Review

Neuropsychiatric Systemic Lupus Erythematosus: Antibodies Involved, Clinical Characteristics and Treatment

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Posted Date: 28 September 2023

doi: 10.20944/preprints202309.2018.v1

Keywords: Systemic Lupus Erythematosus; steroids; psychosis; DSM-V

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Neuropsychiatric Systemic Lupus Erythematosus: Antibodies Involved, Clinical Characteristics and Treatment

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Abstract: Systemic lupus erythematosus (SLE) is a chronic idiopathic autoimmune disease affecting various organs. Patients with SLE also present numerous neuropsychiatric manifestations. These neuropsychiatric manifestations are referred to as neuropsychiatric systemic lupus erythematosus (NPSLE). Neuropsychiatric involvement in patients with SLE was first mentioned by Kaposi more than 100 years ago and is a generic term that refers to neurological and psychiatric symptoms resulting directly from or as a complication of SLE. NPSLE affects both the CNS and PNS and can manifest as various symptoms, such as cognitive dysfunction, organic brain syndromes, delirium, seizures, headache, and psychosis. NPSLE was previously referred to as 'lupus cerebritis' or lupus sclerosis. However, these terms are no longer recommended because there is no definitive pathological cause for the neuropsychiatric manifestations of SLE. [2]

Keywords: systemic lupus erythematosus; steroids; psychosis; DSM-V

1. Introduction

Systemic lupus erythematosus (SLE) [1] is an idiopathic chronic autoimmune disease that affects virtually any organ in the body, including the neurological system. Multiple factors, such as environmental, genetic, and immunological influences on self-antigens, lead to the formation of multiple autoantibodies that cause deleterious damage to bodily tissues and organs. The production of immunologic antibodies, such as antinuclear antibodies, is a characteristic feature of this disease. The diagnosis of SLE is a rheumatological challenge despite the availability of clinical criteria [1].

SLE can affect the brain and produce neuropsychiatric manifestations, which warrant a multidisciplinary approach to further complicate this disease. Notably, the presence of NPS in SLE patients does not explicitly indicate the cause of SLE. This is because neuropsychiatric symptoms can be comorbid, coincidental, or as a complication of SLE treatment, most notably psychotropic drugs such as corticosteroids. Neuro-psychiatric systemic lupus erythematosus (NPSLE)[is further classified as either primary or secondary [2]. Primary NPSLE syndromes result from direct CNS autoimmune inflammatory processes, whereas secondary NPSLE syndromes are caused by indirect complications of SLE such as treatment side effects, CNS infection from chronic immunosuppression, or SLE-related organ damage [3].

Psychosis is an uncommon neuropsychiatric manifestation of NPSLE but can be secondary to long-term, high-dose glucocorticoids. Glucocorticoids are among the mainstay drugs for treatment, which makes management even more difficult as they are known to have psychiatric side effects and can cause a spectrum of psychiatric symptoms, including mania, psychosis, anxiety, and depression. On initial clinical examination, it may be difficult to differentiate the cause of psychosis as a result of steroids or NPSLE because no single laboratory test is currently available to definitively confirm the diagnosis of NPSLE. In clinical practice, corticosteroid-induced psychosis is an uncommon disorder classified as medication-induced psychosis according to the DSM-V. This dose-dependent effect was more prevalent in patients under certain conditions. Patients with systemic lupus erythematosus require long-term steroid therapy. This disorder may be underreported because it is difficult to

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differentiate it from NPSLE. Psychotic symptoms can be mild enough to not raise clinical suspicion and can also be short psychotic episodes that resolve without intervention [4].

Definitions for 19 different neuropsychiatric syndromes are listed in the American College of Rheumatology (ACR) Nomenclature for NPSLE, which are shown in Table 1 [5]. These syndromes affect the central and peripheral nervous systems. CNS syndromes are further divided into four psychiatric and eight neurological syndromes. They can also be further classified as focal neurological complications or diffuse complications such as psychosis, cognitive dysfunction, and depression. While these syndromes are well categorized and easier to classify, their usefulness in clinical practice is limited because many NPSLE syndromes, such as cognitive dysfunction, psychosis, and depression, are nonspecific and can be comorbid with SLE rather than being a manifestation of NPSLE. While SLE spares no organs, this article reviews the specific neuropsychiatric effects of lupus, as it resembles and is often comorbid with steroid-induced psychosis [6]. This article reviews immunopathogenesis, clinical manifestations, diagnosis, and treatment options for NPSLE.

Table 1. illustrating the American College of Rheumatology 1999 case definitions for neuropsychiatric syndromes affecting the CNS and PNS [5,7].

Central Nervous System	Diffuse Syndromes	Focal Syndromes
	Aseptic meningitis	Cerebrovascular disease Seizures Myelopathy Movement disorder
	Acute Confusional State Cognitive dysfunction Demyelinating syndrome Headache Psychosis Mood disorder Anxiety disorder	
Peripheral Nervous system		Acute inflammatory polyradiculoneuropathy (Gullain-Barre syndrome) Cranial neuropathy Mononeuropathy Myasthenia Gravis Plexopathy Autonomic neuropathy Polyneuropathy

2. Epidemiology

The reported prevalence of SLE in the United States varies between 20 and 150 cases per 100 000 [8]. The incidence of SLE has nearly tripled over the last 40 years [9] as a likely combination of improved clinical and laboratory detection. Owing to these advancements, the overall survival (OS) of patients with this prototypic systemic autoimmune disease has increased. SLE is more common among Asian, African American, African Caribbean, and Hispanic American populations than among White Americans. While Asian, African American, African Caribbean, and Hispanic

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American populations have a higher prevalence of SLE than White Americans, the LUMINA and Maryland Lupus [10] cohorts found a higher prevalence of NPSLE among White Americans. NPSLE is also associated with older age, likely because of comorbidities, such as CVD, hypertension, and diabetes [11].

