

Review

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Review

# Neurological Manifestations of Systemic Lupus Erythematosus: A Comprehensive Review

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**Abstract:** Neurological involvement in the course of Systemic Lupus Erythematosus (SLE) is a challenging for the large number of patients it affects. It has a profound impact on morbidity, mortality, and quality of life. This review provides an update on current concepts regarding pathogenesis, clinical presentation, diagnosis issues, and management strategies for neurological SLE. The pathophysiology is complex and involves immune-mediated and vascular mechanisms of neurological involvement in SLE, including autoantibodies, neuroinflammation, dysregulation of complement, and genetic predisposition. Neuropsychiatric systemic lupus erythematosus (NPSLE) can present with a broad spectrum of central and peripheral nervous system manifestations, ranging from neuropsychiatric SLE, one of the most challenging manifestations, such as cognitive dysfunction, mood disorders, and psychosis, to cerebrovascular disease with an increased incidence of stroke and transient ischemic attacks; demyelinating syndromes mimicking multiple sclerosis; and neuropathies of sensory, motor, or autonomic function. The diagnosis of neurological SLE is very challenging due to subtle, nonspecific, and fluctuating symptoms. A meticulous neurological examination along with neuroimaging techniques, autoantibody profiling, and cerebrospinal fluid analysis is needed. Current treatment strategies will be discussed with corticosteroids, conventional immunosuppressants, and emerging biological agents targeting specific immune pathways. It is worth mentioning the complexities of neuropsychiatric symptom management, seizure management, and neuropathic pain.

**Keywords:** systemic lupus erythematosus; collagen vascular disease; neuropsychiatric lupus; NPSLE; central nervous system syndromes; neurolypus; neurologic disease; cognitive dysfunction; peripheral neuropathy; acute ischemic stroke

## 1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by inflammation involving connective tissues. SLE typically tends to impact all organs and tissues in the body, and the specific symptoms experienced by patients might vary significantly. The exact cause of SLE is not fully understood. However, it is thought to arise from the complex interaction of genetic and hormonal factors and environmental exposures, which determine the occurrence of antibodies to nuclear and cytoplasmic antigens [1]. In addition, patients with SLE may have other autoantibodies, including anti-Scl-70 antibodies (found in systemic sclerosis), anti-La and anti-Ro antibodies (found in Sjogren's disease), anticardiolipin antibodies, and antiphospholipid antibodies, suggesting a broad connection between SLE and other autoimmune disorders [2].

The worldwide incidence of SLE varies between 1.5 [3] and 11 [4] cases per 100,000 person-years, whereas the prevalence ranges from 13 to 7,713.5 cases per 100,000 individuals [5]. The female gender

predominance in SLE has been extensively documented, with a male-to-female patient ratio of 1:9. The occurrence and frequency of SLE in females frequently peak between the ages of 15 and 44 and 45 and 64, respectively [6]. SLE has variability across all age groups, but it is more prevalent among those aged 15 to 45 years [7]. Research indicates that between 10% and 20% of individuals diagnosed with SLE develop the disease during childhood. Interestingly, patients with childhood-onset SLE have a higher prevalence of renal, neuropsychiatric, and cardiovascular complications than other groups [8–10].

In North America, the incidence of SLE was estimated to be 23.2 per 100,000 person-years (95% CI: 23.4, 24.0), while the prevalence was estimated to be 241 per 100,000 individuals (95% CI: 130, 352). Africa and Ukraine had the lowest rates of SLE, with an incidence of 0.3 occurrences per 100,000 person-years. Northern Australia had the lowest prevalence, with no recorded cases among a sample of 847 subjects. Individuals of black ethnicity had the highest incidence and prevalence of SLE, while those of white ethnicity displayed the lowest incidence and prevalence. Over time, an increase in the prevalence of SLE was observed [11]. African American populations have the highest SLE incidence and mortality, followed by Hispanic and Asian populations, while Caucasian populations have the lowest rates of the disease [12].

SLE is a prominent contributor to mortality among young women [13]. A meta-analysis of over 26,000 female patients with SLE in the United States (US) found that the overall mortality rate was 2.6 times higher compared to the general population. The standardized mortality ratio (SMR) was more than 2 for cardiovascular disease and over 5 for infection and renal disease [14].

A notable manifestation of nervous system in SLE is known as neuropsychiatric systemic lupus erythematosus (NPSLE). The documented frequency of neurological symptoms associated with SLE varies from 14% to 95%, with a higher occurrence in children compared to adults [15,16]. It can potentially impact the central and peripheral nervous systems (PNS) in various ways. The total prevalence rate was 56.3%, with a higher incidence in the central nervous system (CNS) at 93.1% compared to the PNS at 6.9% [17,18].

In 1999, the American College of Rheumatology (ACR) published a collection of NPSLE case definitions, which included 12 manifestations related to the CNS and seven manifestations associated with the PNS (Table 1) [19]. The CNS manifestations can be categorized into four psychiatric syndromes and eight neurological syndromes. They can also be classified as either focal (presenting as focal neurologic deficits) or diffuse (including cognitive disorder, mood disorder, psychosis, acute confusional state, and anxiety disorder) [19]. However, a study of 128 participants uncovered a significant occurrence of NPSLE in this group of individuals with SLE who were not specifically chosen. The most prevalent NPSLE manifestations seen were headaches, cognitive impairment, and mental illnesses [20].

**Table 1.** The American College of Rheumatology Nomenclature and Case Definitions for Neuropsychiatric Lupus Syndromes (1999), and their frequency.

Central Nervous system	Peripheral Nervous system
Aseptic meningitis (0.3–2.7%)	
Cerebrovascular disease (8.0–15%)	
Headache (including migraine and benign intracranial hypertension) (12.2–28.3%)	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome) (0.08–1.2%)
Movement disorder (chorea) (0.9%)	Autonomic disorder (0.08–1.3%)
Myelopathy (0.9–3.9%)	Mononeuropathy, single/multiplex (0.9–6.9%)
Seizure disorders (7.0–20%)	Myasthenia gravis (0.2%)
Acute confusional state (0.9–7%)	Neuropathy, cranial (1.0%)
Anxiety disorder (6.4–40%)	Plexopathy (Not available data)
Cognitive dysfunction (6.6–80%)	Polyneuropathy (1.5–5.4%)
Mood disorder (7.4–65%)	
Psychosis (0.6–11%)	

Physicians face difficulties in diagnosing NPSLE due to the absence of specific and sensitive laboratory serum or CSF biomarkers, radiographic imaging abnormalities, and formal criteria for establishing the diagnosis and guiding therapy and management decisions in NPSLE [21]. NPSLE diagnosis is facilitated by many clinical, serological, immunological, electrophysiological, and neuroimaging tests [18]. Regrettably, even when healthcare personnel can recognize neurological or psychiatric disorders in patients with SLE, these patients are rarely subjected to thorough evaluation, resulting in a lack of diagnosis and treatment. This is because the required tests are demanding in terms of resources and time [22]. Magro-Checa et al. introduced a diagnostic method for patients with NPSLE that relies on the clinical symptoms observed in patients with SLE [23]. Both patients with significant NPSLE and patients with moderate or non-NPSLE exhibited a higher rate of death compared to the general population [24]. A study revealed that people with NPSLE have a death rate that is 11 to 14 times higher than that of the general population. Interestingly, acute confusional state was the most important indicator for predicting a negative outcome [24].

SLE, a complex autoimmune disease, can profoundly affect the nervous system, leading to a wide range of debilitating conditions that significantly affect patient outcomes. This narrative review presents the current information regarding NPSLE, focusing on the clinical symptoms, pathophysiological pathways that play a role in the condition, diagnostic challenges, and the current strategy for management and treatment.

