

## Neuropsychiatric manifestations in patients with Systemic Lupus Erythematosus: A case series

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### Abstract

Neuropsychiatric systemic lupus erythematosus (NPSLE) can affect both the brain and spinal cord and present with variable neurologic manifestations, including 19 neurologic syndromes according to the ACR (American College of Rheumatology), leading to diverse neurological and psychiatric symptoms ranging from nonspecific symptoms like a headache to devastating symptoms such as seizures and stroke, making NPSLE an important accomplice in morbidity and mortality, which are seen in SLE population. Its management options are still inadequately optimized due to its challenging diversity in presentation, reflecting a range of different pathogenic mechanisms. A better understanding of SLE presentation might improve the present options for managing NPSLE. Here we report a series of five female patients with NPSLE. Out of the five presented cases, four patients have neurological features as an initial manifestation of SLE, which is considered uncommon. The first case is of a 50-year-old female patient who had aseptic meningitis presented with headache, back pain, and lower limb weakness associated with numbness after 11 years of being diagnosed with SLE. The second case is of a 20-year-old female patient who had a generalized tonic-clonic seizure with the acute manifestation of hypertensive urgency and posterior reversible encephalopathy syndrome (PRES) as an initial manifestation of SLE. The third case is of a 38-year-old female patient who presented with an acute focal seizure as an initial manifestation of SLE. In the last two cases, a 38-year-old and a 19-year-old female patient presented with an ischemic stroke as the initial manifestation of SLE. On a final note, clinicians should always have SLE in mind as a differential diagnosis when it comes to acute neurological features presenting in any patient with SLE manifestations.

**Keyword:** Neuropsychiatric systemic lupus erythematosus; Systemic Lupus Erythematosus; Aseptic meningitis; Posterior reversible encephalopathy syndrome; Case series

### 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with varying presentations and systemic involvement. [1] Neuropsychiatric systemic lupus erythematosus (NPSLE) is any neurological defect in an SLE patient involving the peripheral or central nervous system with the exclusion of other causes. [2] A set of definitions for 19 NPSLE syndromes was proposed by the American College of Rheumatology (ACR), including aseptic meningitis, headache (including migraine and benign intracranial hypertension), seizures, Demyelinating syndrome, stroke, mood disorder, and psychosis, all are examples of central NPSLE. Autonomic disorder, simple or complex mononeuritis, cranial neuropathy, polyneuropathy, myasthenia gravis, and cranial neuropathy are examples of peripheral NPSLE. [1] The current gold standard for NPSLE diagnosis is based on physician expertise and the diagnosis of exclusion. Here we present a series of interesting NPSLE cases. In addition, we discuss its course, diagnosis, and management in detail.

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## 2. Case 1

We present the case of a 50-year-old female patient who was diagnosed with systemic lupus erythematosus at the age of 49. She started complaining of progressive lower limb weakness for the last three weeks associated with numbness. Ten days later, she complained of joint pain, morning stiffness for 30 minutes, and back pain in the sacral and lumbar regions, which was not relieved by analgesia. She had a history of headaches with no history of lower limb swelling, discoloration, fever, chills, or photophobia. She has been on her medication (hydroxychloroquine 200 mg twice a day) since she was diagnosed with SLE.

On physical examination, her temperature, heart rate, respiratory rate, O<sub>2</sub> saturation, and blood pressure were in the normal range. The patient looked well, oriented, and alert, with no malar rash and not in respiratory distress. There were no palpable lymph nodes. The strength of the limbs was (3/5) for the lowers and (5/5) for the uppers, within normal reflexes for both uppers and lowers. Neck stiffness, Kernig's and Brudzinski's signs, and other neurological findings suggestive of meningeal irritation were absent. Only red round plaques were over her extremities.