Notably, SLE, like almost all other autoimmune conditions, has a distinct prevalence among women compared with men. Patients with SLE had a female-to-male ratio of 9 1 [12]. Despite its relative rarity, SLE tends to be more severe in males. In females, although there is a greater incidence of neurological involvement, increased seizure risk has been reported in men. However, since studies on NPSLE did not provide appropriate correction for confounders, such as comorbidities, there is insufficient evidence to suggest an association between sex and NPSLE [13]. The incidence and prevalence of SLE vary tremendously among populations [14]; therefore, it is not surprising that the neurological and psychiatric symptoms of SLE also vary considerably. This can be attributed to the heterogeneity of the disease and its definition. However, studies have reported that approximately 1/3–1/2 of patients with SLE report neurological and/or neuropsychiatric symptoms [1]. The most frequent manifestations of NPSLE are headaches, mood disorders, cognitive dysfunction, seizures, and cerebrovascular disease. The LUMINA study found that photosensitivity, Raynaud's phenomenon, anemia, and a medium daily dose of prednisone were associated with a longer time to NPSLE manifestation [15]. NPSLE is a complication of SLE that significantly lowers quality of life and has a poor prognosis in patients with SLE. NPSLE also has significant morbidity and mortality, with a reported 10-fold increase in mortality rates compared with the general public [16].

3. Histopathology

The exact etiology of SLE remains to be fully delineated; however, most systemic lesions are due to loss of tolerance to self-antigens, direct or indirect damage from autoantibody formation, and the generation of immune complexes (type III hypersensitivity) [17]. This was confirmed by the fact that anti-DNA complexes can be found in many organs such as the kidneys, lungs, and blood vessels. Serum complement levels, which are also measured during the initial workup and disease monitoring, can markedly decrease secondary to consumption and granular deposition. Therefore, low serum complement levels and immunofluorescence illustrating granular complement deposits further support the immunological etiology of the disease.

Alterations in B and T cell activation, along with impaired clearance of apoptotic debris, have also been implicated in SLE histopathology. NPSLE patients showed significantly more microinfarction, macroinfarction, vasculitis, and microthrombi on histological analysis than SLE patients without neuropsychiatric manifestations [18]. Histopathological analysis of NPSLE patients varies from nonspecific findings of focal vasculopathy to more specific lesions, including C4d- and C5b-9-associated microthrombi and diffuse vasculopathy [19] which often correlate with the clinical syndromes defining NPSLE [20].

4. Immunopathogenesis

Immunopathogenesis of NPSLE is shown in Figures 1 and 2. The clinical manifestations depend on environmental, hormonal, and genetic factors. The BBB can breach through multiple mechanisms. These include autoimmune processes, such as immune complex deposition and pathologic cytokine-mediated destruction, and environmental factors, such as smoking and hypertension [21]. There are no specific abnormalities noted on the brain images of patients with NPSLE, and some may even have normal findings or nonspecific white matter changes or atrophy [3].Although many mechanisms have been suggested, a full understanding of NPSLE remains to be determined. However, two main mechanisms may lead to NPSLE. These include:

4.1. Autoimmune or inflammation-inflammatory complications

This is directly related to autoimmune and pro-inflammatory states [1,22]. The neuropsychiatric manifestations of SLE are likely due to antibodies that react with neurons either directly or indirectly

 doi:10.20944/preprints202309.2018.v1

via the activation of other neural cells and cross the blood-brain barrier due to its disruption. Other immunological factors, such as cytokine-mediated CNS toxicity, may also play a role. Some of the cytokines found to be elevated in patients with NPSLE include IL-2, IL-10, and IFN-γ [23]. The pathogenesis of compromised BBB integrity is not yet fully understood. However, once they enter the CNS, antibodies and cytokines can cause clinical effects. Therefore, clinically useful biomarkers must be identified.

4.2. Noninflammatory or thrombotic/ischemic vascular injury

Noninflammatory complications are associated with vascular thrombosis and hemorrhage. Thrombosis of large and small intracranial vessels can occur due to immune complex damage, antibody-mediated damage, complete deposition, accelerated atherosclerosis, or leucoagglutination [1,2,24]. Cerebral Vasculitis has also been associated with NPSLE. CNS vasculopathy via antibodies, such as anti-phospholipid antibodies, may damage the blood-brain barrier and allow CNS immune deposition, resulting in NPSLE. However, CNS inflammatory vasculopathy is rare, and non-inflammatory vasculopathy is more commonly observed. Non-inflammatory vasculopathy involves the hyalinization of arteries and capillaries that compromise these small vessels, allowing the entry of pathological cytokines and autoantibodies into the CNS [25].

While this classification is useful for descriptive purposes, both inflammatory and non-inflammatory complications can occur [26]. These manifestations of NPSLE are classified based on the 19 syndromes described by the ACR; however, they are not yet fully understood. Predominant inflammatory syndromes can result from the generation of pathological autoantibodies associated with cytokine-mediated damage [23]. Primary inflammatory syndromes include myelitis, aseptic meningitis, and optic neuritis (ON).