2. Neurological Involvement In SLE: Proposed Mechanisms

In patients with SLE, approximately one-third of neuropsychiatric events can be directly attributed to SLE, and they occur in 21% of SLE patients within the first 6.6 years of their illness [25]. CNS involvement is observed in 90% of the cases, while the PNS is only responsible for 10% [25]. Noteworthy, there is extensive research on CNS disease in people with SLE, but the impact on the PNS is less well-established (Table 2). Such studies have provided a valuable understanding of the range of CNS symptoms as well as the connection between certain CNS disorders and autoantibodies, immunologic markers, and elements of SLE activity [25,26]. However, only a few studies have been conducted on the relationship between peripheral neuropathies and autoantibody patterns and the characteristics of SLE activity [27].

Table 2. Immune-mediated mechanisms in neurological SLE.

Mechanism	Description	Autoantibodies	Manifestations	References
The anti-P antiidiotypic antibody population could induce disease by binding to membrane receptors, as has been shown with experimentally induced antibodies to insulin and acetylcholine.	In 18 of 20 patients with psychosis secondary to systemic lupus erythematosus (SLE), autoantibodies to ribosomal P proteins were detected by immunoblotting and measured with a new radioimmunoassay using a synthetic peptide as antigen.	Anti-ribosomal P protein antibodies (Anti-RP Ab)	Psychosis	Bonfa et al. (1987) [28]
The strong association between aPL and NP manifestations in this study supports the theory that an occlusive vasculopathy may be a major mechanism for NPSLE	The study included 323 consecutive SLE patients and investigated the associations between aPL and neuropsychiatric manifestations.	Antiphospholipid antibodies (aPL antibodies)	Cerebrovascular disease, headache, and seizures	Sanna et al. (2003) [29]
MAP-2, have repetitive microtubule-binding motifs,	Sera from 100 patients with SLE, 74 patients with	Anti-microtubule-	Psychosis, seizure,	Williams et al. (2004) [30]

so that they not only control cytoskeletal integrity but also interact with other structural elements of the cell	other neurologic disorders and injuries, and 60 normal controls were examined both by enzyme immunoassays and by Western immunoblotting for autoantibodies to MAP-2	associated protein 2 antibodies (Anti-MAP-2 Ab)	neuropathy, and cerebritis	
It has been postulated that AECA reactivity may be due in part to the binding to a complex of $\beta$ 2-GPI with phospholipids on endothelial cells	This study included 51 unselected outpatients with SLE (44 women, 7 men; mean age 36.8 years, range 22–54 years; mean disease duration 9.4 years, range 0.5–26 years)	Anti-endothelial-cell antibodies (AECA)	Psychosis and mood disturbances	Conti et al. (2004) [31]
Suggesting that these antibodies, generated in the periphery, penetrate the CNS from the peripheral blood across the altered blood–brain barrier and bind to cell surfaces, possibly interfering with neuronal function	Investigate the potential role of circulating autoantibodies specific to neuronal cell surface antigens in the pathophysiology of neuropsychiatric disorders.	Antibodies against glyceraldehyde 3-phosphate dehydrogenase (GAPDH)	Cognitive dysfunction	Delunardo et al. (2016) [32]

The CNS is affected by SLE and presents a wide range of neuropsychiatric symptoms. These symptoms include aseptic meningitis, cerebrovascular disease, demyelinating syndrome, various types of headaches (such as migraine and benign intracranial hypertension), movement disorders, myelopathy, seizure disorders, acute confusion, anxiety disorders, and psychosis [19]. Although less common than CNS involvement, PNS involvement can still significantly impact patients. The signs include Guillain-Barré syndrome, autonomic dysfunction, mononeuropathy, myasthenia gravis, cranial neuropathy, plexopathy, and polyneuropathy [19].

The autoimmune/inflammatory route involves activating pro-inflammatory substances or producing autoantibodies that target neuronal cells. This leads to damage by forming intrathecal immune complexes and disrupting the blood-brain barrier (BBB). Prior research has commonly maintained that the BBB's permeability significantly contributes to the development of NPSLE [33].

The complement system plays a crucial role in the inflammatory pathway, particularly in disrupting the integrity of the BBB, mainly through the action of complement C5a/C5aR. In vitro experiments have shown that C5a triggers death in endothelial cells, most likely via binding to the C5aR1 receptor. It has been observed that microglia have a high level of C5aR1 receptor mRNA [34]. Endothelial cells are stimulated by immune complexes to produce pro-inflammatory cytokines and cellular adhesion molecules by activating nuclear factor-kappa B (NF- $\kappa$ B) signaling. Jacob et al. investigated the impact of C5a/cluster of differentiation 88 (CD88) signaling on the integrity of the BBB in SLE throughout the NF- $\kappa$ B pathway. The authors revealed an increase in NF- $\kappa$ B translocation. A following study by the same group revealed that the levels of zona occludens have decreased, but the expression of microtubule-associated protein (MAP) levels has increased, which may contribute to an increase in the permeability of the blood-brain barrier [35]. Therefore, elevated systemic signaling, mediated by cytokines and complement, is the primary factor for triggering apoptosis in CNS endothelial cells, resulting in BBB damage and increased permeability. Of particular significance is the involvement of the tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK)/fibroblast growth factor-inducible 14 (Fn14) pathway [34]. Moreover, diffuse NPSLE was already associated with anti-C1q, C3/AP50, and focal NPSLE with C4 levels. This suggests that the disease activity marked by the complement pathway activation may play a role in neurocognitive dysfunction in NPSLE [23].

Inflammatory mediators can disrupt the BBB. At the same time, neuronal or glial cells can also generate these cytokines and chemokines within the intrathecal space, thereby enhancing the BBB's permeability. Both processes could facilitate circulating autoantibodies and leukocytes infiltration into the CNS.

The presence of inflammatory cytokines, including TNF- $\alpha$ , TWEAK, interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-6 (IL-6), interleukin-8 (IL-8), and B-cell activating factor (BAFF), has been observed in the cerebrospinal fluid of patients with NPSLE. This suggests that the acute inflammatory response plays a significant role in the development of NPSLE [36]. Yoshio et al. discovered that the levels of certain cytokines (IL-6, IL-8, MCP-1/CCL2, IP-10/CXCL10, G-CSF, and GM-CSF) in the spinal fluid were not affected by the levels of these cytokines in the blood of patients with central NPSLE. This suggests that these cytokines likely produce chemokines in the CNS, which is apparently needed to develop central NPSLE [37]. Other interleukins involved in the development of NPSLE are interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-10 (IL-10), a proliferation-inducing ligand (APRIL), and interferon- $\alpha$  (IFN- $\alpha$ ) [38]. Also, the chemokine-ligand 5 (CCL-5) was already associated with NPSLE [38].

Previous research has shown strong evidence that IFN- $\alpha$  can lead to neuropsychiatric symptoms in both human and mouse models. Santer et al. propose that the serum and cerebrospinal fluid (CSF) of individuals with NPSLE may have abnormally high levels of IFN- $\alpha$  activity [39]. In addition, inhibiting IFN- $\alpha$  signaling decreases the synaptic loss associated with microglia and improves anxiety-like behavior and cognitive impairments in 564Igi Lupus-prone mice [40].