Routine lab tests revealed a white blood cell count and platelet count in the normal range, a low hemoglobin of (9.5 g/dl), and an MCV of (71  $\mu\text{m}^3$ ). The coagulation profile, normal D-dimer, and fibrinogen were within normal limits. Erythrocyte sedimentation rate and C-reactive protein were high (65 mm/hour) and (67.9 mg/l), respectively. C3 and C4 levels were low (56 mg/dl and 3 mg/dl, respectively). All were suggestive of active SLE.

CSF analysis was obtained from the patient, and the results showed watery, clear CSF with a high WBC count of 45 cells and a protein level of 58 mg/dl. CSF gram stains and cultures for bacteria were negative. The PCR for the viral antigen was negative for influenza virus, herpes simplex virus, varicella zoster virus, cytomegalovirus, coxsackie virus, and Epstein-Barr virus. Spine MRI was normal, along with a normal electromyogram and lower limb US.

The patient was given acyclovir and vancomycin for 3 days with no improvement, then aseptic meningitis was confirmed as the diagnosis, and the patient was treated successfully with prednisone.

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## 3. Case 2

A 20-year-old female patient was admitted to the ICU with a new onset of generalized tonic-clonic seizures presented with loss of consciousness, upward gazing, and confusion before a convulsion. Several days before admission, the patient complained of fever, severe headache attacks, fatigue, arthralgia, abdominal pain, and vomiting.

On physical examination, she had a malar rash, no focal neurological deficit, and negative meningeal signs. Her blood pressure was 180/110 mm Hg with a normal heart rate and oxygen saturation. The initial laboratory test showed the following values: CRP 59.7 mg/l, hemoglobin 9.2 g/dl, platelets 184,000/ $\mu\text{l}$ , white blood cell (WBC) counts 8.381/ $\mu\text{l}$ , and ERS 30 mm/hour. Renal and liver function tests were normal.

A brain computed tomography (CT) scan showed no intracranial hemorrhage. Brain magnetic resonance imaging (MRI) was done and showed abnormal hyperintense signals seen in the cortex and subcortical area for both parieto-occipital regions, mostly representing vasogenic edema with mild swelling of the corresponding gyri. These findings were highly suggestive of posterior reversible encephalopathy syndrome (PRES). Magnetic resonance angiography (MRA) and magnetic resonance venography (MRV) were normal. Echocardiography was done and showed evidence of mild to moderate pericardial effusion.

The patient was suspected of having SLE. The results of laboratory tests to diagnose systemic lupus showed positive ANA titers and positive anti-dsDNA. Based on her clinical symptoms, including malar rash, pericarditis, arthralgia, and a positive ANA titer, a diagnosis of SLE was then made with fulfilled the 2019 EULAR/ACR criteria. The patient was given intravenous (IV) diazepam, which aborted her seizure. A labetalol drip was started for blood pressure control in addition to nifedipine, candesartan, and hydrochlorothiazide. Later on, for her resistant hypertension, carvedilol and spironolactone were added after the weaning of labetalol. Also, she was given mega pulse methylprednisolone 1 gm IV daily for 3 days, then continued on prednisolone 60 mg/day, hydroxychloroquine 400 mg/day, aspirin 100 mg/day, and levetiracetam 500 mg bid that was increased to 1000 mg bid after one week. Mycophenolate mofetil was started at 1000 mg/day in addition to colchicine (1 mg/day), calcium carbonate, and vitamin D. The patient's seizure was not repeated during the rest of the hospital course. She was discharged home in 10 days.

#### 4. Case 3

A 38-year-old female patient presented with a three-day history of intermittent dizziness of gradual onset, related to a sudden change of position from sitting to standing, associated with general weakness, one episode of fainting, and one episode of syncope, upon which she was admitted to the medical center. At that point, the patient had low blood pressure and blood glucose, with a hemoglobin level of 7.5 g/dl. She received an IV fluid, dextrose, metronidazole, multivitamin, and iron supplement, to which she had partial improvement. On the following day, her symptoms persisted and worsened the day after, for which she was referred to the hospital. The patient reported having intermittent epigastric pain of gradual onset, stabbing in nature, not radiated elsewhere, not progressive, and doesn't have an association with oral intake. She also noted nausea, decreased appetite, blurry vision, and diplopia. A review of systems was positive for a history of cough, shortness of breath, tremors, and convulsion.