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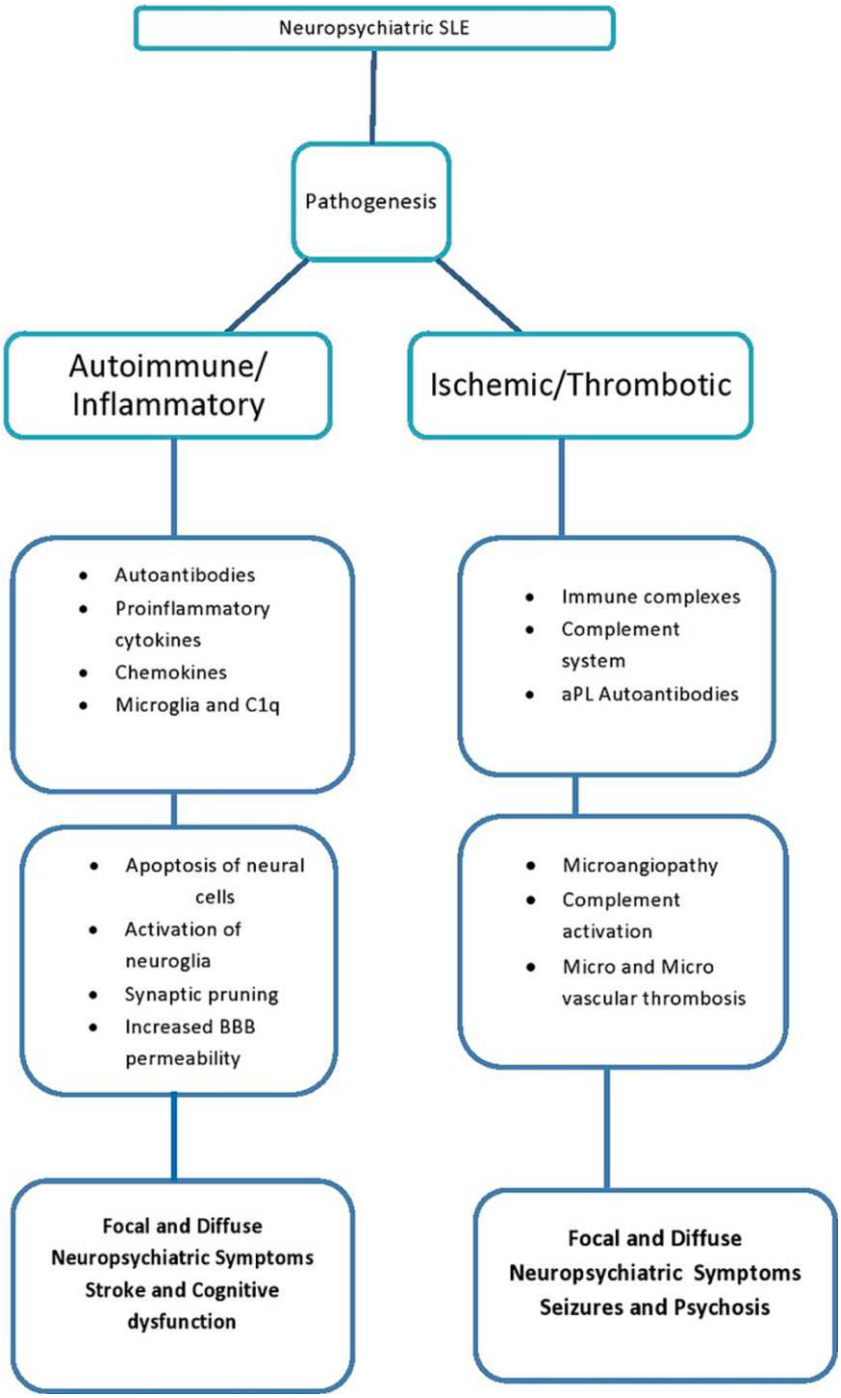

Figure 1. Immunopathogenesis of focal and diffuse NPSLE. Adapted from an open access resource [27].

5. Antibodies Associated with NPSLE

An overriding feature of SLE is the involvement of the immune system and the production of autoantibodies. The immune mediators of NPSLE are quite extensive and include cytokines, chemokines, and autoantibodies. Autoantibodies can lead to neuronal damage and promote the pathogenesis of NPSLE. More than 116 antibodies have been reported for SLE. and at least 20, including 11 brain-specific and nine systemic antibodies, have been associated with NPSLE [27,28]. However, none of these autoantibodies has definitive implications in the pathogenesis of NPSLE, and their association remains controversial [29]. Brain-specific antibodies associated with NPSLE include anti-neuronal Abs and brain-reactive Abs (BRAA). Anti-N-methyl-D-aspartate receptor Abs

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(NMDA), anti-microtubule-associated protein 2 Abs (MAP-2), anti-neurofilament Abs (ANFA), anti-ganglioside Abs (AGA), anti-central nervous system tissue (CNS) Abs, anti-brain-synaptosomal Abs, anti-triosephosphate isomerase (TPI) Abs, anti-glial fibrillary acidic protein (GFAP) Abs, and anti-serum-lymphocytoxic Abs (LCA) [30]. Systemic antibodies include antiphospholipid (aPL)/cardiolipin (aCL) Abs, lupus anticoagulant (LAC), anti-beta2- glycoprotein I (2GPI) Abs, anti-ribosomal P Abs (anti-P), anti-Ro Abs, anti-Sm Abs, antiendothelial Abs (AECA), anti-serine proteinase (anti-PR3/C-ANCA) Abs, anti-Nedd5 Abs [30].

5.1. Antiphospholipid Antibodies (β2-glycoprotein 1, cardiolipin anticardiolipin (anti-CL) and lupus anticoagulant (LA))

The aPL antibodies have an affinity to, and therefore target, anionic phospholipids, including β2GPI (rather than against anionic phospholipids, which their name would suggest [31]) in the plasma membrane that regulates the blood clotting cascade [32]. Subsequent activation of procoagulants promotes thrombosis and cerebral infarction [33], and aPL antibodies have been identified for focal and diffuse NPSLE symptoms such as cognitive dysfunction [34], seizures [35], stroke and Transient Ischemic Attack [36,37], and movement disorders. chorea [38,39] and myelopathy [40].

