Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multiple organs, characterized by the production of autoantibodies and the development of tissue injury. The etiology of SLE is partially known and involves multiple genetic and environmental factors. As many as 50% of patients with SLE have neurological involvement during the course of their disease. Neurological manifestations are associated with impaired quality of life and high morbidity and mortality rates. Nineteen neuropsychiatric syndromes have been identified associated with SLE, and can be divided into central and peripheral manifestations. This article reviews major neuropsychiatric manifestations in patients with SLE and discusses their clinical features, radiological findings and treatment options.

Keywords: systemic lupus erythematosus; lupus vasculitis, central nervous system; seizures; myelitis; autoimmune diseases.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease involving multiple organs, characterized by the production of autoantibodies and the development of tissue injury. The etiology of SLE is partially known and involves multiple genetic and environmental factors. Systemic lupus erythematosus more often affects non-White women of reproductive age and more severe forms are seen in people of African descent, Asians, Hispanics, and Indians.

The pathogenesis of SLE is characterized by immune abnormalities including T-cell and B-cell hyperactivity, abnormal number and function of regulatory T cells, and immune complex deposition in various tissues. A characteristic feature of SLE is the production of autoantibodies against double-stranded DNA, histones and nucleosomes, and other chromatin components. In addition, immune complex and apoptotic cell removal is impaired. These abnormalities could lead to the extracellular presence of chromatin triggering immune cells and activation of the innate and adaptive immune system.

As many as 50% of patients with SLE have neurological involvement during the course of their disease. Approximately 40% of neuropsychiatric SLE (NPSLE) cases are a consequence of the disease itself; other causes of NPSLE are infections, metabolic disorders, and side effects of drugs. We review the major NPSLE manifestations and discuss their clinical features, radiological findings, and treatment options.
NEUROPSYCHIATRIC SYSTEMIC LUPUS ERYTHEMATOSUS

The American College of Rheumatology identified 19 neuropsychiatric syndromes in SLE patients that can be divided into central and peripheral nervous system manifestations (Table 1). Although this classification includes syndromes with no clear physiopathological mechanism and is not specific for neuropsychiatric events caused exclusively by SLE, it helps the physician recognize any neurological involvement.

NPSLE may be the first manifestation of the disease and its prevalence ranges from 21% to 95%5,6. Central nervous system (CNS) syndromes are more common than peripheral and may be further classified into diffuse or focal manifestations7. Patients may present with single or multiple neuropsychiatric events, which may not relate to systemic disease activity5.

Risk factors associated with NPSLE include CNS damage or generalized SLE activity; previous neuropsychiatric events or other concurring neuropsychiatric manifestations; the presence of moderate to high titers of antiphospholipid antibodies (aPL) such as lupus anticoagulant and antiphospholipin, or anti-β2 glycoprotein 1 (either IgG or IgM), especially in cerebrovascular disease, myelopathy, cognitive dysfunction, seizures and movement disorders; and anti-ribosomal P protein antibodies (anti-P antibodies), that have been associated with lupus psychosis in some studies6,7,8,9.

Neurological manifestations are associated with impaired quality of life, and high morbidity and mortality rates. Notably, involvement of the lungs, kidneys and CNS can cause serious sequelae6. Since there are no biomarkers of CNS activity, the diagnosis of NPSLE is often made by ruling out secondary NPSLE. Potential pathogenic mechanisms in primary NPSLE are direct action of intrathecal inflammatory cytokines, blood-brain barrier (BBB) disruption, accelerated atherosclerosis and thrombotic vasculopathy caused by aPL antibodies2. Autoantibodies may also bind to neurons leading to neuronal dysfunction and apoptosis7,10 (Table 2).

Headache

Headache is a common, non-specific symptom for SLE or other rheumatic diseases. Although tension-type headache is the most frequent primary headache syndrome in the general population, there are reports of higher prevalence of migraine in SLE when compared to controls11,12. Nonetheless, a recent meta-analysis did not confirm this finding11. Headache in SLE is not associated with a higher frequency of magnetic resonance imaging (MRI) lesions, disease activity, and biomarkers such as aPL, anti-P, and glutamate receptor antibodies (anti-NR2)2,13.