Among the cytokines that have been documented, IL-6 is considered to have a strong positive relationship with NPSLE activity. Also, IL-6 in the CSF is a reliable indicator for diagnosing central NPSLE, with high sensitivity and specificity. A recent study has identified a more detailed categorization of NPSLE. It has been observed that levels of blood IL-6 and CSF IL-6 are significantly higher in cases of acute confusion states (ACS) compared to non-ACS diffuse NPSLE, which includes conditions such as anxiety disorders, cognitive impairment, mood disorders, and psychosis, as well as localized NPSLE. Furthermore, the Q albumin (CSF/serum albumin quotient) was significantly elevated in ACS compared to the other two categories of NPSLE. Interestingly, Q albumin correlates more strongly with serum IL-6 than CSF IL-6 in patients with diffuse NPSLE, including both ACS and non-ACS cases [41].

An overactive response of microglia in the brains of mice with SLE, known as MRL/MpJ-Fas<sup>lpr</sup>/J mice (MRL-lpr; Strain 000485), was observed, indicating the presence of brain innate immunity. In NPSLE, the interaction between CD40 and hippocampus microglia played a role in the progression of cognitive dysfunction. In mice, inhibiting the activation of microglia can decrease neuropsychiatric symptoms [42].

## 2.1. Autoantibodies in NPSLE

A prominent characteristic of SLE is the generation of autoantibodies, and many antibodies have been discovered to be linked to NPSLE symptoms. A total of 116 antibodies have been identified in SLE thus far. Among them, at least 20 antibodies have been linked to NPSLE, including 11 that specifically target the brain and nine that affect the entire system [43].

### 2.1.1. Antiphospholipid Antibodies Include $\beta$ 2-Glycoprotein 1, Cardiolipin Anticardiolipin (Anti-CL), and Lupus Anticoagulant (LA)

The aPL antibodies specifically bind to anionic phospholipids, such as  $\beta$ 2GPI, instead of being directed against these phospholipids, as their name might imply. These phospholipids are found in the plasma membrane and have a role in regulating the blood clotting cascade [44]. Following this, procoagulant activation leads to thrombosis and cerebral infarction [45]. aPL antibodies have been found to be associated with focal and diffuse NPSLE symptoms, including cognitive dysfunction [46], seizures [47], and myelopathy [29].

### 2.1.2. Anti-Ribosomal P protein Antibodies (anti-RP Ab)

Anti-ribosomal P (anti-RP Ab) antibodies are serological indicators that are frequently seen in patients with SLE psychosis and might be associated with peripheral nervous system complications [48]. Anti-ribosomal-P antibodies are found near the carboxy-terminal end of the 60S subunit of ribosomes. They specifically bind to three phosphorylated proteins, namely P0, P1, and P2 [49]. Anti-ribosomal P-antibodies are thought to cross the BBB, enter neuronal cells, and hinder protein synthesis [50].

#### 2.1.3. Antibodies Against the N-Methyl-D-Aspartate Receptor (anti-NMDA)

The NMDA receptor is a type of glutamate receptor found in the CNS that plays a crucial role in synaptic plasticity and memory formation [51]. The NR2A and NR2B subunits are present in the hippocampus, amygdala, and hypothalamus [52]. NMDA receptors consist of tetramers that are made up of NR1 subunits and two of the four NR2 (A–D) subunits [53]. Anti-NMDAR encephalitis is a neurological disorder caused by the immune system attacking the NMDAR receptors. There are reports of anti-NMDAR encephalitis in patients with SLE, but the exact mechanisms behind its development is not completely understood [54].

#### 2.1.4. Antibodies Against Aquaporin 4 (NMO-IgG/AQP4-Ab)

Aquaporin 4 (AQP4) is the primary protein responsible for facilitating the movement of water in the central nervous system. It is predominantly found at the extremities of astrocytes and is positioned at both the BBB and the brain-cerebrospinal fluid barrier. AQP4 plays a crucial role in regulating the flow of water within cells [55]. Anti-AQP4 antibodies induce damage to astroglial cells by triggering an inflammatory immune response. This response activates complement-dependent cytotoxicity, which in turn disrupts the BBB and leads to the infiltration of white blood cells and the release of cytokines. Consequently, this process causes damage to oligodendrocytes, myelin, and neurons [56]. Myelitis and antiphospholipid syndrome and AQP4-IgG positivity were observed in 6.7% of the patients with SLE [57].

#### 2.1.5. Structural Endothelial Proteins

Endothelial cells (ECs) are located on the inner linings of blood vessels and constitute a layer of cells known as the endothelium. Endothelial cells have not been previously recognized as constituents of the immune system. Endothelial cells (ECs) have a crucial role in maintaining blood pressure and are involved in various physiological and pathological processes such as coagulation, fibrinolysis, angiogenesis, and immune cell activation [58]. In autoimmune disorders, the regulation of endothelial cells by the adaptive and innate immune systems is critical, as endothelial cells contribute to persistent inflammation through angiogenesis, immune cell recruitment, and antigen presentation [59]. The EC dysfunction may lead to microvascular changes in the white matter of patients with SLE leading to vascular dementia features. Also, microvascular abnormalities in the peripheral nerves may be one of the causes of neuropathy in SLE [60].

Anti-suprabasin antibody (Anti-SBSN Ab) are induced by astrocytes exposure to antibodies that have altered senescence and autophagy pathways [61]. It can serve as a useful indicator to distinguish NPSLE from SLE without neuropsychiatric symptoms, as anti-SBSN antibodies and their related immune complex were found solely in the CSF of NPSLE [62].

#### 2.1.6. Anti-Endothelial Cell Antibodies (AECAb)

Anti-endothelial cell antibodies (AECAb) are self-produced antibodies that specifically attack endothelial cells, which are the cells that form the inner lining of blood vessels [63]. Within the framework of NPSLE, these antibodies have been linked to several disease-causing processes [60,64].

#### 2.1.7. Anti-Ubiquitin Carboxyl Hydrolase L1 Antibodies (Anti-UCH-L1 Ab)

Li et al. revealed that antibodies against UCH-L1 can be a dependable biomarker in the CSF to diagnose NPSLE. Additionally, the concentrations of UCH-L1 in the CSF may serve as an indicator of the intensity of NPSLE [65]. Furthermore, this marker was linked to increased severity of the disease and overall disease activity [66]. Similarly, a recent study on autoantibodies found that the autoantibody UCH58-69, which targets amino acids 58–69 of UCH-L1, has a high level of specificity and diagnostic significance in distinguishing NPSLE patients from SLE patients without neuropsychiatric symptoms. The study found that NPSLE patients had significantly elevated levels of anti-UCH58-69 in their serum compared to SLE patients without neuropsychiatric symptoms. Furthermore, these levels were correlated with the severity of the condition [63].

#### 2.1.8. Antibodies Against Glyceraldehyde 3-Phosphate Dehydrogenase (GAPDH)

GAPDH has been identified as a new autoantigen linked to neuropsychiatric diseases. Delunardo et al. revealed a strong positive relationship between levels of anti-GAPDH antibodies in the blood and detrimental cognitive and mood conditions (such as schizophrenia and major depression) in patients with SLE. The levels of anti-GAPDH antibodies were elevated in SLE patients who had psychotic symptoms compared to SLE patients who did not have psychotic symptoms [32]. Anti-GAPDH Ab can induce neurite interaction and impairment of neuronal plasticity by blocking and binding of synaptic molecules. These antibodies level are increased in NPSLE and they are associated with cognitive dysfunction and psychiatric manifestations [67].

#### 2.1.9. Triosephosphate Isomerase (Anti-TPI Antibody)

Triosephosphate isomerase (TPI) is an enzyme involved in the conversion of dihydroxyacetone phosphate (DHAP) to glyceraldehyde-3-phosphate (G3P). It is present in neurons and red blood cells [68]. Anti-TPI antibodies have been linked to NPSLE, mainly showing a greater occurrence of aseptic meningitis and higher levels of serum IgG in NPSLE patients who test positive for anti-TPI compared to those who test negative for anti-TPI [69].

