Chapter

Neuropsychiatric SLE: From Immune Mechanisms to Clinical Management

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Abstract

In this chapter, we will describe neuropsychiatric lupus (NPSLE) as it develops and is treated in lupus patients, as well as means to study the disease using animal models. Based on mouse studies, we will discuss the correlation between inflammatory mediators, such as cytokines and autoantibodies, and the development of neurological symptoms with specific emphasis on the evidence for systemic versus local effects. We will describe specifically the effect of these mediators on the blood-brain barrier, microglia cell function, and the immune system. In addition, we will summarize signs and symptoms in NPSLE patients, especially with respect to primary versus drug-induced neurological issues and current treatment strategies. The chapter will offer a comprehensive review of old and new studies in animal models and patient populations and offer insight into how these results align with current treatment strategies offered to patients.

Keywords: neuropsychiatric lupus, animal models, autoantibodies, cytokines, treatment

1. Introduction

This chapter covers aspects of neuropsychiatric systemic lupus erythematosus (NPSLE), including basic science, as well as clinical features and management. Animal studies have been invaluable in informing our knowledge of pathogenesis and pathophysiology, especially in regard to elucidating immune mechanisms. Studies in two of the most commonly used mouse models, MRL/lpr and (NZB/NZW)F1 (NZB/W), have led to the identification of autoantibodies and cytokines implicated in NPSLE development. Specific antibodies include anti-NMDA-NR2 and anti-ribosomal P antibodies, as well as anti-phospholipid antibodies, that may play a role in perturbing the blood-brain barrier (BBB). There is evidence that BBB permeability may be the second hit needed to induce NPSLE, and cytokines have been repeatedly implicated in this process. Clinical correlations strengthen the argument for autoantibody and cytokine involvement in the pathogenesis, given the discovery of elevated cytokine and autoantibody titers in cerebrospinal fluid (CSF) from patients. Additionally, studies have been performed, whereby autoantibodies identified in NPSLE patients were injected into mouse models to induce an NPSLE phenotype.

Since microglia are the major immune cells of the brain, we separately discuss how their activation can lead to pathophysiology. A connection with estrogen receptors may also exist as seen in MRL/lpr mice. In addition, new evidence suggests that one of the most frequently studied cytokines in SLE, interferon-α (IFNα), may play an important role in NPSLE etiology. As such, studies have shown that deficiency in the IFNα/β receptor can reduce both systemic and neurological diseases in multiple lupus mouse models. Interestingly, IFNα has been independently associated with mood and cognitive symptoms, as seen in the side effects experienced by those who use it as treatment for various cancers and viral infections.

One aspect of NPSLE research that delves more into the clinical realm is the identification of biomarkers. A number of studies have looked at various potential biomarkers, including the aforementioned cytokines and autoantibodies. We review the evidence and emphasize the lack of consistent correlation, which is often a result of the wide ranging, vague, and often subjective manifestations of NPSLE. These include cerebrovascular disease, seizures, myelopathy, aseptic meningitis, movement disorders, and demyelinating syndrome. Psychiatric features have also been described, such as psychosis and mood changes. Some of the more vague symptoms include cognitive dysfunction and acute confusional state. Because these clinical features often overlap with other neuropsychiatric conditions and many of these symptoms are difficult to quantify, reports of epidemiology are highly variable ranging anywhere from a prevalence as low as 12% to as high as 95%. Although NPSLE still often remains a diagnosis of exclusion, we cover consensus case-definition criteria and explore the role, if any, of imaging such as quantitative MRI.

Lastly, we discuss the management of NPSLE, which, due to the complexity in diagnosis and lack of disease activity markers, has been mostly empirical. Corticosteroids and immunomodulators continue to be the mainstays of treatment, although they present numerous side effects. In addition, symptomatic therapy, including anticonvulsants, antidepressants, or antipsychotic medications, can be used. Antiplatelet and anticoagulation therapy should also be considered to manage cerebrovascular risk factors in those with antiphospholipid antibodies. In summary, the body of knowledge about the pathophysiology of NPSLE leaves much to be desired. Further studies in mouse models are necessary to identify more consistent biomarkers and develop targeted treatments for patients suffering from this disease.

2. Animal models used to study neurolupus

Given the difficulties in studying NPSLE in patients due to unclear associations with symptoms and timing of diagnosis, as well as overlap with other neurological and psychiatric syndromes, the use of murine models has been invaluable for elucidation of pathological mechanisms and identification of better therapeutic targets. Three families of murine models for SLE have been studied, including spontaneous models, induced models, and genetically engineered models. Within spontaneous models, typically generated by selective inbreeding, the most commonly used models to study neuropsychiatric manifestations include the F1 hybrid between New Zealand Black (NZB) and New Zealand White (NZW) mice called the (NZB/NZW)F1 hybrid (NZB/W) and the Murphy Roths large (MRL) strain [1]. NPSLE has not been studied extensively in induced or genetically engineered models.

2.1 MRL/lpr mice

The MRL/lpr model carries a spontaneously occurring mutation in the lymphoproliferative (lpr) gene on the MRL inbred background. The lpr mutation is linked to

a variation in the fas gene that causes failure of lymphocytes to undergo apoptosis [2]. The result of this mutation is the accumulation of CD4, CD8, and CD3 T cells in lymphoid tissue [3]. MRL/lpr mice develop an accelerated and aggressive lupus-like disease characterized by immune-mediated damage to the kidneys, skin, heart, lungs, joints, and brain and by the presence of circulating autoantibodies against dsDNA and Smith antigen [1]. Young MRL/lpr mice also spontaneously develop behavioral dysfunction and mood changes, as well as a depressive-like behavior as measured by the forced-swim test [4]. The presence of depressive symptoms in MRL/lpr mice has been found to correlate with titers of autoantibodies against dsDNA, the NMDA receptor, and cardiolipin [4]. Additionally, MRL/lpr mice display loss of preference for sweetened fluids, reflecting anhedonia, which is a core feature of major depression in humans [5].