5.2. Ribosomal P protein (anti-ribosmal P Ab)

Anti-ribosomal P (anti-Rib-P) antibodies are specific serological markers observed in patients [41]. Anti-ribosomal-P antibodies are located at the carboxy-terminal end of the 60S subunit of ribosomes and target three phosphorylated proteins, P0, P1, and P2 [42]. Anti-ribosomal-P - antibodies are believed to breach the BBB, penetrate neuronal cells, and inhibit protein synthesis [43–45]. Antibodies against ribosomal-P proteins are associated with diffuse NPSLE. psychosis and clinically significant depression in patients [46–48]. Its presence may be a risk factor for the development of NPSLE [49] and a predictor of psychosis in patients already diagnosed with NPSLE [50]. These antibodies may also be associated with complications of the peripheral nervous system complications [51]. In animal studies, depressive behavior was noted when anti-ribosomal P antibodies were introduced into the cerebral ventricles [52]. These antibodies cross-react with the neuronal surface P antigen on the membranes of neurons in the hippocampus and can manifest as clinical depression [53,54]. The anti-Rib-P antibody can also cross-react with NMDA receptors, resulting in psychosis [55] the presence of anti-rib-P is not always associated with NPSLE manifestations [56]. Therefore, the clinical significance of anti-rib-P antibodies remains controversial.

5.3. Anti-human N-methyl-D-aspartate receptor Abs (anti- NMDA)

The NMDA receptor is an ionotropic glutamate receptor in the CNS that is responsible for synaptic plasticity and memory [57]. The NR2A and NR2B subunits are found in the hippocampus, amygdala, and hypothalamus [58]. NMDA receptors are tetramers composed of NR1 subunits and two of the four NR2 (A–D) subunits [59]. Anti-NMDAR encephalitis is an autoimmune neurological condition associated with SLE; however, its pathophysiology is not fully understood [60,61]. Anti-NR2 antibodies cross-react with anti-double-stranded DNA antibodies [62]. Anti- NR2 antibodies can enter the CNS via intrathecal IgG synthesis or breaching the BBB [63]. The severity of BBB damage plays a significant role in diffuse NPSLE syndromes, including Acute Confusional State , because it allows large titers of anti-NR2 to enter the CNS [64].

In NPSLE patients, anti-NR2 antibodies pathologically bind to the extracellular domains of the NR2A and/or NR2B subunits of the NMDA receptor. These autoantibodies have a much higher sensitivity to the NR2A subunit, resulting in excessive activation of the NMDA receptor [65].Pathological NMDA receptor activation in patients have been found to manifest as epilepsy, encephalitis, schizophrenia, mania, stroke, cognitive impairment, and acute confusional state [58,66].

5.4. Microtubule-associated protein (anti-MAP-2 Ab)

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MAP-2 is a cytoskeletal protein expressed primarily in neuronal cells that is responsible for microtubule nucleation and stabilization, and regulates organelle transport protein kinases involved in signal transduction [67,68]. Anti-MAP-2 antibodies are associated with neuronal injury and death and are significantly elevated in the CSF of patients with NPSLE [69]. Anti-MAP-2 antibodies are associated with neuropsychiatric symptoms, such as psychosis, schizophrenia [70], bipolar disorder [71], major depression [72], seizures [73], neuropathy [73], and cerebritis [73].

5.5. U1 ribonucleoprotein (Anti-U1RNP Ab)

Anti-UIRNP antibodies are observed in autoimmune conditions such as mixed connective tissue disease (MCTD), systemic sclerosis (SSc), and systemic lupus erythematosus (SLE) [74]. The Small nuclear ribonucleoproteins (snRNP) are RNA-protein complexes found in abundance in the nucleus and are involved in the processing of pre-mRNA and other proteins comprising the spliceosome [75]. Anti-U1RNP antibodies react with one or more of the three proteins (70-kD, A, and C) that are specifically present in the U1 RNP complex to form U1 small nuclear ribonucleoprotein (snRNP) [76]. snRNP is a target of autoreactive B and T cells in several rheumatic diseases, including (SLE) [77]. Anti-U1 RNP antibodies range from 3 to 69 percent in patients with SLE [78]. Anti-U1RNP Ab is associated with NPSLE manifestations such as anxiety, seizures, and CVD [79].

5.6. Structural endothelial proteins (AECA)

Endothelial cells (ECs) are found on the inner wall of blood vessels and form a layer of cells referred to as the endothelium. Endothelial cells have not been previously considered as components of the immune system. ECs are important for regulating blood pressure and play important roles in coagulation, fibrinolysis, angiogenesis, and immune cell activation via both physiological and pathological processes [80]. Modulation of endothelial cells via the adaptive and innate immune systems plays an integral role in autoimmune diseases, as endothelial cells promote chronic inflammation via angiogenesis, attracting immune cells, and antigen presentation [81]. Anti-endothelial cell antibodies (AECA) are a heterogeneous group of autoantibodies directed against structural endothelial proteins, along with antigens on endothelial cells [82]. Activation of ECs leads to increased leukocyte adhesion, activation of coagulation, and vascular thrombosis in a dose-dependent manner [83]. Pathologic activation of ECs results in endothelial injury and an increased risk of complications, such as atherosclerosis and vascular thrombosis, which are the most common causes of premature mortality in patients with SLE [84].

Table 2. illustrating common autoantibodies associated with NPSLE [73].

