivity (20%) and moderate specificity (80%), they appear to be particularly associated with psychosis and severe depression (25). In our series, two patients who presented with depression were positive for anti-ribosomal P antibodies.

It is known that APA positivity is associated with cardiovascular diseases, thrombosis, headaches, chorea, and transverse myelitis (26). In the current cohort, APA was positive in a patient who developed an intracardiac thrombus, whereas it was negative in patients who developed chorea and transverse myelitis (27). This finding underscores the importance of evaluating patients with NPSLE who test positive for APA for early anticoagulant therapy and closely monitoring them for the development of thrombosis.

In this study, disease activity at the time of diagnosis was higher in patients with NP involvement. Similarly, in a study by Pawlak-Buś et al. (18) involving 143 SLE patients, higher disease activity was observed in patients with NPSLE. MAS is a rare but serious and life-threatening complication of SLE. Previous studies have reported that MAS develops in 0.9–4.6% of SLE patients (28). A study from Morocco has emphasized that SLE patients with high disease activity should be closely monitored for the development of MAS (29). In our study, three patients among all SLE cases developed MAS, and all of these patients had NPSLE. This finding supports the view that the presence of NPSLE may be associated with a more severe course of the disease.

The primary goal of SLE treatment is to achieve remission or low disease activity (30). In line with this goal, aggressive immunosuppressive therapy is recommended in the early stages. While glucocorticoids and immunosuppressive agents (CYC, AZA, and MMF) form the basic treatment regimen for NPSLE, antiplatelet and anticoagulant therapies (aspirin, heparin, and warfarin) are recommended in cases associated with atherothrombosis and APA. In refractory cases, RTX, intravenous immunoglobulin (IVIG), and TPE may be considered. Additionally, symptomatic treatments such as antiepileptic, antidepressant, and antipsychotic agents may be used when indicated (31, 32). Recent guidelines emphasize the use of CYC, particularly in cases of severe NP involvement. In our study, treatment with pulsed methylprednisolone (PMP) and CYC was initiated at the time of diagnosis in all patients diagnosed with NPSLE. Similarly, in a one-year follow-up study by Lim et al. (33) involving 28 patients with NPSLE, all patients received PMP therapy at the start of the study; CYC was used in the majority of patients (71.4%), and RTX was added to the treatment regimen in two patients receiving CYC. The achievement of low disease activity in most patients at the final follow-up, along with favorable neurological outcomes, supports the efficacy of early and aggressive treatment in appropriate cases (30).

Limitations

This study has several limitations. First, the retrospective and single-center design of the study limits the generalizability of the findings. Second, the relatively small sample size, particularly in the NPSLE subgroup, reduces the statistical power for subgroup analyses. Third, the NP assessment is based on clinical evaluation and medical records, and standardized neurocognitive or psychiatric assessment tools were not systematically applied to all patients. Additionally, due to the study's retrospective nature, imaging methods and treatment approaches were not fully standardized. Finally, long-term neurological and cognitive outcomes could not be comprehensively assessed. Nevertheless, the presentation of a high-morbidity manifestation of a life-threatening disease such as SLE is a strength of our study and will serve as a guide for healthcare professionals caring for these patients.

Conclusion

It appears that NP involvement in jSLE can present with a broad and heterogeneous clinical spectrum and may be associated with a more severe disease phenotype. In this cohort study, patients with NPSLE had higher disease activity at the time of diagnosis, and NP involvement was present in all patients who developed MAS. Early recognition of NP symptoms and, in particular, early aggressive immunosuppressive treatment with PMP and CYC appear to be associated with low disease activity at the final examination and favourable neurological outcomes without neurological sequelae. These findings emphasise the importance of maintaining a high index of suspicion for NPSLE and conducting systematic neurological and psychiatric assessments.

Ethics committee approval

This study was conducted in accordance with the Helsinki Declaration Principles. The study was approved by Ankara Bilkent City Hospital (08.04.2026, reference number: TABED 1-26-2432).

Contribution of the authors

Study conception and design: ŞET, ZET, MCP, EÖ, BÇA; data collection: ŞET, MCP, EÖ; analysis and interpretation of results: ŞET, ZET; draft manuscript preparation: ŞET, ZET, MCP, EÖ, EÇ, YUS, DÖ, SNY, ENŞ, MIE, EE, NÖ, MG, BÇA. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declare the study received no funding.

Conflict of interest

The authors declare that there is no conflict of interest.