Brain growth appears to be stunted in MRL/lpr mice, and ventricles increase in size along with development of autoimmune manifestations [1, 6]. More specifically, increased neurodegeneration, reduced dendritic complexity, and progressive atrophy of pyramidal neurons have been seen in the hippocampi of MRL/lpr mice [1]. Cyclophosphamide immunosuppression prevented atrophy and increased dendritic branching in MRL/lpr, thereby supporting the notion that autoimmunity is at least partly responsible for decreased brain growth possibly also affecting behavioral alterations [7].

Finally, SLE in humans has a well-known sex bias affecting females 9–10 times more than males [8]. Interestingly, this bias seems to be recapitulated in the depressive phenotype and autoantibody titers of MRL/lpr mice, with females exhibiting accelerated signs of both depression and autoantibodies as early as 5 weeks as compared to 18 weeks in males [9]. This suggests that autoantibodies may be implicated in the pathogenesis of NPSLE phenotype in this mouse model, as will be discussed further below.

2.2 (NZB/NZW)F1 mice

The NZB/W model develops a spontaneous and severe autoimmune disease with autoantibodies and defective immune complex clearance [10]. Manifestations of lupus in the NZB/W model resemble those of MRL/lpr mice. While they do not develop lymph node hyperplasia, they succumb to a progressive glomerulonephritis leading to fatal renal failure [2]. The sex bias of SLE is also recapitulated in NZB/W mice, with female mice exhibiting accelerated disease [11]. Beneficial effects from treatment with antiestrogen agent tamoxifen suggest that the sex difference is at least partly due to estrogen [12]. Signs of neurolupus in NZB/W mice manifest as progressively increasing anxiety behavior and decreasing exploratory behavior [13], as well as learning and memory deficits that develop later in the disease course [14]. Moreover, immunosuppressive treatment with cyclophosphamide and prednisolone alleviated behavioral deficits in this mouse model [15]. Brains of NZB/W mice have mononuclear infiltration of cerebral and hippocampal blood vessels and in the choroid plexus [14]. Moreover, the mice display a reduction in neuropeptides, namely neuropeptide Y, substance P, and calcitonin gene-related peptide P in the cortex, hippocampus, and hypothalamus that correlate with the development of neurological deficits [16]. It was in this mouse model that anti-dsDNA antibodies were found to be cross-reactive with a peptide sequence, which was also found in humans and later identified to be a subunit of a neurotransmitter receptor (NMDAR-NR2) [17, 18], as addressed below.

3. Understanding of NPSLE-like pathogenesis

Polyclonal B cell activation and autoantibody production seem to play a major role in the pathogenesis of SLE; however, the initial events leading to this activation

and deregulation remain undetermined [2]. Still, overwhelming evidence supports a pathogenic role for autoantibodies as will be discussed further below.

One consideration necessary when discussing NPSLE pathogenesis, however, is how antibodies produced subsequent to B cell activation gain access to the CNS. The brain is immunoprivileged due to the existence of multiple barriers regulating entry of immune cells and compounds such as antibodies. As a result, it has long been thought that some kinds of disruption in these barriers are necessary for NPSLE disease to manifest [19]. This notion is further supported by the observation that some SLE patients have brain reactive autoantibodies in their sera but do not have neuropsychiatric disease [20, 21].

3.1 Three types of barriers

In addition to a high metabolic demand, the brain requires a tightly regulated environment free of toxins and pathogens, which is maintained by three types of barriers: the blood-brain barrier (BBB), the meningeal barrier in the arachnoid matter, and the blood-cerebrospinal-fluid-barrier (BCSFB) [19]. Due to the paucity of data in the literature, the meningeal barrier will not be further discussed here.

The BBB is perhaps the most widely discussed of the three, as it protects the brain from toxic elements in the blood but also allows for the entry and exit of compounds in a finely controlled manner [19]. This balance is achieved via coordination between multiple cell types that are collectively known as the neurovascular unit (NVU) [22–24]. The NVU consists of endothelial cells lining the capillaries, neurons, astrocytes, pericytes, and microglia [22]. Tight junctions between endothelial cells form a layer on the luminal side of capillaries, thereby restricting paracellular diffusion. Pericytes are embedded in the basal lamina matrix that surrounds endothelial cells, and astrocyte endfeet reside on the outer surface of the basal lamina [22]. Astrocytes are thus able to communicate with both vasculature, as well as local neurons. Finally, resident microglia use long processes to survey the microenvironment near the NVU [22].

The BCSFB separates the blood from the ventricular system, which is comprised of the lateral, CSF-filled third and fourth ventricles. CSF is produced and secreted by the choroid plexus, which consists of cuboidal epithelium that, among other characteristics, contains transporters that regulate CSF composition [25]. Albumin quotient and IgG index in the CSF are commonly used surrogates for BBB disruption; however, it should be noted that it is difficult to distinguish whether the source of these molecules is from BBB or BCSFB disruption, and further studies are needed to determine the relative importance of these barriers [19].