#### 2.1.10. Microtubule-Associated Protein (Anti-MAP-2 Ab)

MAP-2 is a cytoskeletal protein found in neuronal cells that plays a crucial role in initiating and stabilizing microtubules, regulating the movement of organelles and protein kinases involved in signal transduction [70]. Anti-MAP-2 antibodies are linked to damage and death of neurons and are notably increased in the CSF of individuals with NPSLE [30]. Neuropsychiatric symptoms, such as psychosis, schizophrenia, bipolar disorder, and major depression, have been linked to the presence of anti-MAP-2 antibodies [71].

#### 2.1.11. U1 Ribonucleoprotein (Anti-U1RNP Ab)

Autoimmune disorders such as mixed connective tissue disease (MCTD), systemic sclerosis (SSc), and SLE are associated with the presence of anti-U1RNP antibodies [72]. SnRNPs, or small nuclear ribonucleoproteins, are abundant RNA-protein complexes located in the nucleus. They play a crucial role in the processing of pre-mRNA and other proteins that make up the spliceosome [73]. Anti-U1RNP antibodies are associated with an increased risk of NPSLE, mainly when detected in the CSF [74].

#### 2.1.12. Others

Brain cytoplasmic ribonucleic acid (BC RNA) refers to a type of non-coding RNA molecule, specifically BC200 RNA (also known as brain cytoplasmic RNA 1 or BCYRN1), which is primarily found in the cytoplasm of neurons within the brain and plays a role in regulating protein translation by inhibiting translation initiation factors; essentially controlling gene expression at the post-

transcriptional level. Anti-BC RNA induction decreases the delivery of BC RNA to synaptodendritic sites in the brain. The decrease of BC RNA in CNS was already associated with some types of NPSLE, mainly involving cognitive impairment [75].

## 2.2. The Cerebrovascular Pathway

Cerebrovascular events frequently manifest in the presence of increased disease activity and evidence of illness-related tissue injury [76]. In NPSLE, the most widely accepted cause of cerebrovascular disease is thrombosis induced by antiphospholipid (aPL) antibodies (APLAs). Prominent risk factors for this condition include chronic and high disease activity, a high cumulative corticosteroid dosage, persistent positivity for aPL antibodies at moderate-to-high levels, heart valve disease, and systemic hypertension [77]. The prevalence of SLE infections ranges from 3% to 20%, with a potential contribution of up to 15% to overall mortality [78,79].

Antiphospholipid syndrome (APS) is an autoimmune disorder distinguished by the presence of defined APLAs, namely anti-cardiolipin IgM and IgG, anti-beta-2 glycoprotein IgM and IgG, and lupus anticoagulant. These APLAs induce a condition of hypercoagulability, resulting in the formation of venous and arterial thrombi. The presence of APS can manifest as a primary disease. Nevertheless, it is worth noting that approximately 20–30% of patients with SLE test positive for APLAs [80]. Moreover, when APLA levels reach moderate-to-high levels, patients are at an elevated risk of thrombosis, even in the absence of any prior thrombotic episodes. APLAs have been identified as agents involved in the vascular pathway of NPSLE pathogenesis, leading to various adverse outcomes such as strokes, venous thromboembolism, cerebral venous sinus thrombosis, cognitive impairment, peripheral neuropathy, and chorea. APS has been associated with many clinical manifestations, such as maternal health complications and livedoid vasculopathy [81]. The CNS exhibits a higher vulnerability to thrombus formation than other tissues in APS, which is believed to be associated with some specific receptors in the brain vasculature [82].

Vasculitis is a group of illnesses characterized by inflammation in blood vessels of varying sizes, occasionally accompanied by fibrinoid necrosis and subsequent vessel wall loss. It is an infrequent manifestation in SLE, with a prevalence of less than 7% in patients with NPSLE [83]. Interestingly, CNS SLE vasculopathy is usually a non-inflammatory condition that impacts small arterioles and capillaries, forming micro-infarcts and hemorrhages [84]. Immune complexes can induce endothelial dysfunction by stimulating endothelial cells to express vascular cell adhesion molecule 1, hence facilitating the recruitment of monocytes into the arterial wall [85]. Anti-endothelial cell antibodies, generated in the context of SLE, elicit the production of proinflammatory factors and foster the adherence of monocytes to endothelial cells, resulting in the subsequent inflammation of vessel walls. The presence of anti-endothelial cell antibodies leads to an increased release of cytokines, including interleukin 1, interleukin 6, and interleukin 8. This physiological response ultimately results in endothelial death [85]. Anti-endothelial cell antibodies and complement significantly contribute to vasculitis development in medium-sized arteries. This condition can lead to various complications, including luminal stenosis, small-vessel noninflammatory vasculopathy, microvessel occlusion, multifocal microinfarcts, intracranial embolism, and microhemorrhages [17].

Hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, and a sedentary lifestyle are considered to be both traditional and modifiable risk factors for stroke and cardiovascular diseases. Hypertension is more common in SLE and APS than in the general population, and it can be explained by chronic inflammation [86]. Also, systemic inflammatory processes have been identified as the underlying cause of early atherosclerosis, which is also known as accelerated atherosclerosis [87]. Other factors influencing atherosclerosis are lupus nephritis, steroid therapy, and vitamin D deficiency.

SLE patients who have previously experienced a transient ischemic attack (TIA) have a 57% chance of developing an ischemic stroke [88]. The incidence of stroke in SLE ranges from 2% to 19% [89,90]. The incidence of ischemic stroke is twice as high in patients with SLE than in the general population and encompasses elements beyond the conventional Framingham risk factors. Additional

factors that contribute to the higher risk of an ischemic cerebrovascular event include the presence of vasculitis, associated APS and positive aPL autoantibodies (found in 9.4% of cases), endocarditis, Libman-Sacks endocarditis, hyperviscosity (increased homocysteine levels), genetic polymorphism (the presence of allele GT20), and hypertension [76]. Consistent with this observation, a research study revealed that males with  $\beta$ 2GPI-dependent immunoglobulin (Ig) G anticardiolipin antibodies had a 1.5-fold increased risk of stroke and acute myocardial infarction (AMI) compared to those without such antibodies [20]. Additionally, another study indicated that elevated levels of anticardiolipin antibodies in the bloodstream, irrespective of other cardiovascular risk factors, were a significant predictor of future stroke and TIA in females but not in males [91].

Individuals with autoimmune disorders have a twice-fold increased risk of experiencing an ischemic stroke within the first year of hospitalization compared to those without hospitalization. Interestingly, the risk of having a stroke remains elevated for at least ten years after the first hospitalization [92]. Also, after the first ischemic stroke, the risk of having another stroke in ten years is as high as 35% [93].

### 2.3. Genetic And Environmental Factors

Numerous studies have proven the link between genetic factors and the development of SLE. Nevertheless, investigating the genes responsible for humans' susceptibility to SLE has proven to be a formidable task, mainly due to limited epistasis, genetic heterogeneity, ethnic heterogeneity, and environmental factors. Determining the specific genotypes that contribute to NPSLE pathophysiology remains elusive. A meta-analysis found that the  $Fc\gamma RIIIa$ ,  $Fc\gamma RIIIb$ , and  $ITGAM$  genotypes have been identified as probable susceptibility genes for NPSLE following a comprehensive examination of genetic variants associated with this disorder [94].