Autoantibody	Serum/CSF	Prevalence in SLE patients	Associated NPSLE symptoms
Phospholipid: β2-glycoprotein 1 and cardiolipin (aCL-Ab)	Serum, CSF	Up to 45%	CVD, seizures, chorea cognitive dysfunction, psychosis, depression, headache
Ribosomal P protein (anti-ribosmal P Ab)	Serum, CSF	6%-46%	psychosis, depression
NMDA receptor (anti-NMDA)	Serum, CSF	30%-40%	depression cognitive dysfunction
MAP-2 (anti-MAP-2 Ab)	Serum, CSF	17%, 33.3% (CSF)	seizures, chorea, sensory neuropathy, psychosis, headache)
U1 ribonucleoprotein (Anti-U1RNP Ab)	Serum, CSF	18% (CSF)	NPSLE in general

 doi:10.20944/preprints202309.2018.v1

Structural endothelial proteins (AECA)	Serum	17-75%	Psychosis, depression
TPI (anti-TPI Ab)	Serum, CSF	30%-40%	aseptic meningitis
GAPDH (anti-GAPDH Ab)	Serum	47%	Increased intracranial pressure, cognitive dysfunction

6. Clinical manifestations of NPSLE

6.1. Headache

Headaches are commonly reported in SLE patients. However, studies have found no evidence of an increased prevalence of any type of headache in SLE patients [85]. Therefore, primary headaches in the absence of high-risk predispositions in NPSLE patients require no further investigation other than an initial evaluation, like what would have been done in non-NPSLE patients. However, more serious causes of headaches should be excluded if suspected. In patients with antiphospholipid antibodies, cerebral sinus thrombosis should be excluded as a possible cause of headaches. Other possible causes of red flags, such as meningitis, cerebral hemorrhage, and subarachnoid hemorrhage, should also be excluded if suspected [86].

6.2. Cerebrovascular disease

Patients with SLE have a more than 2-fold increased risk of ischemic stroke, over 3-fold increased risk of hemorrhagic stroke, and almost 4-fold increased risk of subarachnoid hemorrhage compared to the general population. The highest relative risk is observed within the first year of SLE diagnosis; therefore, early screening and intervention are important. Over 80% of CVD cases are due to ischemic strokes or TIA, while CVD due to CNS vasculitis is rare. Risk factors for CVD in NPSLE patients include valvular heart disease, hypertension, age, and antiphospholipid antibodies, such as lupus anticoagulant [87–90]. Antiphospholipid antibodies (aPL) are strongly associated with stroke and are present in approximately 40% of SLE patients [91]. It must be noted that not all SLE patients with aPL have antiphospholipid syndrome (APS) and not all patients with APS have SLE. aPL is a risk factor for cerebral venous thrombosis and can predispose patients with non-bacterial thrombotic endocarditis (NBTE) to ischemic stroke due to arterial thrombosis or cardiogenic embolism. NBTE can still occur in SLE without aPL [92]. CNS vasculitis is rare; however, its presence is supported by evidence of inflammation in the CSF analysis. Confirmation of CNS vasculitis requires pathological examination; however, it is rarely performed. Vasculitis is suggested by the beading appearance of vessels on digital subtraction or magnetic resonance angiography, and diagnostic imaging modalities and treatment algorithms are similar for both SLE and non-SLE patients [93,94]. Owing to the high risk of stroke in SLE patients, aspirin can be used for primary prevention. The secondary prevention of stroke depends on specific subtypes. In most patients with a history of stroke, the general lupus activity can be controlled with immunosuppressants. Glucocorticoids are useful in patients suspected of having CNS vasculitis, and anticoagulation should be considered in patients with moderate to high titers of antiphospholipid antibodies.

6.3. Seizure disorders

Between 4% and 12 percent of patients with SLE experience seizures [95], but most seizures in SLE represent isolated events. Most seizures are focal and manifest as complex partial seizures. However, secondary generalization to tonic-clonic seizures can occur. Risk factors for seizures in patients with NPSLE include aPL, glucocorticoid treatment, severity of disease activity, infection, stroke, and posterior leukoencephalopathy syndrome (RPLS) [96]. Seizures are most often focal and typically manifest as episodes of impaired awareness but can evolve into bilateral tonic-clonic seizures (secondary generalization). In NPSLE patients with seizures, EEG abnormalities are observed in 60 %–70% of patients [97].

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6.4. Acute Mental state

In an NPSLE patient, an acute change in mental status is a medical emergency [98] because the causes are multifactorial. Among the differentials are SLE-related causes such as stroke, seizure, and CNS infection, whereas non-SLE-related causes include drugs and medications. An urgent evaluation with a comprehensive medical history and physical examination is required for patients with NPSLE. Acute mental states include two syndromes: acute confusional state (ACS) /delirium and psychosis [99]. ACS is an acute or subacute fluctuating level of consciousness, characterized by decreased attention, cognition, and arousal. ACS develops within hours to days and tends to worsen in the evening or night. Patients with NPSLE must be evaluated for adequate treatment of the precipitating conditions.

6.5. Psychosis

Psychosis is characterized by delusions, hallucinations, disorganized speech, and/or grossly disorganized behavior. Psychosis occurs in approximately 1 %–2% of SLE patients, and most episodes do not recur. The causes of psychosis in patients with NPSLE are broad and can be directly attributed to SLE or non-SLE. Psychosis caused by the direct inflammatory processes of SLE is sometimes referred to as "lupus psychosis and other causes of psychosis in NPSLE patients include CVD, seizures, infection, glucocorticoids, and macrophage activation syndrome [100].