Historically, studies in mice have suggested that there need to be a "second hit," namely a breach in the BBB for antibodies to access the brain, however, was recently challenged by studies failing to find an effect of BBB disruption [26], but rather an impact of BCSFB disruption [27]. As such, using exogenous tracers, Gelb et al. failed to find significant changes in BBB permeability in MRL/lpr mice but found abnormal function of the BCSFB in the choroid plexus, a potential site for lymphocyte infiltration [27]. Further studies are needed to identify the relative significance of BBB and/or BCSFB disruption in different animal models and in response to different inflammatory factors including cytokines and autoantibodies.

3.2 Evidence for BBB permeability

Older MRL/lpr mice have significant elevations of IgG and albumin levels in the CSF, suggestive of BBB disruption [28]. This is further corroborated by studies showing IgG filtration into brain parenchyma in MRL/lpr mice and increased permeability of nonautoimmune endothelial cells on treatment with serum from MRL/lpr mice compared with serum from controls [29]. Interestingly, these effects were

found to be mediated by terminal complement factor C5a [29], although further studies investigating the influence of complement on neurolupus phenotypes in MRL/lpr mice have yet to be performed. Another possible sign of BBB disruption is the finding that CD3 T cells penetrate into the choroid plexus and parenchyma of MRL/lpr mice [30]. Interestingly, the presence of brain infiltrating CD3 T cells was accompanied by splenomegaly and retarded brain growth [30], suggesting leukocyte infiltration as a mechanism for neurodegeneration. Finally, the BBB of MRL/lpr mice has also been found to stain for C1q complement particles and IgG, suggesting the presence of immune complexes [31], although whether such complexes are functional or diagnostic remains to be determined. Finally, it should be mentioned that aquaporin 4 expression was increased in brains of MRL/lpr mice but reduced in response to a soluble complement inhibitor, suggesting that complement may play a specific role in driving cerebral edema and inflammation [31].

3.3 Brain-reactive antibodies

Evidence for the presence and involvement of brain-reactive antibodies (BRA) comes from the finding that levels of CSF IgG correlate with immobility on the forced-swim test in MRL/lpr mice [32]. Specific BRAs have been identified and suggested to play a role in initiating, driving, or propagating NPSLE and will be discussed below.

3.3.1 Anti-NR2 antibodies

Glutamate is the main excitatory neurotransmitter of the brain, and the N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamate receptor subtype consisting of two NR1 subunits in a complex with two of the four NR2 (a–d) or two NR3 (a and b) subunits [33]. It was discovered in the early 2000s that a subset of anti-dsDNA antibodies cross-react with the NR2 subunit of the NMDA receptor [34]. Anti-NR2 antibodies have been found in the sera of both NZB/W and MRL/lpr mice and correlate with hippocampal and amygdala neuronal dysfunction and death even before NPSLE symptoms [17, 18, 35]. Neurons in the amygdala, anterior hypothalamus, cerebellum, and the hippocampus express a high density of NMDARs with subunits NR2a and NR2b [36], and so it follows that anti-NR2 antibodies would correspond with cognitive dysfunction. In clinical studies of SLE patients, up to 81% carry the anti-NMDA-NR2 antibodies, and anti-NR2 titers in the CSF of SLE patients correlate with diffuse symptoms, such as cognitive impairment, memory decline, impaired attention or executive functions, and depression [37]. The pathogenicity of anti-NR2 antibodies was further corroborated by the finding that transfer of isolated antibodies from lupus patient serum directly into the brains of nonautoimmune mice-induced neuronal cell death and impaired cognition [38, 39]. Interestingly, the concentration of anti-NR2 autoantibodies affects the function of the NMDA receptor differently; while low concentrations change synaptic function, high concentrations promote excitotoxicity, resulting in neuronal cell death by overactivation of glutamate receptors and excessive calcium influx [40], making quantitative measurements important for diagnosis and treatment. It should be noted that in these studies, pharmacological breach of the BBB was necessary for symptoms to occur and only achieved with intravenous administration of lipopolysaccharide or epinephrine, eliciting a strong cytokine response driving BBB disruption.

3.3.2 Antiribosomal P antibodies

In the late 1980s, an association was found between elevated serum titers of antiribosomal protein (RP) antibodies and lupus psychosis in NPSLE patients [41].

Although subsequent studies continued to find an association, an international meta-analysis subsequently found that anti-RP antibodies had limited diagnostic value [20]. Still, when anti-RP antibodies from NPSLE patients were injected into the ventricles of mice, animals developed depressive-like symptoms as measured by immobility [42]. Brains of these mice also showed anti-RP antibody staining in the hippocampus, cingulate cortex, and the primary olfactory piriform cortex [42]. Interestingly, symptoms were partially reversed when a specific anti-idiotypic antibody to anti-RP was administered [42]. Additionally, one study found that human-derived anti-RP antibodies affected glutamatergic synaptic transmission and plasticity related to memory in the hippocampus [43]. These findings are supported by studies showing an association between depression and the presence of anti-RP antibodies in lupus patients [44–46].

3.3.3 Antiphospholipid antibodies

Antiphospholipid syndrome (APS) is defined by the presence of lupus anticoagulant (LA) or anti-β2-glycoprotein-I (β2-GPI), which is a subset of anticardiolipin (aCL) antibodies. SLE patients with APS are more likely to develop infarcts, stenotic arterial lesions, and white matter hypertrophy compared with SLE patients without APS [47]. Antiphospholipid antibodies have also been associated with psychosis in one [48] but not another [49]. Still, a meta-analysis of autoantibodies present in NPSLE patients found an increased prevalence of antiphospholipid (APL) positivity in patients with cerebrovascular disease and cognitive dysfunction [50].

