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Neuropsychiatric Lupus: A Review of Clinical Features and Treatment Strategies

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Abstract

Neuropsychiatric lupus, also known as neuropsychiatric systemic lupus erythematosus (NPSLE), is a subset of systemic lupus erythematosus (SLE) that affects the central nervous system, leading to a range of neurological and psychiatric symptoms. It occurs in approximately 25-75% of SLE patients, varying prevalence across populations. NPSLE primarily affects women of childbearing age but can occur in individuals of any age or gender, with a higher prevalence among non-Caucasian populations and those with severe SLE symptoms. The exact cause of NPSLE is complex, involving immune dysregulation, autoantibody production, and central nervous system inflammation. Autoantibodies, such as anti-phospholipid and anti-NMDA receptor antibodies, may significantly affect neurological symptoms. Immune-complex deposition and proinflammatory cytokines within the brain contribute to the disease's pathophysiology. NPSLE encompasses many symptoms, including cognitive impairment, mood disorders, psychosis, seizures, and headaches. Diagnosis relies on clinical evaluation, neuroimaging, cerebrospinal fluid analysis, and autoantibody testing. A multidisciplinary approach involving rheumatologists, neurologists, and psychiatrists is often necessary. Treatment for NPSLE is tailored to the specific symptoms and their severity. It typically involves immunosuppressive therapies like corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and sometimes biological agents. Adjunctive therapies, including antiepileptic drugs, antipsychotics, and antidepressants, may be necessary for symptom management. Regular monitoring and follow-up are crucial to assess treatment response.

The article discusses the epidemiology of SLE and NPSLE, emphasizing the variability in prevalence across different populations. It highlights the challenges in diagnosing NPSLE due to its diverse and often nonspecific symptoms. Various diagnostic criteria and biomarkers are discussed, emphasizing the need for a personalized diagnostic approach. The article also covers the differential diagnosis of NPSLE, distinguishing it from other autoimmune diseases, infections, and medication-induced symptoms. Regarding prognosis, NPSLE is associated with a poorer quality of life and increased mortality compared to SLE without neuropsychiatric involvement. Specific factors, such as anti-ribosomal P antibodies and acute confusional states, are linked to worse outcomes. Mortality in NPSLE is often due to infections.

Neuropsychiatric lupus is a complex condition characterized by neurological and psychiatric symptoms. Early diagnosis and multidisciplinary management are essential to improve outcomes and the quality of life for patients with NPSLE. Further research is needed to understand its pathogenesis and improve diagnostic and treatment strategies.

Keywords: Neuropsychiatric Lupus; Systemic Lupus Erythematosus; Neuropsychiatric Systemic Lupus Erythematosus; Immune Dysregulation; Central Nervous System; Immune-complex deposition

Abbreviations: NPSLE: Neuropsychiatric Systemic Lupus Erythematosus; SLE: Systemic Lupus Erythematosus; CNS: Central Nervous System; DMARDs: Disease-Modifying Antirheumatic Drugs; IVIG: Intravenous Immunoglobulin; MRI: Magnetic Resonance Imaging; CSF: Cerebrospinal Fluid; MS: Multiple Sclerosis; APS: Antiphospholipid Syndrome; EULAR: European League Against Rheumatism; SLICC: Systemic Lupus International Collaborating Clinics

Introduction

Neuropsychiatric lupus, also known as neuropsychiatric systemic lupus erythematosus (NPSLE), is a subset of systemic lupus erythematosus (SLE) characterized by the involvement of the central nervous system. It encompasses a spectrum

of neuropsychiatric symptoms and manifestations that can significantly impact a patient's quality of life. NPSLE is relatively uncommon, occurring in approximately 25-75% of SLE patients, with variations depending on the population studied and the diagnostic criteria applied [1,2]. The disease predominantly affects women of childbearing age but can occur in individuals of any age or gender. The prevalence of NPSLE is higher among non-Caucasian populations and those with more severe SLE manifestations. The exact pathogenesis of NPSLE remains complex and multifactorial, involving immune dysregulation, autoantibody production, and inflammation within the central nervous system. Autoantibodies, such as anti-phospholipid, anti-NMDA receptor, and anti-ribosomal P antibodies, may play a pivotal role in developing neurological symptoms. Immune-complex deposition and proinflammatory cytokines within the brain parenchyma contribute to the pathophysiology of NPSLE [1-3].

