

Neuropsychiatric manifestation in patients with Systemic Lupus Erythematosus: A unique case series

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Abstract

Neuropsychiatric systemic lupus erythematosus (NPSLE) affects the brain, spinal cord, or other nerves and leads to neurological and psychiatric symptoms directly related to SLE. We report a series of four female patients with NPSLE as the first presentation for SLE. None of them were previously diagnosed with SLE. The first case involved a 50-year-old patient who presented with back pain and lower limb weakness for three weeks associated with numbness. A lumbar puncture was done, and CSF analysis showed high WBC and normal glucose levels with negative CSF cultures for bacteria. The patient was diagnosed with aseptic meningitis and treated with antibiotics and antiviral medication without improvement. So she was treated as a case of SLE aseptic meningitis with steroids. In the second case, a 20-year-old patient had a generalized tonic-clonic seizure with the acute manifestation of hypertensive urgency. Magnetic resonance imaging (MRI) was done and suggested posterior reversible encephalopathy syndrome (PRES). The third case was for a 38-year-old patient who complained of dizziness, general weakness, and convulsion. On review of the systems, the patients had positive symptoms of SLE. Anti-nuclear antibody (ANA) and double-stranded ds-DNA were positive. Computed tomography (CT) scans were done and showed a thymoma. This patient was diagnosed with SLE in association with focal seizures and thymoma. In the last case, a 44-year-old patient presented with tongue heaviness and right-side weakness. MRI revealed small acute lacunar infarction scattered at both cerebral hemispheres and the right side of the cerebellum, and chest CT showed pulmonary embolism (PE). The patient was diagnosed with an acute ischemic stroke and PE related to SLE. In conclusion, the neurological manifestations of SLE are a significant issue for both patients and clinicians. Here we report a unique case series and describe the prognosis and outcome of the treatment in these cases.

Keyword

Neuro-Psychiatric syndromes, Systemic Lupus Erythematosus, seizure, aseptic meningitis, Posterior reversible encephalopathy syndrome, stroke, case series

Introduction

¹⁹ Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with varying presentations and systemic involvement. The only constant things about SLE that are ⁴ more prevalent in women are the genetic association with an elusive trigger. ¹ Neuropsychiatric ¹⁶ 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

³³ A set of definitions for 19 NPSLE syndromes ⁴ was proposed by the American College of Rheumatology (ACR) in ¹⁶ of homogenizing the terminology. Including aseptic meningitis, headaches (including migraine and benign intracranial hypertension), seizures, demyelinating synd ²⁸ ne, mood disorders, and psychosis, all are examples of central NPSLE. Whereas, autonomic disorder, simple or multiple mononeuritis, cranial neuropathy, polyneuropathy, myasthenia gravis, and cranial neuropathy for peripheral NPSLE ¹.

"Gold slandered "for NPSLE is based on physician expertise and diagnosis of exclusion, as there is no ⁴ simple sensitive mechanism or test, including imaging modalities. ³ Multiple factors play a role in defining the prevalence and incidence of NPSLE, including diagnosis difficulties due to no defined test, in addition to the heterogeneity of presentation, which is an obstacle, and depending on this, the prevalence widely varies from 14% to 91%. ^{4, 5, 6}

Here we present a series of interesting NPSLE cases. In addition, we discuss its course, diagnosis, and management in detail.

Case1

¹² We present a case of a 50-year-old female complaining of progressive lower limb weakness for the last three weeks associated with numbness. Ten days later, she also complained of joint pain, morning stiffness for 30 minutes, and back pain in the sacral and lumbar regions, which was not relieved by analgesia. There was no history of lower limb swelling, discoloration, fever, chills, photophobia, or headache. She has been on her medication (hydroxychloroquine, 200 mg BID) since she was diagnosed with SLE.

On physical examination, her temperature, ¹⁰ heart rate, respiratory rate, O₂ 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 power of the lower limbs was (3/5) and for the uppers was

(5/5), 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 tests revealed a white blood cell count and platelet count in the normal range, a low hemoglobin of 9.5 g/dl, and a mean corpuscular volume of 71 m³. 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.