A similar correlation was found in animal models. Mice immunized with a pathogenic monoclonal aCL antibody developed hyperactive behavior in an open field, and examination of brain tissue revealed thrombotic capillary occlusion and mild inflammation [51]. To further explore aCL antibody pathogenicity, Ig from an APS patient was administered into the ventricles of mice and was subsequently found to bind to the hippocampus and cerebral cortex [52]. The level of aCL antibody binding correlated with poor performance on the water maze [52], suggesting a specific role for these autoantibodies.

Other mechanism by which APS antibodies may contribute to NPSLE manifestations are via endothelial activation and the induction of a prothrombotic state [53] or via directly affecting BBB permeability and thus allowing for the penetration of pathogenic autoantibodies such as anti-NR2 antibodies [54]. Further studies are needed to determine the primary mechanism of aCL antibodies and their effect on brain health.

3.4 Cytokines

Cytokines have been implicated in neurotoxicity. For example, when CSF from MRL/lpr mice was administered into the CNS of a nonautoimmune rat, it induced neurotoxicity and periventricular neurodegeneration [55]. Exposure to lupus CSF also led to reduced neuronal viability of hippocampal neurons and astrocytes *in vitro*, suggesting the presence of intrathecal neurotoxic metabolites and/or cytokines [56].

As described above, cytokines may directly act to breach the BBB [19]. For example, peripheral administration of lipopolysaccharide (LPS), a cytokine inducer, or of recombinant IL-1 and TNF-α is sufficient to decrease motor and social activity and reduce food and water intake, reflecting depression and anhedonia, respectively, in C57BL/6 mice [57, 58]. The effect was most likely mediated by TNFα, since mice deficient in TNF-α receptors was resistant to both depression and sickness behavior [59], although specific analyses separating peripheral from brain-specific effects were not done. Further supporting a role for cytokines is the

observation that increased serum levels of IL-1 correlated with blunted responsiveness to palatable stimulation in MRL/lpr mice [60]. Additionally, IL-6 production occurs early on and reduces sucrose preference, which is a behavioral alteration replicated by exogenous IL-6 administration [61]. IL-6 knockout mice are somewhat protected from the behavioral effects of LPS and IL-1 injection [62, 63], suggesting that IL-6, as TNFα, is acting downstream of these mediators. Furthermore, treatment with cyclophosphamide abolished the rise in IL-6, as well as attenuated behavioral deficits and neuronal death in MRL/lpr mice [64, 65]. Finally, injection of IL-6 increased BBB permeability in rats [66].

An additional possible player is TNF-like weak inducer of apoptosis, TWEAK. TWEAK is a secreted ligand of the TNF family that mediates its effects through its receptor Fn14, and Fn14-deficient MRL/lpr mice displayed decreased depressive behavior and cognitive impairment as measured by decreased immobility in forced swim test and maintained preference for sweetened fluids compared to controls [67]. Fn14 knockout mice also showed improved BBB integrity as measured by albumin quotient [67], suggesting a specific effect of TWEAK on the BBB.

Separate from the typical proinflammatory cytokines (TNFα, IL-1, and IL-6), IFNα may play an important role in NPSLE. IFNα is an antiviral cytokine in the type I IFN family strongly implicated in the pathogenesis of SLE. Numerous studies have shown that type I IFN receptor (IFNAR) deficiency reduces disease in multiple lupus mouse models [68–70]. Similarly, clinical data from patients undergoing IFNα therapy have shown neurotoxicity and induction of symptoms similar to those in NPSLE, such as cognitive impairment, seizures, and mood changes [71, 72]. In a bioassay containing plasmacytoid dendritic cells (the main INFα-producing cell type) and a source of antigen, CSF from NPSLE patients induced higher IFNα production than CSF from other autoimmune disease control subject [73], suggesting that specific antibodies and/or cytokines in CSF from SLE patients can stimulate IFNα production, although the nature of such stimulants remains unknown. Most recently, it was shown that treatment of NZB/W mice with anti-IFNAR antibodies effectively blocked neurological symptoms and that IFNα directly affected microglia cells *in vitro* [74]. Future studies evaluating the specific lack of IFNAR expression within the brain will be important to determine if the effect of IFNα in NPSLE is predominantly peripheral or brain specific. Furthermore, studies addressing the importance of IFNAR expression on specific brain-associated cell subsets *in vivo* during disease development are required to develop suitable BBB-breaching therapies if needed.

In addition to a direct effect of cytokines on the BBB, it is possible that cytokines can target the CNS without BBB disruption. This possibility stems from studies showing that cytokines do not need to pass the BBB to regulate behavior [75]. The existence of an entity called "sickness behavior," as characterized by lethargy, depression, malaise, and loss of appetite, supports the notion that immunity can affect behavior [57]. Sickness behavior is considered an adaptive response to infection that is mediated by cytokines, mainly IL-1, IL-6, and TNFα [75]. These cytokines have been separately implicated in the pathogenesis of psychiatric disease and are the same cytokines found to be elevated in MRL/lpr [76–78], NZB/W F1 [66, 79], and human [80] studies of NPSLE as described above.