Non-steroidal anti-inflammatory drugs and triptans can be used for pain relief. Migraine prevention therapy are β-blockers, anticonvulsants such as valproic acid and topiramate, and antidepressants15.

Table 1. Nineteen case definition for NPSLE syndromes.

<table>
<thead>
<tr>
<th>Central nervous system</th>
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<tbody>
<tr>
<td>Headache</td>
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<tr>
<td>Seizure disorders</td>
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<tr>
<td>Cerebrovascular disease</td>
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<tr>
<td>Demyelinating syndrome</td>
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<tr>
<td>Myelopathy</td>
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<tr>
<td>Movement disorder</td>
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<tr>
<td>Aseptic meningitis</td>
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<td>Cognitive dysfunction</td>
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<tr>
<td>Mood disorder</td>
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<tr>
<td>Anxiety disorder</td>
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<tr>
<td>Psychosis</td>
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<tr>
<td>Acute confusional state</td>
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<tr>
<td>Peripheral nervous system</td>
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<tr>
<td>Mononeuropathy</td>
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<tr>
<td>Polyneuropathy</td>
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<tr>
<td>Cranial neuropathy</td>
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<tr>
<td>Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)</td>
</tr>
<tr>
<td>Plexopathy</td>
</tr>
<tr>
<td>Autonomic disorder</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
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</table>

NPSLE: Neuropsychiatric systemic lupus erythematosus.

Table 2. Know autoantibodies association with NPSLE.

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>Syndromes</th>
<th>Source</th>
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<tbody>
<tr>
<td>LA</td>
<td>CVD, CD, seizures</td>
<td>Sciascia, 2014</td>
</tr>
<tr>
<td>aCL</td>
<td>CVD, CD, seizures and epilepsy</td>
<td>Sciascia, 2014</td>
</tr>
<tr>
<td>aβ2GPI</td>
<td>Angina and arterial or venous thrombosis</td>
<td>Sciascia, 2014</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>ACS</td>
<td>Hirohata, 2014</td>
</tr>
<tr>
<td>Anti-P</td>
<td>Psychosis</td>
<td>Bonfa, 1987; Sciascia, 2014</td>
</tr>
<tr>
<td>Anti-NMDA</td>
<td>CD</td>
<td>Faust, 2010</td>
</tr>
<tr>
<td>Anti-NR2</td>
<td>CD</td>
<td>Lauvsnes, 2014</td>
</tr>
<tr>
<td>AQP4</td>
<td>NMO</td>
<td>Bertias, 2010</td>
</tr>
</tbody>
</table>

Cognitive dysfunction

Cognitive dysfunction (CD) is defined as a cognitive decline from a previous level of mental functioning documented by neuropsychological assessments adapted to the target population. The main cognitive domains found to be compromised in SLE are attention, processing speed and memory. The American College of Rheumatology recommends a one-hour neuropsychological battery for CD evaluation in SLE patients. It assesses simple and complex attention, verbal and visual memory, visual spatial processing, language (verbal fluency), reasoning/problem solving, psychomotor speed and executive function (Table 3).

Cognitive decline is defined by scores that fall between 1.5 and 1.9 standard deviations below the mean in one or more cognitive domains. Cognitive impairment is defined by scores that fall 2.0 standard deviations below the mean. Cognitive dysfunction is defined as focal if impairment exists on measures within one domain, or multifocal if impairment exists on measures spanning two or more domains. Screening tests, i.e. Mini Mental State Examination, are non-specific and have low diagnostic sensitivity for CD. Despite that, the Montreal Cognitive Assessment is an appropriate screening tool for CD because it features a frontal subcortical profile of cognitive impairment in SLE. In American patients with SLE, the Montreal Cognitive Assessment tool had a sensitivity of 83% and specificity of 73% for CD using a cutoff score of 26.

Cognitive dysfunction in SLE is associated with aPL antibodies, steroid use, diabetes and low level of education. Although depressive symptoms may reduce cognitive function, CD is not fully explained by depression. In a comparison of neuropsychological scores between patients with depression and those with depression and SLE, the latter showed even lower scores.