References

- Couture J, Silverman ED. Update on the pathogenesis and treatment of childhood-onset systemic lupus erythematosus. *Curr Opin Rheumatol* 2016; 28 (5): 488-96. <https://doi.org/10.1097/BOR.0000000000000317>
- Pineles D, Valente A, Warren B, Peterson MG, Lehman TJ, Moorthy LN. Worldwide incidence and prevalence of pediatric onset systemic lupus erythematosus. *Lupus* 2011; 20(11): 1187-92. <https://doi.org/10.1177/0961203311412096>
- Hiraki LT, Feldman CH, Liu J, et al. Prevalence, incidence, and demographics of systemic lupus erythematosus and lupus nephritis from 2000 to 2004 among children in the US Medicaid beneficiary population. *Arthritis Rheum* 2012; 64(8): 2669-76. <https://doi.org/10.1002/art.34472>
- Artim-Esen B, Şahin S, Çene E, et al. Comparison of disease characteristics, organ damage, and survival in patients with juvenile-onset and adult-onset systemic lupus erythematosus in a combined cohort from 2 tertiary centers in Turkey. *J Rheumatol* 2017; 44(5): 619-25. <https://doi.org/10.3899/jrheum.160340>
- Sahin S, Adrovic A, Barut K, et al. Juvenile systemic lupus erythematosus in Turkey: demographic, clinical and laboratory features with disease activity and outcome. *Lupus* 2018; 27(3): 514-9. <https://doi.org/10.1177/0961203317747717>
- Santos FPST, Nascimento BR, Calderaro DC, Ferreira GA, Correa H. Neuropsychiatric syndromes in childhood-onset systemic lupus erythematosus: a systematic review and meta-analysis. *J Clin Rheumatol* 2021; 27(5): 206-14. <https://doi.org/10.1097/RHU.0000000000001029>
- The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. *Arthritis Rheum* 1999; 42(4): 599-608. [https://doi.org/10.1002/1529-0131\(199904\)42:4<599::AID-ANR2>3.0.CO;2-F](https://doi.org/10.1002/1529-0131(199904)42:4<599::AID-ANR2>3.0.CO;2-F)
- Jeltsch-David H, Muller S. Neuropsychiatric systemic lupus erythematosus: pathogenesis and biomarkers. *Nat Rev Neurol* 2014; 10: 579-96. <https://doi.org/10.1038/nrneurol.2014.148>
- Khajezadeh MA, Zamani G, Moazzami B, Nagahi Z, Mousavi-Torshizi M, Ziaee V. Neuropsychiatric involvement in juvenile-onset systemic lupus erythematosus. *Neurol Res Int* 2018; 2018(1): 2548142. <https://doi.org/10.1155/2018/2548142>
- Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012; 64(8): 2677-86. <https://doi.org/10.1002/art.34473>
- Weening JJ, D'Agati VD, Schwartz MM, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol* 2004; 15(2): 241-50. <https://doi.org/10.1097/01.asn.0000108969.21691.5d>
- Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. *J Rheumatol* 2002; 29: 288-91.