Specifically, it has been observed that patients with NPSLE have mutations in  $TREX1$ , a gene responsible for encoding three-prime repair exonuclease 1 (DNase III) [95]. Furthermore, variations in this gene have been linked to the presentation of CNS involvement, including seizures [96]. There is evidence suggesting that the  $HLA-DRB1^{*04}/^{*13}$  genotype and the SNP rs10181656 in  $STAT4$ , which encodes the signal transducer and activator of transcription 4, are linked to strokes in individuals with SLE [97]. This association remains significant even after controlling for aPL antibody status and conventional cardiovascular risk factors [98,99]. A comprehensive assessment has been conducted on the collective impact of single nucleotide polymorphisms (SNPs) in multiple genes linked to SLE, namely  $HLA-DRB1$ ,  $IRF5$ ,  $STAT4$ ,  $BLK$ ,  $TNFAIP3$ ,  $TNIP1$ ,  $FCGR2B$ , and  $TNFSF13$ , in Japanese individuals diagnosed with SLE. The presence of ten or more SNPs doubled the likelihood of neurological symptoms in these patients [100].

The induction or exacerbation of autoimmune diseases, such as SLE, by infection can be attributed to various mechanisms, including molecular mimicry, epitope spreading, polyclonal activation of B cells, bystander expansion of auto-reactive T cells, and viral and bacterial super-antigens [101]. The clinical presentations observed in NPSLE are a consequence of immunological dysregulation, characterized by the development of autoantibodies or vaso-occlusive events associated with the presence of APLAs. Disease-associated immunological dysfunction and the immunosuppressive effects of treatment contribute to an increased vulnerability to infection [102]. Furthermore, the bimodal survival pattern in SLE has been reevaluated, revealing that death resulting from infections persisted throughout the progression of the disease [103].

The prevalence of CNS involvement in patients with SLE is estimated to range from 18% to 67% [104]. In SLE, infections contribute to around 20–55% of morbidity and mortality [105]. The CNS is accountable for 3% of these infections [105]. However, a significant proportion of NPSLE patients, up to 81%, do not exhibit any accompanying systemic SLE activity [104]. The predominant pathogens are *Mycobacterium tuberculosis* and *Cryptococcus neoformans* [106]. Notwithstanding their infrequent occurrence, CNS infections result in significant morbidity and mortality [107]. The results of the correlation study revealed a subtle positive relationship between rubella IgM antibody titers and the presence of psychosis in individuals with NPSLE [108].

The ultraviolet (UV) radiation emitted by sunlight is typically categorized into three broad bands: UV-C (200–290 nm: distant UV, germicidal UV), UV-B (290–320 nm: midrange UV, sunburn radiation), and UV-A (320–400 nm: near UV, black light). It is observed that the stratospheric ozone layer fully absorbs UV-C light, but UV-B radiation is only partially absorbed. The penetration of UV-B radiation is limited to the epidermis of window glass. Still, UV-A radiation can penetrate both ordinary and colored glass and the epidermis [109]. UV-B radiation, when administered in low concentrations, has been found to induce DNA damage, lymphocyte apoptosis [110], and the production of pro-inflammatory cytokines, adhesion molecules [111], and nitric oxide synthase in keratinocytes [112]. This might potentially have systemic ramifications. The transformation of trans- to cis-urocanic acid produced by UV-B radiation has been observed to inhibit cell-mediated immunity. Furthermore, UV-B radiation reduces Langerhans cells' ability to stimulate CD4<sup>+</sup> Th1 cells. It activates CD4<sup>+</sup>CD45RA<sup>+</sup> suppressor-inducer T cells, thereby altering the immunological landscape in favor of B-cell activation [111,113]. Ultraviolet A (UV-A) radiation has the potential to induce systemic flares by directly infiltrating the subcutaneous vasculature. Conversely, it has been suggested that UV-A1 light with a longer wavelength range of 340–400 nm may possess protective properties against flare-ups in SLE [114]. It found instances of organ involvement, including lupus nephritis, in individuals diagnosed with SLE due to exposure to sunlight [115]. Interestingly, there are anecdotal reports of NPSLE after sunlight in individuals with NPSLE [116].

Pharmaceutical compounds linked to drug-induced lupus erythematosus (DILE) have diverse chemical compositions, including aromatic amines, hydrazine, and sulfhydryl groups. This suggests that DILE does not possess a singular unifying chemical configuration [117]. Pharmacological agents implicated in DILE can be classified into four distinct categories, which include drugs that are definitive, likely, potentially, and recently documented to induce DILE [118]. The medications that are most frequently associated with DILE include hydralazine, procainamide, isoniazid, and TNF- $\alpha$  inhibitors [119]. Hydrochlorothiazide, calcium channel blockers, and angiotensin-converting enzyme inhibitors [120] are among the drugs that are most prone to inducing subacute cutaneous lupus erythematosus (SCLE). Other medications like proton-pump inhibitors (PPIs) [121], terbinafine [122], immunomodulators (leflunomide [123], TNF- $\kappa$  inhibitors [124], and chemotherapeutic agents [125], have the potential to elicit SCLE. Grönghagen et al. found higher odds ratio (OR) for terbinafine (OR 52.9), TNF- $\kappa$  inhibitors (OR 8.0), antiepileptics (OR 3.4), and PPIs (OR 2.9) and SCLE [126]. Fluorouracil substances or their contemporary counterparts, such as capecitabine, have traditionally been identified as the primary triggers of chronic cutaneous DILE [127].

### 3. Spectrum of Neurological Manifestations in SLE

The American College of Rheumatology developed a set of criteria for NPSLE. These include 19 NPSLEs. They are classified into 12 central and seven peripheral nervous system manifestations [19]. NPSLE could develop as a presenting symptom or throughout the disease course [19]. Neuropsychiatric syndromes occur in 56.3% of SLE patients [18]. Furthermore, their prevalence varies according to the age at which the disease begins. Pamuk et al. showed that seizures and psychosis were more common in early-onset SLE patients, while peripheral neuropathy was more prevalent in the late-onset SLE group [128].

#### 3.1. Psychiatric Disorders (Anxiety, Depression, and Psychosis)

Mood disorders are prevalent in around 20% of patients with SLE [18]. The severity of depression and anxiety is associated with SLE activity [129]. Moreover, depression could affect drug adherence [130]. Thus leading to frequent SLE flares and a worse prognosis [131]. Psychosis is considered rare, occurring in 2.5% of patients with SLE [132]. Psychosis is a disorder in the perception of reality; patients with psychosis could experience hallucinations or delusions [19]. In around 5% of patients with SLE, psychosis could be caused by steroid administration [133]. SLE-related psychosis could be managed with steroids and immunosuppressive drugs. This resulted in the full remission

of about 66.7% of patients [132]. Meanwhile, rituximab resulted in a significant improvement in the refractory cases [134].

### 3.2. Cognitive Dysfunction

The ACR defines cognitive dysfunction as impairment in cognitive domains, including attention, memory, reasoning, and language [19]. Cognitive dysfunction is present in 19.7% of SLE patients [18]. However, it is poorly recognized by physicians [135]. Cognitive dysfunction is not correlated with the severity of the disease. However, it is associated with the presence of organ damage. Moreover, anti-dsDNA antibodies are negatively related to cognitive impairment [135]. The ACR has recommended a 1-hour battery test for diagnosing cognitive impairment [19]. The use of psychosocial education helped to improve memory and functioning [136]. Memantine did not significantly improve the cognitive impairment in NPSLE [137].

### 3.3. Seizures

Seizures affect approximately 9.9% of SLE patients. The generalized tonic-clonic seizure is the most frequent semiology in SLE patients [138]. Females and patients who had SLE at a young age are at a higher risk of developing seizures related to SLE [138]. There is no association between auto-antibodies, including the lupus anticoagulant and anticardiolipin, and the risk of developing seizures [138]. The outcome of seizures related to SLE is favorable. Most seizures are resolved without requiring long-term medications or significantly affecting the quality of life [138].