Cerebral atrophy, white matter lesions and cerebral infarction have been correlated with the severity of CD. An apparently normal MRI in CD may be associated with microstructural and metabolic changes in white matter tissue suggesting potentially immune-mediated myelinopathy, which is best seen by spectroscopy and other advanced MRI techniques. The pathophysiology of CD remains to be fully understood and may involve vascular abnormalities, intrathecal inflammatory cytokines and BBB disruption. Autoantibodies might also contribute to the pathogenesis of CD in SLE. Systemic lupus erythematosus patients with lupus anticoagulant are three times more likely to have impaired neuropsychological functioning, with working memory dysfunction, probably due to white matter changes and microvascular thrombosis. Murine models have shown that anti-NMDA antibodies elicit neuronal death producing CD and emotional disturbance. A recent study has shown higher levels of anti-NR2 antibodies in the CSF and reduced hippocampal gray matter in SLE patients when compared with controls.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Domains</th>
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<tr>
<td>North American Adult Reading Test</td>
<td>Premorbid IQ</td>
</tr>
<tr>
<td>Digit Symbol Test</td>
<td>Processing Speed</td>
</tr>
<tr>
<td>Trail Making Test</td>
<td>Attention</td>
</tr>
<tr>
<td>Stroop Color Test</td>
<td>Complex Attention</td>
</tr>
<tr>
<td>California Verbal Learning Test</td>
<td>Verbal Memory</td>
</tr>
<tr>
<td>Rey Complex Figure</td>
<td>Visual Memory</td>
</tr>
<tr>
<td>Letter Number Sequencing</td>
<td>Working Memory</td>
</tr>
<tr>
<td>Controlled Oral Word Association Test</td>
<td>Phonemic Verbal Fluency</td>
</tr>
<tr>
<td>Animal Naming</td>
<td>Semantic Verbal Fluency</td>
</tr>
<tr>
<td>Finger Tapping</td>
<td>Motor Speed</td>
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</table>

SLE: systemic lupus erythematosus.

Figure 1. Cortical atrophy in SLE. A 32-year-old female with SLE had a prior stroke due to SLE vasculitis. After four years, she developed mononeuritis multiplex and cognitive impairment. She was negative for aPL antibodies. (A) Brain MRI T1 sequence. Observe the Sylvian fissure. (B, C) Global cortical atrophy.
The treatment for CD remains uncertain. Identification and management of secondary or exacerbating causes of CD is recommended. Patients may respond to methylphenidate or prednisone (0.5 mg/kg). Aspirin is only indicated for patients with cardiovascular comorbidities to improve cognitive performance; and memantine, an NMDA-receptor antagonist, prevents cognitive impairment from anti-NR2 antibodies in the murine model, but it has not been effective in SLE patients. Cognitive rehabilitation and psychoeducation are complementary treatments that can help improve subjective and objective cognitive complaints.

Seizures
Epilepsy occurs in 12% to 22% of patients with SLE and is associated with increased morbidity and mortality. A single isolated seizure is more frequently seen and a generalized tonic-clonic seizure is the most common type (67% to 88%), but a simple partial and complex seizure can also occur. Abnormalities on the EEG are common (60% to 70%) in SLE, and epileptiform EEG patterns suggest the seizure is likely to recur (73% positive predictive value, 79% negative predictive value). Patients with seizures show more gray matter hyperintensities on MRI images and may develop brain atrophy.

Inflammatory processes are believed to play a major role in the pathogenesis of epileptic seizures. Ischemic vascular disease and antibodies that bind to cerebral tissues such as anticardiolipin and anti-Sm have been associated with seizures. Epilepsy in SLE has also been associated with APS, disease activity, multiple NPSLE manifestations (i.e., psychosis, stroke), and severe baseline organ damage. Although seizure is classified as a diffuse CNS manifestation, it may develop in focal and inflammatory NPSLE. For that reason, the evaluation of patients with seizures should include brain imaging and CSF analysis to rule out infections, vasculitis, and mechanisms suggestive of focal NPSLE.