NPSLE encompasses neurological and psychiatric symptoms, including cognitive impairment, mood disorders (e.g., depression, anxiety), psychosis, seizures, and headaches. Patients may present with focal neurological deficits, aseptic meningitis, or cerebrovascular events. Symptoms can be episodic and fluctuate, making diagnosis and management challenging [1,4]. The diagnosis of NPSLE is primarily clinical and relies on a combination of neurological and psychiatric assessments, neuroimaging studies, cerebrospinal fluid analysis, and excluding other possible causes of neuropsychiatric symptoms. Autoantibody testing, such as anti-dsDNA and anti-cardiolipin antibodies, can aid in diagnosis. A multidisciplinary approach involving rheumatologists, neurologists, and psychiatrists is often necessary for a comprehensive evaluation [5].

The management of NPSLE requires a tailored approach based on the specific neurological or psychiatric manifestations and their severity. Treatment typically involves immunosuppressive therapies, including corticosteroids, disease-modifying antirheumatic drugs (DMARDs), and, in some cases, biological agents. Adjunctive therapies such as antiepileptic drugs, antipsychotics, and antidepressants may be necessary to control specific symptoms. Regular monitoring and follow-up are essential to assess treatment response and adjust therapies as needed [3,6]. This narrative review aims to provide an overview of neuropsychiatric lupus's clinical features and treatment strategies. Despite the complexity of this condition, early diagnosis and multidisciplinary management can help improve outcomes and the quality of life for patients with NPSLE.

Epidemiology

Patients diagnosed with systemic lupus erythematosus (SLE) may experience neuropsychiatric clinical manifestations due to abnormalities affecting the central, peripheral, and autonomic nervous systems. Considerable heterogeneity exists in the published estimates of SLE occurrence, even when examining data from within a single country or geographical area [7]. The available evidence from cohorts of patients diagnosed with SLE indicates that approximately 50% of these individuals will experience neuropsychiatric manifestations of the disease at some point during their illness [8]. A comprehensive analysis of several studies completed worldwide over the past 15 years shows that SLE's prevalence varies between 9 and 241 cases per 100,000 person-years [7]. Similarly, the incidence of SLE ranges from 0.3 to 23.2 cases per 100,000 person-years. The observed variance may be attributable to genetic variation and exposure to environmental factors [7].

The American College of Rheumatology (ACR) categorization criteria for neuropsychiatric systemic lupus erythematosus (NPSLE) have gained significant acceptance in clinical research about NPSLE. Recent studies imply that SLE is responsible for 30 - 50% of all NP episodes in SLE patients, while the actual amount differs based on the type of NP event [8]. Some studies utilizing ACR criteria estimated the prevalence of NPSLE to be between 37% and 95%, though 90% of the estimate is pure CNS manifestations [7-9]. The prevalence of neuropsychiatric systemic lupus erythematosus (NPSLE) is estimated to be approximately 50 in 500,000 in the United States [8,9]. However, this statistic is challenging due to numerous study designs. The clinical manifestations of SLE can range from minor or organ-restricted disease to full-blown life-threatening illness. The most noted presentations of NPSLE were headache, mood disorders, cognitive dysfunction, seizures, cerebrovascular disease, and other minor nonspecific central nervous system (CNS) symptoms [7-9].

Pathogenesis

Two pathways have been proposed: an autoimmune or inflammatory pathway that causes damage to the blood-brain barrier through the deposition of unclean complexes and inflammatory mediators. And the ischemic route through thrombosis that causes cerebral microangiopathy. Autoantibodies are considered a possible culprit in the pathogenesis of NPSLE [10].