Cerebrospinal Fluid (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 gramme stain 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 ultrasound. Moreover, the brain CT scan was normal.

The patient was given acyclovir and vancomycin for 8 days with no improvement, then aseptic meningitis was confirmed as the diagnosis, and the patient was treated successfully with prednisone.

Case 2

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

On physical examination, she had 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/ul, white blood cell (WBC) counts 8.381/ul, ERS 30 mm/hour, calcium 7.9 mg/dl, and vit-D-25OH 2.4 ng/ml. Serology tests showed ANA positive 1:320, Ds-DNA-IgM 131 IU/ml, and Ds-DNA-IgG 150 IU/ml. Renal function tests showed a serum creatinine level of 0.62 mg/dL and a urine protein-to-Cr ratio of 0.65.

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 oedema 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. Renal doppler ultrasound was normal.

The patient was given intravenous 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 s³⁵onolactone were added after the weaning of IV labetalol. Also, she ¹⁷s 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, which was increased to 1000 mg 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 ³during the rest of the hospital course. She was discharged home in 10 days.

Case 3

³⁴A 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. An electrocardiogram showed sinus tachycardia with premature ventricular contractions in the inferior leads.

The initial laboratory results showed a hemoglobin ⁵level of 6.6 g/dl, mean corpuscular volume of 65.28 μm^3 , mean corpuscular hemoglobin concentration of 28.06%, mean corpuscular hemoglobin of 18.32 pg/ml, red cell distribution width of 20.98, hematocrit of 32.96%, and total iron binding capacity of 443 $\mu\text{g/dl}$. Ferritin 4.23 ng/ml, Folic acid 12.9 ng/ml, B12 617 pg/ml, white blood cells of 12.1 /ul, neutrophils 70%, lymphocytes 22%, monocytes 4.59%, eosinophils 627%, basophils 2.72%, a ²⁶platelet 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. Serological studies showed a positive ANA with a titer of 2.8 (positive >1.2 index), positive anti-SS-A, anti-SS-B, and Ds-DNA-IgG. Brain MRIs and brain CTs 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). (Figure 2)

³⁷ The patient was diagnosed with SLE and fulfilled the 2019 EULAR²⁷ ACR criteria (positive ANA, alopecia, photosensitivity, and Ds-DNA-IgG). In addition, the patient was diagnosed with focal seizures and thymoma. She was started on hydroxychloroquine, steroids, 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.

Case 4

⁸ 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. The patient has been on methylprednisolone for SLE since one month ago.

On physical examination, her temperature (37.3 °C),¹⁰ heart rate (72), respiratory rate (18), O₂ saturation (94%), and blood pressure (119/85) were in the normal range. The patient looked well-oriented and alert, with⁶ 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 strength¹ 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.

²⁴ The initial laboratory results showed a hemoglobin level of 8.5 g/dl, MCV of 79.76 μm³, RBC of 3.055*10⁶/ul, white blood cells of 3.891/ul, CRP titer of 32.8mg/l, D-Dimer of 1162.7ng/mL, APTT 24.2 seconds, Control 25 seconds, C3 of 91mg/dl, and C4 of 13.4mg/dl. The immunological tests showed ds-DNA-IgG >150 IU/mL (positive) and ds-DNA-IgM of 18.5 IU/mL (negative).

The chest CT angiography showed a small-branch filling defect in the segmental portion of³⁰ the right lower lung lobe artery, representing a segmental pulmonary embolism. The brain CT showed no intracranial hemorrhage, and the brain MRI revealed small acute lacunar infarction scattered at both cerebral hemispheres and the right side of the cerebellum (Figure 1). The patient was diagnosed with acute ischemic stroke and was given t-PA at the first three hours of disease onset without complication. On admission,³⁹ she received steroids, hydroxychloroquine, and therapeutic-dose anticoagulation. She was discharged from the hospital after five days in good general condition.