### 3.4. Stroke and Transient Ischemic Attacks (TIAs)

Cerebrovascular diseases (CVD) are prevalent among 8% of SLE patients [18]. The typical risk factors for CVD include diabetes, hypertension, and dyslipidemia [139]. Other risk factors include cutaneous vasculitis, anticardiolipin antibodies, and lupus anticoagulant antibodies [140]. Moreover, the antiphospholipid syndrome is an important risk factor as it leads to a hypercoagulable state [139]. This is done by inhibiting protein C, reducing prostacyclin, activating platelets, and activating endothelial cells [141]. TIAs are reversible neurological events. However, they are considered important stroke predictors in SLE patients [139].

### 3.5. Peripheral Neuropathy

Polyneuropathy occurs in 3% of SLE patients, while mononeuropathy occurs in 1.5% [18]. Jasmin et al. reported that sensory neuropathy was the most prevalent type among SLE patients [142]. Mahran et al. showed that neuromuscular ultrasound could be used in addition to nerve conduction studies in patients with SLE and concerning neuropathy as it provided additional information on the pathophysiology of nerve affection [143]. Guillain-Barré syndrome (GBS) is a rare presenting symptom in around 1.3% of SLE patients [144]. However, its incidence has been increasing. There are 27 cases of GBS associated with SLE that have been reported in the literature [145]. These patients were aged 20–60, and 77% were females. They were managed with various immunosuppressive drugs, including steroids and cyclophosphamide; 63% of them achieved complete recovery [145]. However, it is essential to differentiate between GBS as a symptom of SLE and pure GBS co-occurring with SLE, as cyclophosphamide is ineffective in patients with pure GBS [146].

### 3.6. Demyelinating Syndromes

Demyelinating syndromes (DS) are rare, occurring in around 0.3% of SLE patients [18]. The manifestations of DS include vision loss, diplopia, lower limb weakness, cranial nerve palsy, nystagmus, cognitive impairment, and an acute confusional state [147]. Differentiating SLE from multiple sclerosis (MS) can be challenging in clinical practice. However, the presence of certain manifestations could guide the diagnosis of SLE. These include the presence of rash, arthralgia,

myalgia, and renal affection [148]. Furthermore, the involvement of the peripheral nervous system could indicate SLE, since MS only affects the CNS [149].

The pathology of MS is different compared to SLE. Plaques, which are focal areas of demyelination, characterize MS. They are present, along with inflammatory changes and axonal degeneration. Meanwhile, the pathology of SLE-related DS relies on cerebrovascular disease. Therefore, there are multiple areas of infarction, along with atherosclerosis and angiopathy [149]. However, Nikolopoulos et al. reported that patients with SLE demyelinating diseases (SLE-DS) and those with SLE fulfilling the criteria for multiple sclerosis had similar neurological findings on MRI. Moreover, they had similar rates of optic nerve affection. Patients with SLE-DS, however, had low odds of achieving an elevated IgG index. None of the SLE-DS patients had positive type II oligoclonal bands [150].

4. Diagnostic Challenges in Neurological SLE

Neurological and psychiatric symptoms are known as NPSLE. The reported prevalence of NPSLE ranges between 14 to 95% and is more common in children than adults [15,16]. Diagnosing neurological SLE is challenging due to the complexity and variability of its manifestations. There are no specific criteria to diagnose NPSLE; based on the diagnosis of exclusion, less than 40 % of neuropsychiatric symptoms will be attributed to SLE-induced nervous system damage. In the remaining cases, other causes (e.g., drug-induced, primary disorders) better explain these symptoms. Thus, the physician has to exclude other causes and assess neurological and psychiatric symptoms. Further evaluation includes assessing general SLE activity, cardiovascular risk factors, atherosclerotic disease, and thrombotic events [18,76].

Neurological assessment should be focused on headaches, signs of seizures, and motor and sensory deficits, while psychiatric evaluation should assess behavior, cognition, perception, thinking, mood, and affect. The diagnostic evaluation of patients with neurological manifestations in SLE should involve all the appropriate investigations that would typically be conducted for non-SLE patients presenting with similar symptoms and signs [76]. For example, a patient with stroke symptoms should undergo a screening echocardiogram and vessel imaging of carotids and vertebral arteries, in addition to testing for SLE-specific causes such as APLAs [151]. Another example is when a patient presents with a psychiatric disorder, such as confusion. The physician should identify the cause, whether it is metabolic abnormalities, infection, or psychoactive drug use.

Several studies have investigated a correlation between disease activity and neuropsychiatric events in SLE patients. Some studies have demonstrated a connection between heightened overall SLE disease activity and neuropsychiatric manifestations attributed to the disease. This correlation is stronger for diffuse rather than focal events [27]. Neuroimaging and laboratory tests are integral to diagnosing neurological SLE, particularly distinguishing its manifestations from other neurological conditions. The table below will provide examples of investigations used for diagnosis (Table 3).

Table 3. Diagnostic tests for neurological SLE.

Test	Utility in Neurological SLE	Reference
MRI (Magnetic Resonance Imaging)	The imaging technique of choice is MRI especially T2-weighted images. The most frequent pathological pattern is small punctate hyperintense T2-weighted focal lesions in subcortical and periventricular white matter (WM), usually in the frontal-parietal regions. Unfortunately, these MRI lesions are also present in many patients without neuropsychiatric manifestations. MRI can exclude multiple sclerosis, malignancy, infarction, subarachnoid hemorrhage.	Kozora et al. (1998) [152] Nomura et al. (1999) [153] Magro-Checa et al. (2016) [23]
Computed tomography	Used to exclude other causes of neurological symptoms such as bleeding, tumors and hemorrhage.	Magro-Checa et al. (2016) [23]

PET (Positron Emission Tomography)	SPECT imaging has detected both widespread and localized deficits in patients with SLE, which may be either persistent or reversible. SPECT imaging can be abnormal in up to half of patients with SLE with no clinical manifestations of neuropsychiatric disease. Thus, SPECT findings are not unique to SLE.	Sibbitt et al. (1999) [154] Waterloo et al. (2001) [155]
Autoantibody Profiling	Several circulating autoantibodies like apl (antiphospholipid antibodies) and $\beta$ 2-glycoprotein antibodies both correlate with disease activities specially with focal events such as cerebrovascular disease and seizures. Antiribosomal P antibodies found to be specifically related to lupus psychosis. Aquaporin 4 autoantibodies can help in the diagnostic process of a patient presenting with myelopathy and optic neuritis and Neuromyelitis optica (NMO).	Zirkzee et al. (2014) [156] Birnbaum et al. (2007) [157] Birnbaum et al. (2009) [158]
Cerebrospinal Fluid (CSF) Analysis	Help to exclude CNS infection in patients with fever or other signs and symptoms suggestive of infection; mild CSF abnormalities are common (40–50%) but are not specific to the neuropsychiatric SLE. It can exclude infection,malignancy,myasthenia gravis and oligoclonal bands.	Kozora et al. (1998) [152] Nomura et al. (1999) [153] 1/23/2025 9:34:00 AM
Electroencephalogram (EEG)	EEG studies help to diagnose underlying seizure disorder.	González-Duarte et al. (2008) [159] Appenzeller et al. (2004) [160]
Neuropsychological Testing	It's carried out when suspicion of impaired cognitive abilities is present. Patients with suspected impaired cognitive ability should be referred for full neuropsychological assessment.	Hanly et al. (2014) [161] Zirkzee et al. (2012) [162]

5. Management and Treatment Strategies for Neurological SLE

The primary goal in managing neurological SLE is to control SLE disease activity, minimize neurological symptoms, and improve overall function and quality of life. Due to the diverse clinical presentations and difficulties in diagnosis, managing patients with SLE who experience neuropsychiatric symptoms is most effective when approached by a multidisciplinary team coordinated by a rheumatologist. Identifying and treating non-SLE-related factors in all cases is essential, even when SLE is the primary contributor. For instance, infections or metabolic issues must be managed in patients presenting with acute neuropsychiatric symptoms, while those with vascular-related neuropsychiatric events should be evaluated for cardiovascular risk factors. Specific therapies for primary SLE manifestations are chosen based on the predominant immunopathogenic mechanism in neuropsychiatric SLE, whether the injury is inflammatory-mediated or vascular-mediated.