There are two ways by which cytokines can affect the brain *without* involving BBB disruption. First, cytokines may enter the brain through afferent branches of the vagus nerve, which contain macrophages and dendritic cells in their sheath [81], and secondly, phagocytic cells in brain regions surrounding the ventricles and the choroid plexus may themselves produce and release cytokines [82]. Evidence for the role of the vagus nerve includes studies that show that vagotomy reduces sickness behavior [83, 84] and brain IL-1 expression [85–87] in response to intraperitoneal LPS and IL-1. This finding may be mediated through cytokine

production by immune cells in the vagus perineural sheath [81]. It has also been found that macrophage-like cells and microglia in the brain regions surrounding the ventricles and the choroid plexus, which lack BBB, produce IL-1 in response to LPS administration [88, 89]. Thus, although the prevailing hypothesis is that BBB dysfunction is necessary for NPSLE manifestation, data from sickness behavior and depression research suggest that there may be BBB-independent cytokine-mediated mechanisms.

In summary, cytokines contribute to NPSLE via a variety of mechanisms, including through the vagus nerve and periventricular brain regions without crossing the BBB, by directly causing BBB disruption, and/or by causing specific neurotoxicity.

3.5 Microglial activation

As the major immune cell type of the brain, microglia phagocytize redundant and unnecessary synaptic connections, thereby contributing to the structural organization of the brain and facilitating learning and memory [90]. Estrogen has been implicated in the pathogenesis of NPSLE via microglial activation. In female MRL/lpr mice, global estrogen receptor (ER) α deficiency resulted in reduced numbers of activated hippocampal microglia and improved spatial memory, as measured by the Morris water maze performance, in a manner independent of serum autoantibody and estrogen levels [91]. However, it remains unknown if this effect was direct or mediated by reduced immune reactivity.

Recently, it was shown that also IFNα stimulates microglial reactivity, and treatment of lupus-prone mice with anti-IFNAR antibody was sufficient to reduce percentages of activated microglia and synapse loss, as well as prevent behavioral phenotypes [74]. Moreover, increased IFNα signaling was also observed in postmortem hippocampal brain sections from patients [74], further supporting a pathogenic role for IFNα in NPSLE. Taken together, these data suggest that the pathogenesis of NPSLE may involve IFNα-driven and ER-mediated microglial activation.

4. Clinical phenotypes

4.1 Epidemiology

A prevalence as low as 12% and as high as 95% has been described for NPSLE manifestations. Different study designs, NPSLE symptoms studied, and population selection have contributed to discrepancies in reports.

The first set of standardized nomenclature was developed in 1999 by the American College of Rheumatology (ACR) Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. Case definitions were established for 19 different neuropsychiatric syndromes and divided into 12 central nervous system (CNS) and 7 peripheral nervous system (PNS) manifestations, as listed in **Table 1** [92]. The PNS manifestations are less common than CNS syndromes and are addressed elsewhere [93, 94]. CNS syndromes were further categorized into focal neurologic syndromes (cerebrovascular disease, seizures, myelopathy, aseptic meningitis, movement disorder, and demyelinating syndrome) and diffuse psychiatric/neuropsychological syndromes (cognitive dysfunction, mood and anxiety disorders, psychosis, acute confusional state, and headache).

As expected, the diffuse psychiatric/neuropsychological syndromes presented with more difficulties in diagnostic agreement due to their diverse presentations

	ACR criteria [92]	**Modified criteria by Ainiala** [95]
Central nervous system—manifestations	*Focal neurologic syndromes* Aseptic meningitis Cerebrovascular disease Demyelinating syndrome Movement disorder (chorea) Myelopathy Seizure disorders *Diffuse psychiatric/neuropsychologica syndromes* Headache (including migraine and benign intracranial hypertension) Acute confusional state Anxiety disorder Cognitive dysfunction Mood disorder Psychosis	Aseptic meningitis Cerebrovascular disease Demyelinating syndrome Movement disorder (chorea) Myelopathy Seizure disorders Acute confusional state Cognitive dysfunction (moderate or severe) Severe depression Psychosis
Peripheral nervous system—manifestations	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre´ syndrome) Autonomic disorder Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy, cranial Plexopathy Polyneuropathy	Acute inflammatory demyelinating polyradiculoneuropathy Autonomic disorder Mononeuropathy, single/multiplex Myasthenia gravis Neuropathy, cranial Plexopathy Polyneuropathy (with ENMG confirmation)

Table 1.
ACR criteria for NPSLE syndromes.

and subjective nature [92]. In a subsequent cross-sectional validation study, these criteria were found to have a 46% specificity, thereby demonstrating inability of criteria to distinguish NPSLE patients from controls [95]. This low specificity was speculated to be partly attributed to the manifestations of NPSLE that overlap with other CNS conditions, as well as discrepancies in diagnosis of the diffuse neuropsychological syndromes. When the validation study excluded syndromes without any indication of neurologic dysfunction, including headache, mild cognitive dysfunction, mild mood and anxiety disorders, and polyneuropathy without electrophysiological confirmation, they were able to improve specificity to 91% [95].

To better understand the reasons for the high variability of prevalence estimates between different studies, Unterman et al. [96] performed a meta-analysis of 17 studies from 1999 to 2008 that applied the 1999 ACR case definitions. Using a subanalysis of 10 prospective studies, they found the prevalence of NP syndromes in SLE patients to be 56.3%, with a range from 23 to 95% [96]. In contrast, analyses of retrospective studies presented with a cumulative prevalence of only 17.6% [96]. A reason for this discrepancy may be that the syndromes that are more subjective to diagnose, such as headache, mood disorders, cognitive dysfunction, and anxiety, often had increased prevalence in prospective studies as compared to numbers obtained from retrospective studies [96]. In contrast, syndromes that may be considered more objective due to their measurability, such as seizures and movement disorders, showed little variability in prevalence from prospective versus retrospective studies and thus would be equally suitable for retrospective or prospective review.