A physical examination revealed a pale, ill-looking patient with conjunctival pallor. However, the patient was conscious and oriented. The patient had alopecia and showed photosensitivity. The rest of the clinical examination was insignificant except for tachycardia, which was noted on the cardiovascular examination. ECG showed sinus tachycardia with PVC in inferior leads.

The initial laboratory results showed a hemoglobin level of 6.6 g/dl, an MCV of 65.28  $\mu\text{m}^3$ , a platelet count of  $201.5 \times 10^3/\text{ul}$ , and an ESR of 180 mm/hour. Serum electrolytes, kidney function tests, liver function tests, and cerebrospinal fluid (CSF) analysis were normal. Brain magnetic resonance imaging (MRI) and brain CT were done, and both were normal. However, the EEG test showed focal activity on the temporal lobes. A chest CT revealed mild cardiomegaly and an enlarged thymus gland (thymoma). The patient was suspected of having SLE. Serological studies showed a positive antinuclear antibody (ANA) and anti-dsDNA. She was diagnosed with SLE and fulfilled the 2019 EULAR/ACR criteria (positive ANA and anti-dsDNA, alopecia, and photosensitivity). In addition, the patient was diagnosed with focal seizures and thymoma.

She was started on hydroxychloroquine, prednisone, vitamin D, calcium, and other supportive therapy. She was instructed to follow up in an outpatient clinic and was recommended for surgery for the thymoma by a thoracic surgeon.

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#### 5. Case 4

A 44-year-old female patient presented with difficulty speaking and right upper limb weakness in the past 3 hours. She denied any history of chest pain, palpitations, headache, confusion, convulsion, or head trauma. However, she complained of joint pain, hair loss, and a malar rash.

On physical examination, her temperature (37.3 °C), heart rate (72), respiratory rate (18), O<sub>2</sub> saturation (94%), and blood pressure (119/85) were in the normal range. The patient looked well, was oriented and alert, had no pallor, and was not in respiratory distress. On neurologic examination, she was alert and oriented to person, place, and time, with slurred speech. No motor deficits are noted, with muscle strength 5/5 bilaterally and 4/5 on the right upper limb. The sensation was intact bilaterally. Neck stiffness, Kernig's and Brudzinski's signs, and other neurological findings suggestive of meningeal irritation were absent, and no nystagmus was noted.

The initial laboratory results showed a hemoglobin level of 8.5 g/dl, MCV of 79.76  $\mu\text{m}^3$ , white blood cells of 3.891/ $\mu\text{l}$ , CRP titer of 32.8mg/l, and D-dimer of 1162.7ng/mL. The chest CT angiography showed a small-branch filling defect in the segmental portion of the right lower lung lobe artery, representing a segmental pulmonary embolism. The brain CT showed no intracranial hemorrhage, and the brain MRI revealed a small acute lacunar infarction scattered on both cerebral hemispheres and the right side of the cerebellum. The patient was diagnosed with acute ischemic stroke and was given t-PA within the first three hours of disease onset without complication.

The results of laboratory tests showed negative anticardiolipin antibodies and positive ANA, anti-dsDNA, anti-Smith antibodies, and anti-RNP antibodies. The diagnosis of SLE was confirmed and fulfilled the 2019 EULAR/ACR criteria. She received steroids, hydroxychloroquine, and therapeutic-dose anticoagulants. She was discharged from the hospital after five days in good general condition.

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#### 6. Case 5

A 19-year-old female patient with no past medical history presented to the emergency department complaining of sudden onset slurred speech for 3 minutes, which was resolved spontaneously. She had the same attack two times in

the last ten days, lasting one minute. She had a positive history of diffuse hair loss and Raynaud's phenomenon. There was no history of paresthesia, general weakness, confusion, loss of consciousness, or abnormal movements.