When the etiology is thought to be inflammatory/neurotoxic (especially aseptic meningitis, optic neuritis, transverse myelitis, peripheral neuropathy, refractory seizures, psychosis, and acute confusional state) and in the presence of lupus activity, management includes glucocorticoids alone or in combination with other immunosuppressants such as azathioprine or cyclophosphamide [163]. In cases of severe symptoms refractory to standard therapy, plasma exchange [164], intravenous immunoglobulin [165], and rituximab (an anti-CD20 monoclonal antibody) have been used [166]. A randomized controlled trial by Barile-Fabris in 32 patients with acute, severe neuropsychiatric SLE reported a significantly better response to therapy with intermittent intravenous cyclophosphamide than with intravenous methylprednisolone (95% versus 54%,  $P < 0.03$ ) [167]. In patients with APS, anticoagulation therapy is more effective than antiplatelet therapy. For secondary prevention of arterial events such as stroke and TIA [168]. In patients with recurrent thrombosis while on warfarin, adjuvant therapies are added to their treatment plans, such as antiplatelet agents, antimalarial agents, and statins [169].

Antidepressants, anxiolytics, and antipsychotic agents are prescribed according to their standard indications in psychiatric disorders. At the same time, antiseizure therapy is initiated when

high-risk features are present, such as serious brain injury, brain structural abnormalities (MRI), focal neurological signs, and epileptiform discharges [170].

Antimalarial drugs (hydroxychloroquine and chloroquine) are used in the primary prevention of SLE symptoms, especially for cutaneous and musculoskeletal involvement [76] and reduction in mortality [171]. Although no studies specifically address its effect on neuropsychiatric SLE symptoms, a preventive role of these drugs in CNS lupus has been suggested, especially in cerebrovascular disease [172]. As shown in Table 4, immunosuppressants and biological therapy are the main lines of treatment for NPSLE.

**Table 4.** Management of neuropsychiatric manifestations in SLE.

Drug name	Mechanism of action	Indication	Administration	Side effects	References
Corticosteroids	Modulate immune response and inflammation via glucocorticoid receptors	First line drug and used to control of SLE flares (mild-severe)	IV Methylprednisolone (1g/day x 3 days), oral Prednisolone (1 mg/kg/day) tapering over 3-12 months	Hypertension, dyslipidemia, osteoporosis, diabetes, cataract, glaucoma psychiatric issues (10% risk), infections, and peptic ulcer disease	Schäcke et al. (2002) [173] Bertsias et al. (2010) [76] Buttgereit et al. (2002) [174]
Cyclophosphamide	Impairs DNA replication and immune cell proliferation. It is a prodrug that is converted by liver cytochrome 450 enzymes to its metabolite 4-hydroxy cyclophosphamide.	Severe NPSLE manifestations, mainly CNS involvement	Monthly IV regimen (0.75–1.5 g/m <sup>2</sup> ), 500 mg fixed dose in less severe cases	Alopecia, nausea, leukopenia, hemorrhagic cystitis, cardiotoxicity, gonadal failure	Hejaili et al. (2003) [175] Houssiau et al. (2010) [176] Ognenovski et al. (2004) [177]
Azathioprine	Inhibits purine synthesis, affects both cellular and humoral immune functions	Used as maintenance therapy. In prevention of flares. It is a first option in mild NPSLE symptoms as a glucocorticoid-sparing agent	Oral (2–3 mg/kg/day)	Bone marrow suppression, hepatotoxicity, increased risk of infection	DiPiero et al. (2015) [178] Oelzner et al. (1996) [179]
Mycophenolate mofetil	Inhibits lymphocyte proliferation via inosine-5'-monophosphate dehydrogenase	Maintenance after induction in renal SLE the efficacy of this drug in NPSLE patients is very modest and lacks strong evidence for its efficacy in neuropsychiatric symptoms	Oral (1000–3000 mg/day)	GI intolerance, bone marrow suppression, infections	Allison et al. (2005) [180] Pisoni et al. (2005) [181]

Methotrexate	Methotrexate is a folic acid antagonist. It inhibits IL-2 transcription, suppresses T-cell activity	Limited evidence for NPSLE, some reports suggest positive effects with intrathecal administration	Oral, subcutaneous, or intrathecal in CNS involvement	GI symptoms, stomatitis, increased levels of liver enzymes and mild cytopenia. In severe cases liver fibrosis, interstitial pneumonitis, and severe pancytopenia	Zhou et al. (2008) [182] Wang et al. (2014) [183]
Cyclosporin A	Inhibits IL-2 transcription, suppresses T-cell activity	Rarely used in NPSLE with Limited evidence, but may aid in organic brain syndrome and psychosis when combined with therapeutic plasma exchange (TPE)	Oral (2.5–3 mg/kg/day), sometimes with plasma exchange	Hypertension, renal dysfunction, hypertrichosis	Bambauer et al. (2000) [184] Yang et al. (2014) [185]
Rituximab	Rituximab is a chimeric monoclonal antibody directed against the B-cell-specific antigen CD20.	It is used in severe refractory NPSLE. But, it lacks of long-term data.	IV (1000 mg doses separated by 15 days)	Infusion reactions, infections	Glennie et al. (2007) [186] Tokunaga et al. (2007) [134]
IVIG (intravenous immunoglobulin)	Mixture of natural IgG antibodies derived from the blood of healthy donors. It inhibits the activity of autoreactive B lymphocytes and suppresses typeI interferon-driven differentiation of dendritic cells and reduces nucleosome endocytosis.	Positive effects in small case reports, with limited evidence. But, it is used a adjunctive therapy in refractory cases	IV administration 2g/kg, with divided doses over 2–5 days	Mild and self-limited such as headaches, fever, flushing, chills, arthralgia and myalgia. Infusion reactions, risk of thrombosis	Camara et al. (2014) [187] Milstone et al. (2005) [165]

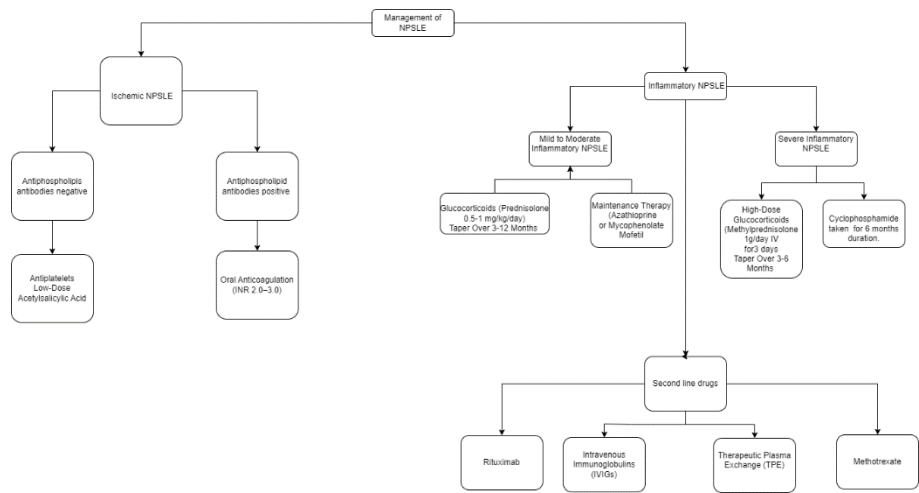
As shown in the previous table, corticosteroids are first-line for acute symptoms, especially during flares, but they are associated with significant long-term risks. Cyclophosphamide is preferred in severe cases due to its efficacy despite its side effects. Azathioprine and Mycophenolate Mofetil are used for maintenance therapy, though their role in neuropsychiatric symptoms is not well studied. Rituximab offers the potential for refractory cases.