Examination of studies at either end of the prevalence spectrum revealed several key characteristics influencing variability, including exclusion of subjective syndromes such as headache, differences in population characteristics such as age

and race, and the level of detail in diagnosis, including the use of a comprehensive neurocognitive battery [96]. It should be noted that of the 19 syndromes defined by the ACR, none is specific to NPSLE, and thus when assessing prevalence and impact, comparison to control populations and attribution to SLE versus other diseases are important.

NPSLE diagnosis is still currently a process of exclusion, which requires a detailed history and comprehensive evaluation to rule out other causes of symptoms, such as primary neurological or psychiatric disease [97]. Laboratory studies are important to support a NPSLE diagnosis, in particular markers of inflammation such as erythrocyte sedimentation rate and complement levels [97]. Of the serum autoantibodies, perhaps the most consistently present are the serum aPL, with an estimated prevalence of 45% in NPSLE patients [98, 99], although it should be noted that presence of these autoantibodies does not preclude the possibility of concurrent SLE and primary neuropsychological disease.

4.2 Cerebrovascular disease

Cerebrovascular disease stemming from SLE is thought to be at least partially caused by antiphospholipid (aPL) antibodies, leading to thrombosis in cerebral vasculature [1]. Identified risk factors for cerebrovascular disease include chronic and high disease activity, high cumulative corticosteroid dose, persistently elevated titers of aPL antibodies, heart valve disease, and systemic hypertension [100, 101]. An additional contributor to cerebrovascular disease is the observation of premature atherosclerosis in the vasculature of SLE patients, which occurs independently of traditional cardiovascular risk factors [102]. Data in support of this include increased prevalence of carotid plaque in SLE patients compared with age- and sex-matched controls even after adjustment for traditional risk factors [103]. A recent study shows that the relative risk of subclinical atherosclerosis in SLE was comparable to that found in diabetes mellitus, a well-known and major risk factor for cerebrovascular disease [104]. Cerebrovascular disease can lead to events such as stroke, which can then lead to other NPSLE syndromes such as cognitive dysfunction [105].

4.3 Seizures

Seizures often occur early in NPSLE disease progression and are positively correlated with African race/ethnicity, lower educational status, and cumulative organ damage [106]. The correlation with race and education may be a reflection of socioeconomic status [107], which is a predictor of both functional status and mortality [108] and may influence access and adherence to treatment [106]. In prospective cohort studies, the most common seizure type was primary generalized; however, some patients also had partial episodes [109, 110]. Cerebral atrophy and cerebrospinal fluid (CSF) pleocytosis are common findings in NPSLE, perhaps suggesting that there may be a lupus-related encephalopathic process seizure pathogenesis [93]. Independently of other symptoms, seizure occurrence can be an indicator of the level of disease activity [109, 111].

Seizures may occur many years before SLE diagnosis, potentially leading to erroneous diagnoses of epilepsy [109]. This misdiagnosis may be prevented by obtaining antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) levels, as these are commonly elevated in patients with seizures attributable to SLE [112] and would further support SLE as the etiology. In one larger prospective study, most seizures resolved without a negative impact on quality of life and did not require long-term antiseizure medication, although a smaller study

found a need for long-term continuous treatment with antiepileptics [113]. This discrepancy may be due to the latter study being retrospective, allowing for longer follow-up time. Seizure prevalence varies, as is the case with estimates of all NPSLE symptoms; however, most larger studies found a cumulative frequency of 5–10% of SLE patients [106, 109, 113].

It remains unclear if aPL antibodies are associated with seizure occurrence, as one study showed a positive correlation with seizure recurrence [114], while others did not [106, 111, 113]. Because antibody titers were not always measured close to seizure event time points, further studies are needed to better understand how antibodies may change with disease activity and therefore influence seizure occurrence. There is evidence, however, that antibodies may directly induce seizures by increasing neuronal excitability through inhibition of GABA receptors [115] and permeabilization and depolarization of brain synaptoneurosomes [116]; however, it is also possible that aPL antibodies lead to strokes, which predispose patients to seizures [111, 117]. Thus, aPL antibodies and strokes are confounding factors for seizure etiology [114].

Finally, consistent evidence supports a protective effect of antimalarials for seizure occurrence as well as overall survival [106, 118]. Evidence for a mechanism includes studies that show antimalarials interfering with interferon-α production and immune complex formation by preventing incorporation of RNA and DNA fragments into Toll-like receptors 7 and 9, respectively [119, 120]. Authors have also found lipid-lowering effects of antimalarials via interference with lipoprotein lipase activity [121–123]. Lastly, antithrombotic properties of antimalarials have been demonstrated in both mice [124] and patients [125, 126]. Thus, protection from seizures with the use of antimalarial agents may be related to the prevention of thrombosis.

4.4 Myelopathy and demyelination syndrome

Myelopathy is a general term used to describe any disorder of the spinal cord leading to paraparesis and/or sensory impairment, which can arise from a number of etiologies, such as ischemia, compression, metabolic, and inflammatory causes [127]. Myelitis technically refers to when a spinal lesion is secondary to inflammation; however, the two are often used interchangeably in the literature [127]. In the 1999 ACR criteria (see **Table 1**), myelopathy and demyelination syndrome are considered separate entities, with myelopathy referring to any rapidly involving spinal cord lesion, whereas demyelination syndrome encompassed demyelinating lesions anywhere in the CNS, which includes transverse myelopathy [92]. Due to the considerable overlap in these two syndromes, they will be considered together here.