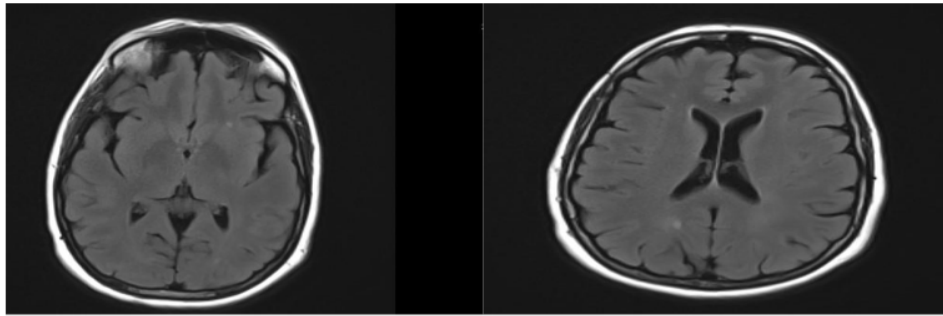


Figure 1

Brain MRI revealed a small acute lacunar infarction scattered at both cerebral hemispheres and the right side of the cerebellum.

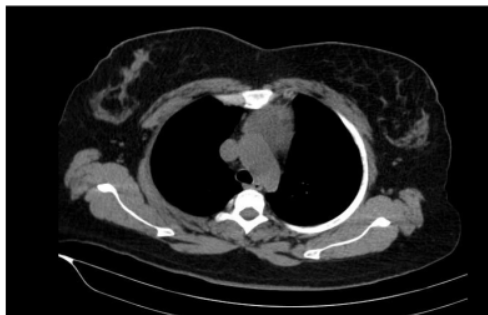


Figure 2

A chest CT showed an enlarged thymus gland.

Discussion

Systemic Lupus Erythematosus (SLE) can affect multiple systems and present with different clinical manifestations. However, the most common or ³⁸ affected were skin, bones, muscles, tendons, serosal, renal, and hematological. The neurological and psychiatric clinical presentation of systemic lupus erythematosus ²⁹ (SLE) has various groups of conditions and variable clinical manifestations. ⁷ The incidence of neuropsychiatric systemic lupus erythematosus (NPSLE) ranged from 10.6% to 96.4%.

²¹ The American College of Rheumatology (ACR) ⁴¹ nomenclature identified 19 neuropsychiatric syndromes in SLE, which are divided into central (12) and peripheral (7), whether diffuse or focal ³² 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. ⁸ 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%).⁹

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 the 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%.¹⁰ 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.¹¹ Here we present two cases of seizure related to SLE; one of them had a tonic-clonic seizure after three days of SLE diagnosis, and another 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.¹² Our first patient had PRES beside a seizure, which may be the most important risk factor for 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 a 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%.

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.¹⁴ Many causes can induce RPES disease, for example, hypertension, chronic renal failure, and some drugs. Although RPES related to connective tissue disease was a rare cause, it was reported. The pathophysiology of PRES in SLE is still unclear.¹⁴ 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.¹⁴ The most common clinical manifestations include headaches, seizures (almost the first clinical symptom), disorders of consciousness, and visual disturbances.¹⁵ Here we report a case of PRES with an initial presentation of seizures and an acute manifestation 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 DNA-anti-DNA immune complexes precipitation in the choroid plexus of the lateral ventricles and was hypothesized to the low cerebrospinal fluid (CSF) levels of complement during active central nervous system (CNS) disorder. Another hypothesis was reported that vasculitis could be an explanation for SLE meningitis by autoreactive antibodies. Some studies suggested that drugs used in SLE treatment could induce aseptic meningitis as hydroxychloroquine or nonsteroidal anti-inflammatory drugs (NSAIDs).¹⁶ 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 the 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.¹⁷

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.

Conclusion

The neurological manifestations of systemic lupus erythematosus (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, the morbidity and mortality rate are still high in neuropsychiatric lupus (NPSLE) patients compared to other patients who have the same disease.

Source of funding

The study did not receive any funding.

Ethical approval

This study is exempt from ethical approval at our hospital.

Consent

Written informed consent was obtained from the patient for reporting this case. The consent is available for review on request.

Authors' contributions

Data collection: Aseel Abuhammad

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Study concept or design: Aseel Abuhammad

Review & editing the manuscript: Yousef Mahmoud Nimer Habes

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Registration of research studies

N/A.

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Declaration of competing interest

There is no conflict of interest to declare.

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