6.6. Cognitive dysfunction

Cognitive dysfunction is common in patients with SLE, with most patients having mild-to-moderate symptoms that are generally benign. Only 3 %–5% of patients develop severe cognitive dysfunction. Attention, memory, and executive functions were most affected. Although administrative data studies pose the possibility of selection bias, one database study found that SLE was a risk factor for dementia. The etiology of cognitive dysfunction in patients with NPSLE is unclear and likely multifactorial. This may have been due to microvascular and white matter damage. MRI findings in patients with NPSLE showed greater brain atrophy than in controls. The severity of cognitive dysfunction in patients is correlated with cerebral atrophy, cerebral infarctions, and the number and size of white matter lesions [101–103].

6.7. Movement disorders

Chorea is the most documented movement disorder in patients with SLE [104]. Chorea is a disorder that involves irregular and involuntary jerky movements of any part of the body. Chorea may precede the diagnosis of SLE or coexist with other syndromes such as stroke or cognitive impairment. Many patients with NPSLE and chorea have aPL, and some show evidence of infarctions in the basal ganglia. Brain imaging can be considered when other focal neurological signs are present and secondary causes of chorea are excluded. Chorea is self-limited in many cases and subsides within weeks to months, with or without treatment [105,106],

6.8. Myelopathy

Myelopathy in NPSLE can present with transverse myelitis [107], a rare comorbid condition; however, ischemic/thrombotic myelopathy can also occur. Transverse myelitis is an immune-mediated disorder characterized by infiltration of inflammatory cells into a segment of the spinal cord, leading to neuronal demyelination and oligodendrocyte death. Inflammation localizes to ≥1 contiguous spinal cord segment, which leads to rapidly progressive myelopathy characterized by motor weakness that progresses from flaccid to spastic signs of UMN (eg. paraparesis or quadriparesis), autonomic dysfunction (e.g., bowel or bladder dysfunction, sexual dysfunction), and sensory deficits (for example, pain, and paresthesia) at a distinct sensory level. Patients with NPSLE myelitis often show T2 hyperintensity on MRI, without evidence of compression. CSF analysis often reveals pleocytosis and elevated IgG levels [108,109]. Neuromyelitis optica spectrum disorder (NMOSD) is characterized by the presence of anti-aquaporin-4 IgG antibodies. Some NPSLE patients

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with transverse myelitis are positive for anti-aquaporin-4 antibodies and therefore can have comorbid NMOSD [110].

6.9. Peripheral nervous system disorders

Peripheral nervous system involvement in patients with SLE is relatively rare [111]. NPSLE PNS include polyneuropathy, mononeuropathy, cranial neuropathies, and neuromuscular disorders. myasthenia gravis. The etiology is still not fully understood, but it can be a direct consequence of SLE or coexisting with other disorders. Peripheral neuropathy in SLE is usually asymmetric and affects more than one nerve [112]. These include sensorimotor polyneuropathy, acute inflammatory demyelinating polyradiculoneuropathy, autonomic neuropathy, and plexopathies. Cranial neuropathies can affect any cranial nerve, and the manifestation is dependent on the location of the neuropathy.Myasthenia gravis (MG) is a neuromuscular disorder that manifests as NPSLE [113]. MG may be a coexisting autoimmune disorder that is associated with SLE.

7. Signs and symptoms of NPSLE

NPSLE may precede the early or late manifestations of SLE. As many as 40% of NPSLE symptoms manifest within the first year of SLE diagnosis. NPSLE manifestations include headache, depression, anxiety, psychosis, and cognitive dysfunction. Strokes have been reported in up to 19% of SLE patients, while seizures have been reported in 4%–12% of patients. An altered mental status can occur in patients and is considered a medical emergency. An altered mental status can present as delirium or psychosis; the latter is sometimes referred to as lupus psychosis. Fatigue is seen in over 80% of SLE patients and is a multifactorial manifestation of NPSLE. Headaches are common in patients with SLE, and since they are common in the general population, they can exacerbate pre-existing primary headaches. However, red flag headaches are a cause for concern and must be evaluated judiciously.

Mood disorders such as depression and anxiety are common in patients with SLE, with a prevalence of over 24% and 37%, respectively. Therefore, it is important to inquire about and appropriately treat these symptoms. Mood disorders are multifactorial in nature and studies have not found a clear association between mood disorders and SLE disease activity, cumulative organ damage, or autoantibodies from SLE. Fatigue, depression, anxiety disorders, and headaches are common in SLE patients and have uncertain disease associations. The patients were managed similarly to those without SLE. Cognitive impairment is another manifestation of NPSLE that can occur in > 30% of patients with SLE. This is likely due to microvascular injury in the CNS, with some studies showing brain atrophy and white matter changes on imaging in SLE patients. Demyelinating diseases are a manifestation of NPSLE, according to the ACR. Demyelinating diseases, such as optic neuritis, myelitis, chorea, and aseptic meningitis, can be direct complications of SLE. Demyelinating diseases can also occur in SLE, neuromyelitis optica spectrum disorder (NMOSD), or multiple sclerosis.

8. Investigations

The diagnosis of SLE remains challenging. NPSLE symptoms are a direct consequence of SLE injury, whereas other NPSLE syndromes can be caused by treatment complications or by primary NPSLE disorders. As there is currently no gold standard diagnostic criterion, NPSLE remains a diagnosis of exclusion according to experts. Therefore, organic causes, such as infection, drug side effects, and comorbid conditions, must be ruled out. The initial diagnostic workup should characterize neuropsychiatric symptoms, and like non-SLE patients presenting with NP manifestations, diagnostic workup of NPSLE patients is necessary. Investigations. Diagnosis is achieved on a case-by-case basis based on the constellation of clinical signs and symptoms, along with laboratory, electrophysiological, and neuroimaging findings. Imaging and histopathological findings can also aid in diagnosis [114,115].