Myelopathy in NPSLE usually refers to transverse myelitis (TM), which is an early, rapidly evolving but very rare manifestation (~1%) [96, 97]. The mechanism can be ischemic or inflammatory in nature, and symptoms typically manifest as flaccidity and hyporeflexia or spasticity and hyperreflexia [128]. Transverse myelopathy has been identified as the first manifestation of SLE [129] and has been associated with aPL positivity [130], suggesting aPL-induced thrombosis as a potential mechanism [131]. The evidence, however, has not been consistent [132, 133], and the presence of thrombosis does not explain involvement of different levels of the spinal cord [134]. Some have suggested an aPL-induced vasculitis of spinal vessels [135] and loss of perfusion secondary to spinal cord swelling [128] as alternative mechanisms.

Demyelinating syndrome in lupus has been termed lupus sclerosis to indicate the clinical similarities with MS, such as optic neuritis, brainstem and cerebellar syndromes, spastic paraplegia, and other transient neurological deficits [93].

The term "clinically isolated syndrome" was originally developed to describe the first demyelinating episode suggestive of MS [136], but it could also be the first demyelinating episode of NPSLE [134]. Pathological studies confirmed that lupus sclerosis was indeed distinct from MS, with no evidence of primary demyelination [137]. Misdiagnosis can have disastrous consequences, as treatments for MS, especially interferon-based therapies, can exacerbate SLE [138]. Certain clinical findings, such as the concomitant presence of renal involvement, rash, arthritis, myalgia, PNS involvement, and meningismus, might indicate SLE as the underlying diagnosis [134]. Moreover, the presence of cerebrovascular disease or thrombotic events is the clue for concomitant or primary APS [139]. In fact, one study found that 8% of patients with aPL positivity had a previous diagnosis of MS or MS-like symptoms [140], suggesting that aPL screening should be conducted in patients presenting with MS-like symptoms, particularly since it is noninvasive and inexpensive [134, 141].
Additionally, high ESR, ANA, and lack of oligoclonal immunoglobulin bands in the CSF would support NPSLE etiology. Whereas type I IFN activity is elevated in SLE and implicated in its pathogenesis, type I IFN activity is low in MS [142] and IFNβ is actually used as a treatment for MS [143]. This difference suggests that measuring serum type I IFN activity may be a useful way to distinguish patients who have demyelinating syndrome from SLE versus MS [142].

Optic neuritis in NPSLE is characterized by pain with ocular movements and visual impairment [134], and similarly, TM can be the first presentation of SLE and has been associated with aPL [144]. The combination of TM and optic neuritis is termed neuromyelitis optica (NMO). In a small cohort of SLE patients with white matter myelitis, NMO was found in roughly half of the patient population [128]. Interestingly, NMO is also associated with aPL positivity in addition to the presence of antiaquaporin autoantibodies [128, 145]. Antiaquaporin antibodies are specific to NMO and present in the sera of SLE patients years before the first NMO attack [146]. Additionally, serum IFNα activity was found to be high in NMO patients, similarly to patients with SLE [142], suggesting that NMO and SLE may share at least some similarities in pathophysiology.

NMO was only recently recognized to be an independent entity rather than a subset of MS [145, 147]. Additionally, because TM, optic neuritis, and NMO all have associations with aPL positivity, studies have suggested an intersection between SLE, MS, and APS [138, 141, 148]. Given that the literature on myelopathy in SLE still consists of mostly case studies [129, 130, 149–152], larger cohort studies are needed to better characterize these patients and distinguish pathogenesis of myelopathy from SLE versus MS. Additionally, a considerable amount of knowledge has been gained in the past two decades about various forms of myelopathy, and it is reasonable to consider reorganizing these syndromes in a revision of the 1999 ACR classification system [153].

4.5 Aseptic meningitis

Aseptic meningitis is a rare feature of NPSLE, but when it does present, it is usually earlier in the disease course and may signal the advent of other CNS complications such as transverse myelitis and strokes [93]. Diagnosis usually involves leukocytosis evident on cerebrospinal fluid analysis. Notably, nonsteroidal antiinflammatory drugs (NSAIDs) can cause aseptic meningitis [93]. Anywhere from 25 to 84% of lupus patients are treated with NSAIDs for symptoms such as synovitis, serositis, fever, soft tissue pain, and headache [154], making it difficult to determine the initiating factor. Regardless, many patients who experience drug-induced aseptic meningitis have SLE, suggesting that there may be some inherent

predisposition, although the mechanism is unknown [155]. In summary, adverse medication events may complicate the diagnosis of primary versus treatment-induced aseptic meningitis. Drug discontinuation is currently the only method to distinguish between these, as complete recovery can be observed after several days of drug discontinuation in drug-induced aseptic meningitis [155].

4.6 Movement disorders

Movement disorders in SLE are infrequent in adult NPSLE patients (<2%), although more frequently observed in juvenile SLE. When it occurs, it is often associated with an acute flare and predominantly in women under the age of 30 years [93]. Manifestations include rigidity, tremors, masked facies, chorea, and akinesia, although symptoms are often transient in nature [93, 97].