Posterior reversible encephalopathy syndrome is a clinical-radiological syndrome characterized by seizures, altered mental status, and visual impairment. It is an uncommon condition with a good prognosis, usually reversible and rarely recurrent. An MRI in this syndrome shows bilateral asymmetrical isointensities or hypointensities in T1, hyperintensities in T2 and fluid-attenuated inversion recovery sequences in the parietal-temporal-occipital regions. Approximately 50% of patients require treatment with both anticonvulsants and antihypertensive drugs.

Long-term anticonvulsants are recommended for patients with recurrent seizures or risk of recurrence (i.e., recurrent seizures in 24 hours, EEG abnormalities, prior brain injury with structural abnormalities in brain MRI). Immunosuppressive therapy is indicated for those with systemic disease activity.

Acute confusional state
Acute confusional state is a disturbance in consciousness or alertness, and subsequent attentional deficits that are accompanied by cognitive decline and/or affect or mood changes. It has been associated with the presence of anti-NR2 antibodies and anti-Sm antibodies in the CSF. The pathogenic mechanism behind this diffuse neuropsychiatric manifestation seems to be primarily inflammatory with increased production of inflammatory mediators, BBB disruption, and intrathecal immune complex formation. Risperidone (2 mg/day) may be a therapeutic option for an acute confusional state. Yet, corticosteroids and immunosuppression should be considered depending on the patient’s condition.

Psychosis, depression and anxiety
A systematic review found a prevalence of 17% to 75% of depressive disorders among patients with SLE. Mood disorders were associated with disease activity, high prednisone doses (≥ 20 mg), cutaneous disease, and longitudinal extensive transverse myelitis. Adverse drug events may also contribute to the occurrence or exacerbation of depressive symptoms in some patients. There is no evidence on the use of neuroimaging or serological markers for diagnosing mood and anxiety disorders, although anti-P and anti-NMDA receptor autoantibodies have been associated with a higher incidence of depression in patients with SLE. Serum levels of tumor necrosis factor alpha are also increased in SLE patients with mood and anxiety disorders suggesting the role of inflammation in depression.

Anti-P antibodies have been specifically associated with psychosis in patients with SLE, although some studies have failed to verify this association. High levels of anti-P antibodies found in serum samples of SLE patients with psychosis were compared to those of SLE patients with other neuropsychiatric manifestations, patients with non-SLE psychosis, and controls. Anti-P antibody levels were 5- to 30-fold higher during the active phase of SLE psychosis, but not during other SLE manifestations. In fact, several in vivo and in vitro studies have shown that anti-P antibodies can bind to neuronal antigens, penetrate neuronal cells, and inhibit protein synthesis in neuronal cells including in hippocampal neurons. Moreover, a recent study has shown that anti-P antibodies interact with neuronal antigens leading to neuronal apoptosis.

Both psychosis and major depressive disorders due to SLE are rare, while steroid-induced psychosis is an uncommon side effect. Glucocorticoids and immunosuppressive therapy may be considered for psychosis associated with SLE, especially in the presence of generalized disease activity.

Cerebrovascular disease
Cerebrovascular events account for 10% to 15% of deaths in SLE patients. Ischemic stroke (IS) is the most common condition. Patients with SLE have a twofold increase in the risk of IS, a threefold increase in the risk of intracerebral stroke, and a fourfold increase in the risk of subarachnoid hemorrhage compared to the general population. Intracerebral and subarachnoid hemorrhages are
infrequent in SLE patients, and affect mostly young individuals. They usually occur in the first year following the diagnosis, and result in high mortality and long-term morbidity\(^3\).

Systemic lupus erythematosus disease severity, hypertension and hyperlipidemia were independent predictors of stroke and stroke severity in a follow-up study\(^3\). However, traditional risk factors do not fully explain the high prevalence of IS in patients with SLE. Accelerated atherosclerosis, and inflammatory mediators such as complement components, cytokines and aPL antibodies may also play a role in the development of cerebrovascular disease\(^4\). It is noteworthy that high cumulative doses of steroids could also be a risk factor for accelerated atherosclerosis, leading to increased risk of stroke\(^3\). Vasculitis is a rare cause of stroke in SLE, accounting for 7% of cases in some case series.