8.1. Biomarkers

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Anti-nuclear antibodies (ANA) are positive for most patients with SLE. However, ANA is also found in the healthy general population and has a low specificity. Therefore, ANA titers cannot be used to diagnose SLE, and must be followed up with specific antibodies. However, ANA has high sensitivity; therefore, the lack of this antibody in laboratory work makes SLE unlikely, and other diagnoses should be considered. To further complicate the diagnosis, cases of ANA-negative SLE have been reported; therefore, clinical suspicion is of utmost importance, and once ANA is positive, follow-up tests for specific antibodies should be performed. These antibodies include anti-dsDNA, anti-Smith, anti-Ro/SSA, anti-La/SSB, and U1 ribonucleoprotein (RNP) antibodies. Anti – dsDNA has a very high specificity of > 95%) for SLE, and its presence virtually confirms the diagnosis. Anti-Smith antibodies have an even higher specificity of > 90%), and their presence virtually confirms the diagnosis. However, anti-dsDNA and anti-Smith antibodies are observed in only 70% and 30% of patients with SLE, respectively. Therefore, negative anti-dsDNA and anti-Smith antibodies should not rule out the diagnosis of SLE if there is a high clinical suspicion [116–118]. Anti-Ro/SSA and anti-La/SSB antibodies were observed in only 30% and 20% of patients with SLE [119], respectively. These antibodies are observed in > 90% of patients with Sjögren's syndrome. Their presence in patients with SLE warrants workup for secondary Sjögren's syndrome. Pregnant mothers should also be advised about the possibility of a congenital heart block.Anti-U1 RNP antibodies are present in approximately 25% of patients with SLE. Its presence is typically observed in mixed connective tissue diseases. It is almost always found concurrently with the anti-Smith antibodies [119,120].

A complete blood count with a differential diagnosis can also be performed as it may reveal thrombocytopenia, anemia, and/or leukopenia. Inflammatory markers, such as ESR and CRP, may also be elevated. Creatinine levels can also be elevated in patients with renal involvement along with an elevated urine protein-to-creatinine ratio. Urine analysis can reveal proteinuria, hematuria, and cellular casts.C3, C4, and CH50 levels can also be checked, as a decrease in their levels suggests complement activation and consumption, and can be related to disease activity [121]. Antiphospholipid antibodies (e.g.) lupus anticoagulant, anticardiolipin antibodies, and anti-beta2-glycoprotein 1) can also be checked and are associated with higher thrombotic events. Anti-ribosomal P protein antibodies have high specificity but low sensitivity for SLE [122,123]. They are present in a minority of SLE patients; however, some studies have suggested that this antibody is a marker of CNS disease, although this is controversial. Testing for anti-ribosomal P protein antibodies has limited clinical value; however, there is an association between their presence and neuropsychiatric manifestations of SLE, especially psychosis.

8.2. Serum analysis

The 2019 EULAR/ACR classification criteria for SLE and the SLE Disease Activity Index (SLEDAI) include several serological parameters along with signs, symptoms, radiological features, histologic, and pathological findings for the classification of SLE [124,125] however, in the absence of concurrent systemic inflammation, these parameters often cannot be used to predict neuropsychiatric disease activity [126].

8.3. CSF analysis

CSF analysis can be useful in excluding other etiologies; however, the findings are often nonspecific. CSF analysis can reveal nonspecific findings of inflammation such as elevated total protein, elevated IgG, pleocytosis, and mildly reduced CSF glucose levels. Pleocytosis observed in CSF analysis is associated with 'lupus psychosis' and delirium [127]. Pleocytosis has been reported in approximately 20% of NPSLE cases and is typically at low-level, although has been reported with white cell counts greater than 100 cells/μl [128,129]. Protein elevation may be observed in 20–30% of NPSLE patients, with levels ranging from 1 g/L to greater than 2 g/L [130,131]. CSF abnormalities are seen in 30- 40% of cases and therefore do not provide a reliable differentiation of NPSLE from non-neuropsychiatric SLE patients [132].

8.4. Neuroimaging

 doi:10.20944/preprints202309.2018.v1

MRI remains the imaging modality of choice for the diagnosis of NPSLE [133–135]. The diagnosis of NPSLE requires rigorous exclusion of other causes, and various pathologies including atrophy, demyelination, and ischemic, hemorrhagic, or inflammatory lesions can be readily visualized on MRI with high sensitivity and specificity [136–138].

9. Complications

NPSLE complications can be caused directly by NPSLE or because of treatment. Drug-induced psychosis can occur at any time during the treatment. The symptoms include anxiety, agitation, irritability, and insomnia. More severe symptoms, such as mania, psychosis, and depression, can also occur. Steroid-induced psychosis is thought to be dose-dependent and more likely to occur in patients on long-term therapy, as well as in patients who are on medications that are likely to augment the effects of steroids [139].

9.1. Steroid induced Psychosis

In patients receiving long-term steroid therapy for the management of systemic lupus erythematosus, the diagnosis becomes more complicated as the differentiation of a neuropsychiatric flare from steroid-induced psychosis at the initial presentation is often clinically difficult [7,140]. Steroid-induced psychosis occurs due to abnormalities in the hypothalamic-pituitary-adrenal axis [141]. Exogenously administered steroids lead to the suppression of steroid secretion via the adrenal glands and eventual atrophy, resulting disturbances in cortisol levels.The imbalance between glucocorticoid receptor stimulation can lead to cognitive impairment and psychiatric disturbances such as psychosis [141,142].Psychosis is not the only known neuropsychiatric effect of steroids. Steroids are known to cause depressive symptoms [143], further complicating the initial presentation in contrast to the spectrum of psychosis. In a retrospective analysis in the United Kingdom, there was a five- to sevenfold increased risk of completed or attempted suicide among patients receiving glucocorticoids compared with patients with the same diagnoses who were not receiving such medications [144].