The mechanisms by which inflammation contributes to neuropsychiatric symptoms are unclear. Some lupus autoantibodies cross-react with the N-methyl-D-aspartate (NMDA) receptor, a brain glutamate receptor. These antibodies are increased in acute confusional states in lupus, but there are no clear correlations between can cause mood alterations and fatigue and autoantibodies in SLE [11]. Most cerebrovascular disorders in NeuroPsychiatric Lupus (NPSLE) are due to antiphospholipid antibodies (aPL) associated with developing thrombosis. In addition, aPL has been reported to be associated with headaches, chorea, transverse myelitis, and epileptic seizures [12,13]. Anti-DNA/NR2 and anti-ribosomal P antibodies are considered to target specific parenchymal structures in the brain and underlie the onset of NP manifestations. Anti-Sm antibodies (anti-Sm) and

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anti-U1-ribonucleoprotein antibodies (anti-RNP) are frequently found in patients with NPSLE. In addition, anti-aquaporin 4 antibodies (anti-AQP4), diagnostic markers for neuromyelitis optica spectrum disorder (NMOSD), contribute to NPSLE [14].

Experimental studies in humans show that inflammatory cytokines released by the immune system can cause mood disorders and fatigue, and animal studies show that these cytokines can alter behavior by acting directly on the brain and brain endothelium. However, it is unclear to what extent immune activation and cytokine release contribute to altered mood and fatigue in SLE [15].

Clinical Features

Neuropsychiatric manifestation of systemic lupus erythematosus (NPSLE) is incredibly challenging. NPSLE has diverse and highly heterogeneous clinical phenotypes, including headaches, psychiatric symptoms, and peripheral neuropathy [16]. The symptoms of NPSLE have been classified into 19 neuropsychiatric (NP) manifestations by the American College of Rheumatology (ACR). The defined 19 NP manifestations consisted of two major classifications: central nervous system (CNS) and peripheral nervous system. CNS manifestations are further divided into focal and diffuse [17]. These manifestations are listed in Table 1.

Table 1: Neuropsychiatric manifestation of SLE.

	Central nervous system (CNS)	Peripheral nervous system (PNS)
Diffuse manifestations	Acute confusional state Anxiety disorder Cognitive dysfunction Mood disorders Psychosis	
Focal manifestations	Aseptic meningitis Cerebrovascular disease Demyelinating syndrome Headache Movement disorder Myelopathy Seizures	Guillain-Barre syndrome Autonomic disorder Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy Cranial Plexopathy Polyneuropathy

Table adapted from the guidelines to define neuropsychiatric nomenclature by the American College of Rheumatology in 1999 [17].

The prevalence of NPSLE in patients with SLE is 30–40%. Additionally, 50–60% of these develop NPSLE within one year of the SLE onset [18]. The prevalence of each type of NPSLE significantly differs according to the study design followed. These discrepancies might be due to the ambiguity in diagnosing NP symptoms, especially those non-specific to SLE, such as headache or mood disorders. Cerebrovascular disorders and epileptic seizures are found in 5–15% of patients with NPSLE. Cognitive impairment, mood disorders, acute confusional state, or peripheral neuropathy are found in only 1–5% of patients. In contrast, psychosis, myelitis, involuntary movements of the limbs and facial muscles, and aseptic meningitis are extremely rare. In Systemic Lupus International Collaborating Clinic Criteria (SLICC) proposed in 2012 for the classification of SLE, epileptic seizures, psychosis, mononeuritis multiplex, myelitis, peripheral neuropathy, cranial nerve disorders, and acute confusional state are defined as the NP manifestations of SLE. In contrast, other types of NP symptoms, such as headaches, mood disorders, and cerebrovascular disorders, are excluded due to their low specificity [19]. In 2019, new classification criteria for SLE were proposed by the European League Against Rheumatism (EULAR)/ American College of Rheumatology (ACR) [20,21]. In the new criteria, only delirium, psychosis, and seizure are defined as the NP manifestations to improve specificity for diagnosis with SLE.