Patients with SLE and stroke should be routinely screened for APS, which is characterized by the presence of aPL antibodies, (arterial or venous) vascular thrombosis and pregnancy complications including eclampsia or pre-eclampsia and miscarriage\(^3\) (Figure 2). Stroke in APS is either thrombotic or embolic\(^3\). Patients with SLE and APS may also present with renal involvement and valvulopathy due to immune complex deposition. One-third or more of APS strokes are due to embolism associated with cardiac valve vegetations, and some patients may have sterile endocarditis\(^3\).

A recent systematic review pointed to a fivefold increase in the risk of IS or transient ischemic attack in patients with aPL antibodies compared to controls\(^3\). The RATIO (Risk of Arterial Thrombosis in Relation to Oral Contraceptives) study showed that lupus anticoagulant is a major risk factor for IS, particularly in young women. Anti-β2-glycoprotein is also associated with higher IS risk\(^3\). Lupus anticoagulant is a stronger predictor of thrombosis compared to anticardiolipin and usually involves large and small vessels.

Modifiable risk factors should be focused upon as part of primary and secondary IS prevention strategies for patients with SLE\(^3\). Long-term oral anticoagulant is recommended for patients with APS and SLE, to prevent recurrence of both arterial and venous thrombosis, and also for patients with a high-risk cardioembolic source. Glucocorticoids and immunosuppressive therapies do not reduce the risk of IS\(^3\).

**Movement disorders**

Movement disorders are uncommon neuropsychiatric manifestations in SLE. Nonetheless, parkinsonism, myoclonus and dystonia were described and an autoimmune or thromboembolic disease mechanism has been proposed for their occurrence\(^3\). Chorea is the most described manifestation and may be the first manifestation in SLE occurring in 2% of adult patients, predominantly in women. It can be unilateral or bilateral and remit spontaneously. Current evidence suggests an autoimmune mechanism related to aPL antibodies, but focal cerebral ischemia is rarely evidenced\(^3\).

Sydenham chorea is the most common cause of acute chorea in children and it is one important differential diagnosis in chorea associated with lupus, especially in pediatric patients. Sydenham chorea is an autoimmune disorder and most cases develop following a rheumatic fever or streptococcal infection\(^3\). Sydenham chorea and lupus may have similar findings in brain single-photon emission computed tomography. Both diseases showed hyperconcentration of the radiotracer in the basal ganglia, possibly due to changes in the basal ganglia microcirculation or to a BBB abnormality secondary to the inflammatory process\(^3\).

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**Figure 2.** Large vessel thrombosis in antiphospholipid syndrome. (A) Digital arteriography showing normal left carotid artery. (B) Right carotid thrombosis in an SLE patient with stroke and positive lupus anticoagulant antibodies.
Painful muscular weakness may occur in children or adult patients. Dopaminergic drugs as well as immunomodulatory therapy may improve their symptoms. Antiphospholipid syndrome-related parkinsonism is associated with vasculopathy, poor response to levodopa and cerebral infarction. Systemic lupus erythematosus patients with APS may also present with tremor, tics, myoclonus and corticobasal degeneration-like syndrome.52

Focal dystonia including torticollis and blepharospasm have also been reported. They may respond to immunomodulatory therapies. Some patients with SLE may have complex movement disorders including an association of hypokinetic and hyperkinetic manifestations that are frequently associated with other neuropsychiatric symptoms.45

**Aseptic meningitis**

The incidence of aseptic meningitis in SLE patients has been estimated at 1.4% to 1.6% in retrospective studies. It can occur at any time during the disease course, usually during flares.52,53 Because patients are often receiving immunosuppressant agents, bacterial, viral, fungal and tuberculosis infection must be ruled out.45 Clinical features of aseptic meningitis include headache and altered mental status. Cerebrospinal fluid analysis may reveal lymphocytic cells and protein. Although spontaneous remission may occur, most cases are effectively treated with glucocorticoids and immunosuppressive therapy.8

**Myelopathy**

Lupus myelitis occurs in 1% to 1.5% of cases.44 It manifests as transverse myelitis or asymmetrical spinal cord syndrome with hemiparesis, tetraparesis, bladder involvement, neuropathic pain, and presence of a sensory level. Acute transverse myelitis is the first clinical manifestation in nearly half of the patients with SLE and it usually occurs within the first five years after diagnosis.44 Underlying pathophysiological mechanisms are not yet known. Histopathology findings have revealed ischemic/thrombotic myelopathy (especially in acute cases) or localized acute inflammation.44