9.2. progressive multifocal leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) is caused by reactivation of the JC virus in immunosuppressed individuals with SLE and/or drug therapy [145,146]. CN infections such as encephalitis and meningitis are also possible complications of chronic immunosuppressive therapy. Reversible posterior leukoencephalopathy syndrome is another neurological complication of SLE that can be a direct complication or, more commonly, a complication of chronic immunosuppressive therapy.

10. Management of NPSLE

The validity of biomarkers for systemic lupus erythematosus used for making clinical decisions is limited. The lack of reliable and specific biomarkers for SLE negatively affects the current and future management of patients with SLE [147]. No laboratory, radiological biomarkers, or other formal systems exist to diagnose and guide therapeutic decisions in NPSLE. Management is multimodal and is based on a case-by-case approach. General management includes prevention or treatment of aggravating factors when symptomatic. The initial management of these patients did not differ from that of patients without SLE who presented with the same neuropsychiatric manifestations. Specific treatment modalities depend on whether the symptoms are due to inflammatory or non-inflammatory/thrombotic reasons [148]. Currently, the treatment options are primarily based on symptomatic presentations. These include the use of antipsychotics, antidepressants, and anxiolytic medications for the treatment of psychiatric and mood disorders. Antiepileptic medications and immunosuppressant drugs are used to treat seizures and immunosuppressant drugs (eg. Corticosteroids, azathioprine, and mycophenolate mofetil) are directed against inflammatory responses.

 doi:10.20944/preprints202309.2018.v1

10.1. Immunosuppressants

Immunosuppressants are the mainstay of lupus psychosis treatment. As NPSLE syndromes are suggested to be caused by autoimmune inflammatory processes, such as psychosis, acute confusional state, and transverse myelitis, high-dose glucocorticoids, and steroid-sparing agents, such as cyclophosphamide and mycophenolate, are the mainstay of treatment. Refractory cases of NPSLE can be treated using rituximab, intravenous immunoglobulin, or plasmapheresis. NPSLE syndromes attributed to the prothrombotic state due to the presence of antiphospholipid antibodies warrant the use of anticoagulants and antiplatelet drugs. Anticoagulation may be superior to antiplatelet therapy for secondary prevention of thrombotic events in patients undergoing antiphospholipid therapy [19]. In NPSLE patients with mood disorders such as depression, psychosis, and anxiety, standard treatment with antidepressants, antipsychotics, and anxiolytics is warranted according to the standard indications in psychiatric diagnostic criteria, without considering NPSLE as the underlying cause of these mood disorders.

10.2. Antiepileptics

Antiepileptic treatment is indicated for NPSLE patients with seizures, especially those with high-risk features, such as a second seizure, evidence of brain injury, and focal neurological deficits. Generalized and recurrent seizures warrant the use of antiepileptic drugs such as phenytoin and barbiturates. Partial complex seizures are managed with drugs, such as carbamazepine, valproic acid, and gabapentin. Patients with generalized convulsive status epilepticus (GCSE) require immediate treatment to prevent neurological injury and death. After treatment and stabilization, neuroimaging should be performed as in non-NPSLE patients to evaluate any underlying structural abnormality, hemorrhage, or area of ischemia. Patients with seizures who do not return to normal consciousness can undergo continuous electroencephalography to rule out non-convulsive status epilepticus, and there is no consistent evidence-based therapy for cognitive dysfunction in SLE patients. This is likely because cognitive dysfunction has been associated with many psychosocial factors such as fatigue, sleep deprivation, depression, and anxiety. However, antidepressants and psychotherapy may improve symptoms in patients with comorbid depression. Antimalarial drugs are commonly used in patients with SLE, and there is evidence supporting its use in patients with NPSLE. Antimalarials have been demonstrated to reduce the risk of CVD and antiphospholipid antibody titers. Another benefit of antimalarials is their antithrombotic effect. Antimalarials also been shown to protect against seizures. However, antimalarial drugs are rarely known to cause psychosis, and chloroquine is associated with epilepsy in patients with a history of epilepsy. The LUMINA study showed a protective role for hydroxychloroquine and time to NPSLE manifestation, but it may have been confounded by indication since patients with milder disease were more likely to be treated with this drug [7,148–150].

11. Conclusion

The pathogenesis of NPSLE is complex and remains a major cause of mortality in patients with SLE. The immune mediators of NPSLE includes cytokines, chemokines, and autoantibodies. Despite the increasing number of biomarkers and autoantibodies that have been tested and advancements in imaging techniques, there is still no 'gold standard' for NPSLE diagnosis. Treatment options often requires multiple medical therapy to manage symptoms. Immunosuppressants are the mainstay of management, and the use of antidepressants, antipsychotics, anxiolytics and antiseizure medications are often required.

Author Contributions: The manuscript was conceptualized by D.G., and planning and discussion were conducted by both authors. D.G. wrote the initial drafted the manuscript. Both authors reviewed and revised the final manuscript. Both authors read and agreed to the published version of the manuscript.

Funding: This study did not receive any external funding.

Data Availability Statement: Not applicable. The authors would like to sincerely thank The West Indian Immunology Society for their assistance.

Conflicts of Interest: The authors declare no conflict of interest.

Ethical Compliance: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. [13] [AV14] [AV15].

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