Diagnosis

The numerous clinical symptoms of neuropsychiatric lupus (NPSLE) can complicate obtaining an accurate diagnosis. Standard neuropsychiatric features of systemic lupus erythematosus (SLE) encompass cognitive dysfunction, mood disorders, seizures, and psychosis, which can manifest as focal or diffuse and vary in severity, making diagnosis complex [22]. Diagnosing neuropsychiatric lupus typically involves a comprehensive evaluation, including clinical assessment, neuroimaging, cerebrospinal fluid analysis, and laboratory tests. Physicians often rely on established criteria, such as the American College of Rheumatology (ACR) criteria and the Systemic Lupus International Collaborating Clinics (SLICC) criteria, to aid in diagnosis and classification [23].

Given the mild, nonspecific symptoms of NPSLE, absence of specific diagnostic markers, overlap with typical symptoms, comorbid conditions, potential medication side effects, and symptoms occurring independently from SLE activity, various biomarkers are employed in the diagnosis and treatment

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monitoring of NPSLE [24]. These include autoantibodies like antineuronal, anti-ribosomal P, anti-NR2 antibodies, chemokines, cytokines, and intrathecal levels of PAI-1 and MMP-9. It is crucial to rule out conditions that mimic NPSLE symptoms, such as infections or metabolic disorders. CSF analysis, including interleukin-6 levels, plays a role in differential diagnosis [25,26].

Assessment for neuropsychiatric lupus should be personalized. While neuroimaging is beneficial, it has limitations. Traditional MRI suits localized symptoms, whereas functional imaging is better for demonstrating perfusion and neurometabolic changes. However, more than half of NPSLE patients exhibit regular brain MRIs. Single photon emission computed tomography (SPECT), measuring cerebral blood flow, can be more sensitive than MRI for NPSLE, although research results vary. Functional MRI (fMRI) is also employed to assess cognitive function in SLE [25,26]. Various classification criteria, such as the American College of Rheumatology (ACR) criteria, have been developed to assist in NPSLE diagnosis based on specific clinical and laboratory features. Magro-Checa et al. proposed a diagnostic approach for NPSLE that aligns clinical symptoms with specific diagnostic tests or procedures. At the same time, attribution models have been devised to enhance diagnosis, considering their limitations [25,27].

Cognitive function and psychological well-being assessments can provide valuable information for diagnosis. Without more reliable diagnostic tools, identifying neuropsychiatric symptoms due to SLE depends on the clinician's judgment, suspicion, and clinical analysis. A comprehensive approach involving neuropsychological, radiological, laboratory assessments, and rheumatology evaluation enhances the accuracy of diagnosing NPSLE [24,29]. Distinguishing whether neuropsychiatric symptoms are directly caused by SLE or result from other factors like corticosteroid treatment or psychological burden is crucial for treatment decisions. Various models have been developed to enhance the identification of SLE-related neuropsychiatric symptoms [24,28]. Individualizing the diagnostic approach for each NPSLE patient is necessary because there's no one-size-fits-all method. The diverse signs and symptoms require a diagnostic algorithm that can be applied to a broad range of cases [24,29].

Differential diagnosis

Neuropsychiatric manifestations of systemic lupus erythematosus can vary, so its differential diagnosis becomes a challenge. The neuropsychiatric signs and symptoms of SLE are often relatively nonspecific. They may share many standard features with well-established psychiatric disorders, including paranoid and grandiose delusions as well as auditory and visual hallucinations, hyperactive and hypoactive delirium, anxiety, and depression.

Mood disorders and anxiety are prevalent among the general population, and their occurrence is higher in individuals with chronic illnesses. Unsurprisingly, a significant percentage of lupus patients, precisely 15%, experience mood disorders, while 5% develop anxiety disorders [30]. A meta-analysis conducted in 2017 on 59 studies involving a certain number of adult SLE patients showed that some studies, which used reliable clinical interviews such as DSM and/or ICD, found that 24% of SLE patients had major depression while 37% of them suffered from anxiety [31]. A proportion of psychotic events in lupus are temporally related to corticosteroid use. However, such observations are likely to be confounded by increases in systemic disease activity, which might precede increased steroid dose [32].