In the case of ischemic NPSLE, the main line of treatments are anticoagulants and antiplatelets. Platelet activation is increased in SLE patients, and the presence of antiphospholipid antibodies add additional risk of thrombosis [188].

It's recommended to use low-dose acetylsalicylic acid as primary thromboprophylaxis for SLE in patients who have positive lupus anticoagulant (LAC) or persistently elevated anticardiolipin antibodies (aCL) at medium to high levels [189].

For secondary prevention for patients with antiphospholipid antibodies, acetylsalicylic acid monotherapy, clopidogrel 75 mg monotherapy, and the combination of acetylsalicylic acid and extended-release dipyridamole are acceptable options for initial treatment [190,191]. On the other

hand, anticoagulation therapy is preferred for secondary prevention in high-risk patients. It is more effective at preventing stroke recurrence. However, the bleeding risk is higher, necessitating close monitoring with INR to ensure that the benefits of preventing thrombosis outweigh the risk of hemorrhagic complications. Sometimes, a combination of antiplatelet and anticoagulation therapies is used [192]. The following chart summarizes the management of neuropsychiatric SLE according to its etiology (Figure 1).



**Figure 1.** Algorithm for the management of NPSLE (neuropsychiatric systemic lupus erythematosus).

6. Prognosis And Long-Term Outcomes In NPSLE

NPSLE is associated with a negative impact on quality of life and severe fatigue, regardless of the level of disease activity [193]. Moreover, patients with SLE are at increased risk of work incapacity compared to normal individuals [194]. Up to 34% of patients with SLE are unable to work. This is attributed to many factors, including socioeconomic status, disease activity, pain, fatigue, anxiety, and neurocognitive disorders [195]. Furthermore, cognitive impairment negatively impacts quality of life and participation in social activities [196].

Patients with NPSLE have an increased risk of mortality and morbidity compared to the general population. Li et al. reported an 11-fold increase in the risk of death [62]. The leading causes of death were related to NPLSE and involved increased intracranial pressure, cerebrovascular disease, and motor neuron disorders [62]. On the other hand, a focal CNS lesion is associated with a 7-fold increase in mortality [197]. Furthermore, the state of acute confusion, the level of C-reactive protein, and the increased intracranial pressure are associated with mortality [62]. Also, receiving the appropriate treatment could affect the prognosis. Patients with neuropsychiatric events attributed to SLE who received steroids and immunosuppressive drugs had improved outcomes [198].

Many biomarkers have the potential to predict the prognosis of patients with SLE. Kostopoulou et al. showed that low levels of complement C3 and high levels of anti-dsDNA were associated with SLE flares [199]. Moreover, the presence of certain biomarkers could predict certain neuropsychiatric manifestations. Jiang et al. reported an association between psychosis and anti-β2GPI antibodies; polyneuropathy and anti-Scf70 antibodies; and demyelinating syndrome and anti-cardiolipin antibodies. Meanwhile, anti-Sjogren syndrome antigen B antibodies and high complement C3 were associated with a low risk of NPSLE [200]. Additionally, the prognosis of NPSLE could be predicted. Low C4 levels, lupus anticoagulant, and anti-cardiolipin antibodies were associated with severe neuropsychiatric manifestations [201,202]. Moreover, the treatment response could also be predicted. Zheng et al. showed that patients with low C3 or C4 levels or positive anti-dsDNA had better outcomes following belimumab administration [203].

For patients with SLE, there is a need for regular follow-up to monitor disease activity and treatment effects. Hsu et al. reported a case of GBS that was regularly followed up for a year after

complete recovery [204]. This is critical because patients may not respond to treatment or experience a relapse. For example, in the case of demyelinating diseases, approximately 42% of patients with SLE and demyelinating syndrome experienced a relapse [150]. In GBS associated with SLE, only 63% of patients experienced complete recovery [145]. Meanwhile, refractory symptoms could be managed with other approaches. Tokunaga et al. reported that patients with refractory NPSLE significantly improved following cyclophosphamide administration [134]. Moreover, SLE activity should be monitored as it could be associated with the severity of NPSLE [129].

7. Neurological SLE Research's Future Directions

In recent years, numerous multinational initiatives have recorded advancements in systemic lupus erythematosus clinical management. The 2019 classification by the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) established positive antinuclear antibodies (ANA) as a mandatory entry criterion, organized items into weighted organ domains, and substituted individual exclusion criteria with a singular attribution rule, stipulating that items should only be considered if no more plausible explanation than SLE exists. The revised EULAR recommendations explicitly outline significant advancements in SLE therapy, emphasizing the administration of hydroxychloroquine to all SLE patients without contraindications, the necessity of risk factor modification, treatment aimed at specific targets, and the reduction of glucocorticoid exposure. The Latin American Grupo Latino Americano de Estudio del Lupus (GLADEL) recommendations conveyed the same perspectives concerning antimalarials for all SLE patients and advocated for maintaining modest glucocorticoid dosages.

SLE is a frequently observed disease in clinical practice, but the neurological symptoms related to this rheumatologic disorder are still poorly understood (Figure 2). There is an urgent need for studies involving this specific group of patients because they have a significantly worsened quality of life when compared to individuals without neuropsychiatric manifestations. Therefore, the development of biomarkers specific to NPSLE is mandatory. Also, the current biomarkers should be evaluated with meta-analysis regarding their benefit in diagnosing and assessing disease activity. As a general statement, a prompt diagnosis and treatment of NPSLE will likely result in a better prognosis.

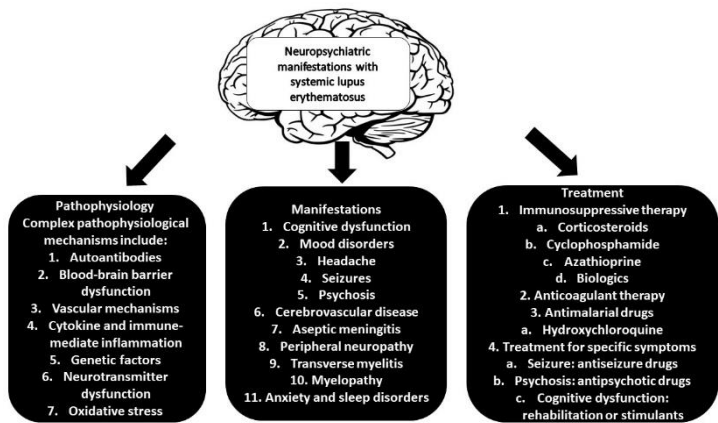


Figure 2. Pathophysiology, clinical manifestations, and treatment of neuropsychiatric systemic lupus erythematosus.

8. Conclusions

NPSLE is a broad term for a long list of neurological manifestations associated with SLE, which can significantly impact a patient's quality of life and may lead to long-term disability. The pathophysiology is complex and involves autoantibodies, neuroinflammation, dysregulation of complement, and genetic predisposition. Although challenging, early recognition and diagnosis of

NPSLE are essential for initiating appropriate treatment and preventing irreversible neurological damage.

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