13. Jesus D, Rodrigues M, Matos A, Henriques C, Pereira da Silva JA, Inês LS. Performance of SLEDAI-2K to detect a clinically meaningful change in SLE disease activity: a 36-month prospective cohort study of 334 patients. *Lupus* 2019; 28(5): 607-12. <https://doi.org/10.1177/0961203319836717>
14. Ugarte-Gil MF, Gamboa-Cárdenas RV, Reátegui-Sokolova C, et al. Better health-related quality of life in systemic lupus erythematosus predicted by low disease activity state/remission: data from the Peruvian Almenara Lupus Cohort. *Arthritis Care Res (Hoboken)* 2020; 72(8): 1159-62. <https://doi.org/10.1002/acr.24009>
15. Carrión-Barberà I, Salman-Monte TC, Vilchez-Oya F, Monfort J. Neuropsychiatric involvement in systemic lupus erythematosus: a review. *Autoimmun Rev* 2021; 20(4): 102780. <https://doi.org/10.1016/j.autrev.2021.102780>
16. Balci S, Ekinci RMK, Bayazit AK, et al. Juvenile systemic lupus erythematosus: a single-center experience from southern Turkey. *Clin Rheumatol* 2019; 38: 1459-68. <https://doi.org/10.1007/s10067-019-04433-4>
17. Kisaarslan AP, Çiçek SÖ, Batu ED, et al. Neuropsychiatric involvement in juvenile-onset systemic lupus erythematosus: a multicenter study. *Joint Bone Spine* 2023; 90(4): 105559. <https://doi.org/10.1016/j.jbspin.2023.105559>
18. Pawlak-Buś K, Schmidt W, Leszczyński P. Neuropsychiatric manifestations and their attribution to systemic lupus erythematosus: a retrospective single-center study in a Polish population. *Pol Arch Intern Med* 2022; 132(11): 16319. <https://doi.org/10.20452/pamw.16319>
19. Abdel-Hafez MA, Abdel-Nabi H. Juvenile systemic lupus erythematosus: onset patterns and short-term outcome in Egyptian children, a single-center experience. *Lupus* 2015; 24(13): 1455-61. <https://doi.org/10.1177/0961203315598016>
20. Appenzeller S, Pereira DR, Julio PR, Reis F, Rittner L, Marini R. Neuropsychiatric manifestations in childhood-onset systemic lupus erythematosus. *Lancet Child Adolesc Health* 2022; 6(8): 571-81. [https://doi.org/10.1016/S2352-4642\(22\)00157-2](https://doi.org/10.1016/S2352-4642(22)00157-2)
21. Giani T, Smith EM, Al-Abadi E, et al. Neuropsychiatric involvement in juvenile-onset systemic lupus erythematosus: data from the UK Juvenile-onset systemic lupus erythematosus cohort study. *Lupus* 2021; 30(12): 1955-65. <https://doi.org/10.1177/09612033211045050>
22. Hanly JG. Diagnosis and management of neuropsychiatric SLE. *Nat Rev Rheumatol* 2014; 10: 338-47. <https://doi.org/10.1038/nrrheum.2014.15>
23. Valdez-López M, Aguirre-Aguilar E, Valdés-Ferrer SI, et al. Posterior reversible encephalopathy syndrome: a neuropsychiatric manifestation of systemic lupus erythematosus. *Autoimmun Rev* 2021; 20(2): 102739. <https://doi.org/10.1016/j.autrev.2020.102739>
24. Kwan A, Marzouk S, Ghanean H, et al. Assessment of the psychometric properties of patient-reported outcomes of depression and anxiety in systemic lupus erythematosus. *Semin Arthritis Rheum* 2019; 49(2): 260-6. <https://doi.org/10.1016/j.semarthrit.2019.03.004>
25. Tayer-Shifman OE, Bingham KS, Toura Z. Neuropsychiatric systemic lupus erythematosus in older adults: diagnosis and management. *Drugs Aging* 2022; 39: 129-42. <https://doi.org/10.1007/s40266-021-00911-0>
26. Fujieda Y. Diversity of neuropsychiatric manifestations in systemic lupus erythematosus. *Immunol Med* 2020; 43(4): 135-41. <https://doi.org/10.1080/25785826.2020.1770947>
27. Gupta R, Agapoff M, Diamond B. Neuropsychiatric systemic lupus erythematosus-current and novel treatments. *Curr Opin Rheumatol* 2026; 38(2): 115-20. <https://doi.org/10.1097/BOR.0000000000001141>
28. Vilaiyuk S, Sirachainan N, Wanitkun S, Pirojsakul K, Vaewpanich J. Recurrent macrophage activation syndrome as the primary manifestation in systemic lupus erythematosus and the benefit of serial ferritin measurements: a case-based review. *Clin Rheumatol* 2013; 32: 899-904. <https://doi.org/10.1007/s10067-013-2227-1>
29. Wafa A, Hicham H, Naoufal R, et al. Clinical spectrum and therapeutic management of systemic lupus erythematosus-associated macrophage activation syndrome: a study of 20 Moroccan adult patients. *Clin Rheumatol* 2022; 41: 2021-33. <https://doi.org/10.1007/s10067-022-06055-9>
30. Sammaritano LR, Askanase A, Bermas BL, et al. 2025 American College of Rheumatology guideline for the treatment of systemic lupus erythematosus. *Arthritis Rheumatol* 2026; 78(7): 1361-86. <https://doi.org/10.1002/art.43452>
31. Fanouriakis A, Kostopoulou M, Alunno A, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019; 78(6): 736-45. <https://doi.org/10.1136/annrheumdis-2019-215089>
32. Bertsias GK, Ioannidis JP, Aringer M, et al. EULAR recommendations for the management of systemic lupus erythematosus with neuropsychiatric manifestations: report of a task force of the EULAR standing committee for clinical affairs. *Ann Rheum Dis* 2010; 69(12): 2074-82. <https://doi.org/10.1136/ard.2010.130476>
33. Lim SC, Md-Yusof YL, Johari B, Abdul-Kadir RF, Tang SP. Neuropsychiatric lupus in Malaysian children: clinical characteristics, imaging features and 12-month outcomes. *Turk J Pediatr* 2021; 63(5): 743-51. <https://doi.org/10.24953/turkjp.2021.05.002>