Systemic lupus erythematosus myelitis has two distinct clinical patterns: gray-matter and white-matter myelitis. Patients with gray-matter myelitis often have a prodromal phase of fever and urinary retention at onset that rapidly evolves to paraplegia during disease activity. An MRI reveals spinal cord swelling and enhancement.45 White-matter myelitis has been associated with a less severe presentation and slower progression, characterized by upper motor neuron spasticity and hyperreflexia.45

The CSF analysis may show mild pleocytosis exceeding 10 cells/mm³, but polymorphonuclear predominance has also been reported. There is often an elevation of IgG in CSF.44 An MRI may show increased signal and longitudinal extensive transverse myelitis involving at least three vertebral segments has been observed in 91.7% of gray-matter myelitis.45 There may be no MRI abnormalities in some cases. Approximately 30% of patients may have brain involvement, and therefore it is advisable to perform brain MRI.44

There may also be a co-occurrence of SLE with neuromyelitis optica (NMO). So patients should be tested for NMO-IgG anti-aquaporin 4 (AQP4) antibodies. Neuromyelitis optica-IgG is positive in 10% of SLE cases with myelitis and approximately 20% of patients may fulfill clinical criteria for NMO as reported in some series. Because myelitis in SLE may respond to cyclophosphamide whereas patients with NMO tend to have a worse outcome, it is important to test patients at the first manifestation of the disease before immunosuppression and to repeat it during the disease course (Figure 3).

In the presence of myelitis, overlap of APS, Sjögren's syndrome, and NMO should be investigated. The prevalence of aPL ranges from 18% to 60% in SLE patients with myelitis. Spinal cord necrosis secondary to thrombosis has been proposed as an etiological factor for transverse myelitis in SLE.52

Treatment involves therapy with high-dose steroids followed by intravenous cyclophosphamide. The addition of plasmapheresis to a regimen of intravenous cyclophosphamide and steroids led to higher remission rates.52 Relapse of lupus-associated acute transverse myelitis is common (50–60%) during steroid tapering. Severity of neurological impairment (muscle strength < 3/5) is the most important prognostic variable. Other prognostic variables in SLE-associated myelitis are urinary catheter use at the neurological nadir and no cyclophosphamide therapy. Only a small proportion of patients fully recover.

**Peripheral nervous system involvement**

Some SLE patients may present with peripheral nervous system involvement (2–3%) (Table 1). Clinical symptoms include combined paresthesia, pain, autonomic dysfunction, peripheral ataxia, weakness, and atrophy. Peripheral neuropathy is most often seen in older patients at diagnosis, and those with CNS manifestations and active systemic disease. Differences in disease activity may account for variation in the frequency and spectrum of peripheral neuropathies in different cohorts.57,48 Electroneuromyography can help identify neurophysiological patterns. Analysis of the CSF is useful in inflammatory demyelinating polyradiculoneuropathy. Nerve biopsy is rarely useful in such patients.4

Mild distal symmetric axonal sensory or sensorimotor neuropathy is the most common subtype of peripheral involvement, whereas mononeuropathies are the second most common presentation. Patients may present with sudden weakness requiring aggressive immunosuppressive therapy. Although small-fiber neuropathy is not included in the American College of Rheumatology definitions, Oomatia reported a prevalence of 17.1% in SLE patients with peripheral involvement.54,55 Electrodiagnostic studies are usually normal and a skin biopsy demonstrates loss of intraepidermal nerve fibers. There are two distinct clinicopathologic
Alessi H et al. Neuropsychiatric Lupus

entities: length-dependent, small-fiber neuropathy with a
stocking-and-glove distribution and abnormal skin biopsy
findings restricted to the distal leg and non-length-depen-
dent, small-fiber neuropathy with an unorthodox pattern
of patchy, asymmetric, and proximal neuropathic pain that
can affect the face, torso, and proximal extremities.