In addition to primary neuropsychiatric disorders, other autoimmune diseases should be ruled out, including multiple sclerosis (MS), antiphospholipid syndrome (APS), and autoimmune encephalitis. MS can present with focal neurological deficits and cognitive impairment, while APS may cause cerebrovascular events similar to those seen in NPSLE. Autoimmune encephalitis, characterized by autoantibodies targeting neuronal antigens, can manifest as seizures, psychosis, and cognitive dysfunction, closely mimicking NPSLE [33,34]. Furthermore, infectious causes of neuropsychiatric symptoms, such as neurosyphilis, HIV-associated neurocognitive disorders, and viral encephalitis, should be considered. Neurosyphilis can present with a wide range of neurological and psychiatric symptoms, while HIV-associated neurocognitive disorders can lead to cognitive impairment. Viral encephalitis can cause seizures and altered mental status, resembling certain NPSLE presentations [35,36,38].

Structural brain lesions, including brain tumors, stroke, and vascular diseases, can also produce neurological symptoms akin to NPSLE. Imaging studies, cerebrospinal fluid analysis, and thorough neurological assessments are vital in distinguishing these conditions from NPSLE [35,39]. Moreover, medication-induced neuropsychiatric symptoms should be considered, as certain drugs, such as corticosteroids or antiepileptic drugs commonly used to manage lupus, can lead to mood disturbances and cognitive changes [37,40].

Treatment strategies

Treating neuropsychiatric lupus, a complex facet of systemic lupus impacting the nervous system and cognitive function, demands careful consideration. This condition presents a diverse range of neurological and psychiatric symptoms, encompassing memory impairment, mood disorders, seizures, and, occasionally, psychosis. Given its multifaceted nature, a collaborative approach involving specialists such as rheumatologists, neurologists, and psychiatrists is often warranted to devise a tailored treatment strategy aligned with the patient's specific clinical presentation [41].

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The foremost objective in managing neuropsychiatric lupus centers on mitigating the underlying inflammatory and autoimmune processes, the condition's root causes [41]. Mild symptoms have been alleviated with immunosuppressive agents such as azathioprine and mycophenolate [42]. Treatment regimens may incorporate immunomodulator agents like high-dose corticosteroids, intravenous disease-modifying antirheumatic drugs (DMARDs)-cyclophosphamide, or biologic therapies to temper the hyperactive immune response and diminish inflammatory activity [42]. However, it is pertinent to acknowledge that these medications may entail side effects, necessitating vigilant surveillance and meticulous side effect management. In cases characterized by recalcitrance or severe manifestations, therapies such as intravenous immunoglobulin (IVIG), plasmapheresis, or rituximab might be contemplated to alleviate the burden of pathogenic antibodies [42,43]. Additionally, antiplatelet and anticoagulation agents have also been recommended by the European League Against Rheumatism (EULAR) committee in patients who carry antiphospholipid antibodies to try to prevent a thrombotic episode [41].

Concurrently, addressing the neuropsychiatric symptoms constitutes a vital aspect of treatment [42,43]. Pharmacotherapy may include antidepressants or antipsychotics for mood disturbances, acute confusional states and psychosis, and antiepileptic drugs for seizure control. Biofeedback-cognitive rehabilitation therapy, complemented by cognitive-enhancing strategies, proves beneficial for individuals grappling with cognitive dysfunction [41]. Routine follow-up with healthcare providers is essential for assessing the efficacy of treatment, managing potential side effects, and fine-tuning the therapeutic regimen to optimize outcomes for patients navigating the complexities of neuropsychiatric lupus.