On physical examination, her temperature (36.6 °C), heart rate (93), O<sub>2</sub> saturation (99%), and blood pressure (115/88) were in the normal range. The patient looked well, was oriented, alert, and not in respiratory distress. On neurologic examination, she had no focal neurological deficit, abnormal gait, or motor deficits noted. The muscle strength was 5/5 on bilateral upper and lower limbs with intact sensation. Neck stiffness, Kernig's and Brudzinski's signs, and other neurological findings suggestive of meningeal irritation were negative.

A brain MRI demonstrated an acute ischemic infarct in the right frontal lobe. Admission laboratory tests showed a hemoglobin level of 11.2 g/dl, an MCV of 75.2  $\mu\text{m}^3$ , white blood cells of 8.4/ul, a platelet count of  $321 \times 10^3/\text{ul}$ , and an ESR of 180 mm/hour. Serum electrolytes, kidney function tests, liver function tests, C3, C4, ESR, and CRP were normal. Testing for protein C and protein S showed negative results. ANA was positive, and antiphospholipid antibodies were negative.

The diagnosis of SLE was confirmed and fulfilled the 2019 EULAR/ACR criteria. She was treated with hydroxychloroquine and acetylsalicylic acid (ASA). After three days, she was discharged from the hospital in good clinical condition and with no neurological or functional abnormalities.

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## 7. Discussion

Systemic Lupus Erythematosus (SLE) can affect multiple systems and present with different clinical manifestations. However, the most common ones affected were skin, bones, muscles, tendons, serosal, renal, and hematological. The neurological and psychiatric clinical presentation of systemic lupus erythematosus (SLE) has various groups of conditions and variable clinical manifestations. [3] The incidence of neuropsychiatric systemic lupus erythematosus (NPSLE) ranged from 10.6% to 96.4%. [3]

The American College of Rheumatology (ACR) nomenclature identified 19 neuro-psychiatric syndromes in SLE, which are divided into central (12) and peripheral (7), whether diffuse or focal neurological deficits. Clinical manifestations range from mild presentations such as headache, cognitive disorder, or mood disturbance to severe forms like seizures or cerebrovascular accidents. A systematic review showed that stroke, epilepsy, and psychosis were reported in 7.1%, 5.3%, and 6.5% of NPSLE patients, respectively. [4] Another study (prospective cohort) reported 4.3% CNS manifestation in 370 SLE patients. Seizures were the most common incidence of 1.6%, followed by strokes (1.4%), spinal cord injury (1.1%), optic nerve inflammation (0.3%), meningeal inflammation (0.3%), and psychotic disorder (0.3%). [5]

The seizures that affect SLE patients are severe and the most serious neurological manifestations, with the highest related clinical presentation in SLE, and have a higher incidence in young female patients with a range of age from 22.9 to 36.5 years old. More than two-thirds of affected patients had a seizure within the first year of the disease (51 days of median time). The tonic-clonic seizure is the most common type, with an incidence of 60-88%. [6] Moreover, one study (prospective inception cohort included 1631 SLE patients) noted that 4.6% of SLE patients had a seizure with a total number of 91 during four years of follow-up, 66% of it was a generalized seizure, and 34% was focal. [7] Here we present two cases that had seizures related to SLE; one of them had a tonic-clonic seizure after three days of SLE diagnosis, and another one had a focal seizure as the first presentation of SLE.

Furthermore, previous studies suggest that multiple risk factors could be the reason behind the seizure in SLE patients, and cerebrovascular disease with ischemic or hemorrhagic damage to brain tissue was one of them. In addition, myasthenia gravis (MG) in SLE patients is a risk factor for epilepsy. [8] Our first patient had PRES beside seizure, which may be the most important risk factor background to epilepsy in the context of SLE in this patient, and the second one presented with thymoma and MG symptoms (general weakness and diplopia), which could increase the possibility of seizure.