Mononeuritis multiplex is found in 33% of SLE patients
with peripheral involvement, usually with sudden weakness
in different nerve territories. It can occur at any time dur-
ing disease course, either at the onset of SLE or later dur-
ing its evolution. In most cases, the onset was dramatic
with sudden weakness in different nerve territories. These
patients, in general, had substantially higher disease activity,
showed more severe deficits and often required more aggres-
sive immunosuppressive therapy.

Chronic inflammatory demyelinating polyneuropathy and
acute inflammatory demyelinating polyneuropathy are severe. Forms of chronic inflammatory demyelinating
polyneuropathy can present before or at the onset of another
clinical manifestations of SLE. Acute inflammatory demy-
elinating polyneuropathy, an ascending motor radiculoneu-
ropathy that resembles Guillain-Barré syndrome clinically
and electrodiagnostically, is a relatively rare condition, affect-
ing up to 1% of the lupus patients.

Symptomatic therapy alone may be considered for mild
peripheral neuropathy, especially when there is no motor
impairment. Glucocorticoids alone or together with immu-
nosuppressive therapy have been used with good outcomes
(60–75% response rate). Intravenous immunoglobulin,
plasma exchange, and rituximab have been used in severe
and refractory cases.

Cranial neuropathies

Cranial neuropathies may involve the eighth nerve, the
oculomotor nerve (third, fourth and sixth), and less com-
monly the fifth and the seventh nerves. Cranial neuropathies

Figure 3. Myelitis in SLE. (A, B, C) Brain MRI fluid-attenuated inversion recovery sequence. Arrows: extensive myelitis extending to
the area postrema in the dorsal medulla. (D) Axial T2 sequence showing spinal cord involvement in the dorsal region. (E) Sagittal
T2 sequence. Arrows: Observe the multiple lesions, one involving more than three spinal segments. (F) Sagittal T1 sequence; pial
contrast enhancement. Patient with SLE and APS negative for AQP4, had an isolate demyelinating episode, was treated with
plasmapheresis, cyclophosphamide and steroids with complete recovery.
have been reported in 5–42%, rarely as an isolated manifestation55. When the oculomotor, trochlear and abducent nerves are involved, myasthenia gravis should be ruled out. Different mechanisms have been proposed such as vasculitis secondary to SLE, microinfarction of the capillaries or arterioles in the temporal bone, and thrombosis in the otologic region56. Autoimmune sensory neural hearing loss in SLE is associated with a poor prognosis.

Optic neuropathy is infrequent (<1%) and can manifest as optic neuritis and ischemic/thrombotic optic neuropathy, which is usually unilateral and related to aPL57. Only 50% of patients with SLE-associated optic neuritis recovered complete visual acuity (visual acuity better than 20/25)58. Bilateral or chiasm involvement, severe pain accentuated by ocular movements and profound visual impairment are characteristic of SLE-associated optic neuritis. The differential diagnosis includes NMO and multiple sclerosis.

More recently, studies with small samples reported a frequency of audiovestibular symptoms between 25% and 67% in SLE patients59,60. Such manifestations include sensorineural hearing loss, often accompanied by vertigo and tinnitus and other symptoms compatible with Menière’s disease60. Autoimmune sensory neural hearing loss in SLE is associated with a poor prognosis.

Patients with SLE may present with asymptomatic cranial neuropathies, and the eighth nerve is the most commonly affected, followed by the seventh, the second, and the fifth nerves. Anti-ribosomal P protein and anti-DNA antibodies are associated with such subclinical manifestation55.

In conclusion, NSLE exhibits variable clinical manifestations and a heterogeneous disease course and prognosis. Since there are no biomarkers for CNS involvement and disease activity, diagnosis should be based on clinical features as well as imaging and laboratory findings. Central nervous system infections, metabolic abnormalities, valvular heart disease, and adverse drug effects should be ruled out. All patients with NPSLE should be routinely screened for APS, since overlap may occur even in non-ischemic manifestation.

For therapeutic purposes, the most important decision is to classify primary NPSLE into either ischemic or inflammatory phenotypes and treatment should be individualized61. Severe inflammatory phenotypes should receive immunosuppressant and/or steroid therapy, whereas ischemic phenotypes should receive aspirin or anticoagulation. In mild cases, therapy consists of antidepressants, anticonvulsants, or antipsychotics only.

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References