Prognosis & Outcomes

Little is known about the outcome of neuropsychiatric (NP) involvement in systemic lupus erythematosus (SLE). However, it is generally associated with a poorer prognosis. Hanly JG et al. (2020) found that neuropsychiatric events significantly decrease the quality of life and increase mortality in SLE patients, with a 16% risk of death over 10 years for those with SLE-related events [44]. A study published in Modern Rheumatology (2019) emphasized the correlation between the anti-ribosomal P protein antibody and a heightened risk of death in patients with diffuse SLE NP involvement (NPSLE) [45]. A report from Seoul identified that NPSLE, especially of the focal type in the central nervous system, triples the mortality risk [46]. Zirkzee and his team pinpointed a high mortality rate in patients with acute confusional states and those diagnosed with NPSLE at older ages [47]. Jönsen et al., analyzing a Swedish cohort, observed that while mortality didn't show significant discrepancies, there was a pronounced work disability and a notable clinical impact of the neuropsychiatric manifestations in SLE patients compared to those without these manifestations [48]. Finally, Monahan et al. (2020) highlighted an increase in mortality in NPSLE patients compared to the general population, with infections being the leading cause of death [49].

Xue Li et al. (2019) outlined an overall survival of 89%, 85%, and 84% at 1, 3, and 5 years respectively, with a higher mortality in females. They also deduced that acute confusional states are linked to a worse prognosis, with a survival rate of 64% and 52% at 1 and 3 years, respectively. The latter, combined with elevated intracranial pressure (>250cmH2O), were independent prognostic factors for death [50]. According to another study by Shangzhu Zhang et al., a SLEDAI score >15, proteinuria, raised serum creatinine, and hypocomplementemia are independent prognostic factors for death [51]. In summary, systemic lupus erythematosus with neuropsychiatric manifestations (NPSLE) poses a challenging prognosis associated with diminished quality of life and heightened mortality. Despite identifying specific indicators, the comprehensive prognosis landscape calls for more detailed research.

Conclusion

Neuropsychiatric lupus, or neuropsychiatric systemic lupus erythematosus (NPSLE), represents a complex subset of systemic lupus erythematosus (SLE) characterized by central nervous system involvement. It encompasses a broad spectrum of neuropsychiatric symptoms that can significantly impact a patient's quality of life. While NPSLE is relatively uncommon, its prevalence varies depending on diagnostic criteria and the population studied, affecting mainly women of childbearing age and those with more severe SLE manifestations. The pathogenesis of NPSLE is multifactorial, involving immune dysregulation, autoantibody production, and inflammation within the central nervous system. Autoantibodies like anti-phospholipid, anti-NMDA receptor and anti-ribosomal P antibodies may be crucial in developing neurological symptoms. The clinical presentation of NPSLE is highly heterogeneous, including cognitive impairment, mood disorders, seizures, and more, often challenging diagnosis and management.

Diagnosing NPSLE relies on clinical assessments, neuroimaging, cerebrospinal fluid analysis, and excluding other potential causes of neuropsychiatric symptoms. Various autoantibodies and biomarkers can aid in diagnosis, but it remains a clinical challenge. A multidisciplinary approach involving rheumatologists, neurologists, and psychiatrists is crucial for accurate evaluation. The treatment of NPSLE necessitates a tailored approach based on the specific neurological or psychiatric manifestations and their severity. Immunosuppressive therapies aim to target the underlying autoimmune and inflammatory processes, including corticosteroids, disease-modifying

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antirheumatic drugs (DMARDs), and sometimes biologic agents. Adjunctive therapies, such as antiepileptic drugs, antipsychotics, and antidepressants, may be required to manage specific symptoms. Regular monitoring and follow-up are essential to assess treatment response and adjust therapies as needed.

It is important to note that NPSLE poses a challenging prognosis, potentially decreasing the quality of life and increasing mortality compared to SLE without neuropsychiatric involvement. The prognosis varies based on the specific manifestations and individual factors, and further research is needed to understand the long-term outcomes better and improve management strategies for this complex condition.

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