Thymoma has an association with autoimmune disorders, and the most common one is myasthenia gravis, with an incidence of 10-15% in MG patients. Moreover, more than half of thymoma cases may present with MG. However, thymoma in association with SLE is very rare, with an incidence of 1.5%. [9]

RPES is an uncommon neurological disorder that affects the cerebral hemisphere, mainly the posterior white matter, in addition to the presence of clinical manifestations and imaging abnormalities related to this disease, and with complete remission of it in a short period when treatment is started immediately, but permanent brain function loss may occur if

the diagnosis and treatment are late. [10] The pathophysiology of PRES in SLE is still unclear. [10] However, some theories were reported, and the most commonly accepted one was related to hypertension with an arterial blood pressure of more than 150 mmHg. Also, renal failure, low serum albumin levels, and low platelets are potentially associated with PRES. [10] The most common clinical manifestations include headache, seizures (almost the first clinical symptom), disorder of consciousness, and visual disturbance. [11] Here we report a case of PRES with an initial presentation of seizures and acute manifestations of hypertensive urgency in a 20-year-old female patient with newly diagnosed SLE.

In addition, we report a case of aseptic meningitis related to SLE in a 50-year-old female patient diagnosed with SLE 13 years before meningitis who presented with acute lower limb weakness and back pain. In light of her clinical manifestation, history of SLE, negative CSF culture, negative viral panel, minimal improvement on antibiotic and antiviral medication, and significant improvement after steroid administration, she was diagnosed with aseptic meningitis in association with SLE.

The mechanism of SLE-associated aseptic meningitis is unclear and is presumed to be related to anti-DNA immune complex precipitation in the choroid plexus of the lateral ventricles. It was also hypothesized to be due to the low cerebrospinal fluid (CSF) levels of complement during an active central nervous system (CNS) disorder. Another hypothesis was reported that vasculitis could be an explanation for SLE meningitis by autoreactive antibodies. [12] Some studies suggest that drugs used in SLE treatment could induce aseptic meningitis, such as hydroxychloroquine or nonsteroidal anti-inflammatory drugs (NSAIDs). [12] However, in our case, the patient has still been on these drugs since hospital discharge without recurrent symptoms.

A cohort study analyzed data on patients with stroke related to systemic lupus erythematosus (SLE), including 139 patients from 4451 cases of SLE followed from 1993 to 2018, with an incidence of 3.1% of SLE patients. 58.3% of patients presented with acute ischemic stroke, 23% had a hemorrhagic stroke, 12.2% had a brain's venous sinus thrombosis, and 6.5% of them came with transient ischemic attack (TIA). The time between SLE diagnosis and stroke event ranged from 12-132 months, with a median time of 60 months. 48% of these patients had antiphospholipid syndrome. Hypertension and aneurysmal rupture were also reported as underlying causes of hemorrhagic stroke, besides SLE. A good prognosis was reported in 65% of patients, and 7% had a recurrent stroke. In addition, 8% was the mortality rate in these patients in the long term, with different causes. [13]

We report a case of ischemic stroke co-existing with SLE and pulmonary embolism (PE) in a female patient newly diagnosed with SLE who presented with tongue heaviness and right-side body weakness without any evidence of antiphospholipid syndrome. In addition, we present a case of acute ischemic infarction as the initial manifestation of SLE.

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## 8. Conclusions

The neurological manifestations of SLE are a significant issue for both patients and clinicians and affect the prognosis and outcome of the disease, diagnosis, and therapeutic options that could be given to SLE patients. In addition, SLE patients are at higher risk of developing seizures, aseptic meningitis, PRES syndrome, and stroke than the healthy population. Also, the morbidity and mortality rate are still high in NSLE patients compared to other patients with the same disease.

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## Compliance with ethical standards

### *Disclosure of conflict of interest*

No conflict of interest to be disclosed.

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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