4.7 Cognitive dysfunction

In 1999, the ACR committee proposed a standard 1-hour battery of neuropsychological tests to assess cognitive function [92], which has since been tested and established for reliability and validity [156]. The definition of dysfunction included significant deficits in simple or complex attention, reasoning, executive skills, memory, visual-spatial processing, language, or psychomotor speed [92]. Studies have used different types and lengths of neuropsychological testing, thus contributing to a wide range of prevalence anywhere from 0 to 80% [156]. When the 1-hour battery as proposed by the ACR is used, the prevalence of cognitive dysfunction has a narrower range of between 23 and 60% [156].

Cardiovascular risk factors have been found to be related to the severity of cognitive dysfunction in SLE, in particular hypertension, which is also a risk factor for cognitive impairment in the general population [105]. In addition, hypertension itself has been associated with brain atrophy and cognitive dysfunction [157] and thus may contribute to the risk of cognitive dysfunction independently of SLE. Because cognitive impairment is also a common sequela of stroke [158], the association with aPL positivity may in fact be due to an occlusive vasculopathy [49]. Thus, screening for cardiovascular risk factors in SLE patients presenting with aPL positivity is important, as the risk for stroke may be significantly increased above baseline in these patients. Furthermore, this finding emphasizes that cognitive dysfunction is often sequelae of cerebrovascular events and may be prevented in some cases by addressing hypercoagulability and cardiovascular risk in SLE patients.

4.8 Mood changes

Mood changes in NPSLE encompass major depressive-like episodes, mood disorders with depressive, manic or mixed features, anxiety, panic disorders, and compulsion, with depression being the most common [97]. Not surprisingly, SLE disease activity is correlated with the presence and severity of major depression [159]. This connection may be a result of a multitude of mechanisms, including an independent association between mood and cardiovascular risk factors [100], as well as the psychological burden of having SLE in the first place, including illness stigma [160]. As discussed previously, elevated cytokine levels may also contribute to depression and anhedonia in NPSLE patients [75].

Similarly to psychosis (see below), it is important to determine if mood disorders are a result of primary psychiatric disease or secondary to corticosteroid therapy, as studies have shown a correlation between corticosteroid usage and several mood disorders [161–164]. Mania seems to be more commonly caused by

acute corticosteroid therapy [161, 163], whereas long-term therapy is more likely to lead to depressive symptoms [164]. Psychiatric disorders typically occur within the first 6 weeks of corticosteroid treatment and are dose dependent [161]. Up to 90% of patients recover completely with discontinuation or a reduction in dosage [161]. Additionally, when mood disorders are the initial presentation of NPSLE, corticosteroids are not typically used. Rather, patients usually receive antidepressant and antipsychotic medications, which are effective in treating mood disorders secondary to NPSLE [162]. Thus, corticosteroid-induced mood changes are a confounding factor only when mood changes develop after NPSLE diagnosis and subsequent steroid therapy, and withdrawal of steroids and use of antidepressant/antipsychotic medications would be warranted at that time. Factors that would suggest an SLE etiology rather than an iatrogenic one include the presence of a chronological association, imaging and EEG abnormalities, non-CNS manifestations of SLE, and serious disturbances in memory and concentration [162].

4.9 Lupus psychosis

Psychosis is a disturbance in perception of reality usually characterized by delusions and/or hallucinations, in the absence of delirium, and causing significant distress or functional impairment [165]. Psychosis is a relatively rare event in SLE that, similarly to seizures, occurs early and transiently in disease course, if at all [144, 166]. The reported prevalence varies from 0 to 11% [167–169].

The ACR Committee adopted terminology from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) [170], and lupus psychosis falls under "psychosis due to a general medical condition" (DSM-IV 293.81/82), which excludes schizophrenia and brief psychotic disorder, as well as bipolar disorder [170]. Thus, NPSLE patients with psychosis secondary to schizophrenia, brief psychotic disorder, or bipolar disorder, although few, would not be captured under the category of lupus psychosis per strict ACR case definitions [166].

In a retrospective study of 11 patients with primary lupus psychosis and a mean follow-up of 13 years, all had good response to intensive immunosuppressive treatment at the time of diagnosis and 70% achieved complete remission, suggesting a favorable long-term prognosis [166]. When diagnosing patients, it is important to distinguish lupus psychosis from iatrogenic steroid psychosis, for which hypoalbuminemia may be a risk factor [171]. Steroid psychosis is typically dose-dependent, occurs within 8 weeks of initiation, and usually resolves completely with dose reduction [162]. It should be noted that SLE itself is linked to a higher risk of steroid psychosis, possibly related to BBB damage, another risk factor for steroid psychosis. Therefore, it is important to identify new clinical readouts that are more suggestive of NPSLE, such as non-CNS manifestations, severe deficits in memory and concentration, or focal neurologic deficits [162]. Moreover, there are a number of agents that can be used for prophylaxis of steroid-induced neuropsychiatric disorders; thus, if steroid therapy is unavoidable, concurrent administration with valproate and lithium should be considered.

4.10 Acute confusional state

Acute confusional state is synonymous with encephalopathy and is characterized by impaired consciousness or level of arousal, which can progress to coma [172]. It is rarer than the other CNS syndromes, with a reported prevalence of 4–7% of SLE patients [173]. The etiology of acute confusional state in SLE remains to be determined, as SLE-nonspecific events such as infections and metabolic disturbances can also cause this syndrome [174].

4.11 Headache

In a meta-analysis of 35 studies of headache in NPSLE, the prevalence of all headache types, including migraine, was not different from controls, and insufficient evidence was found for the concept of "lupus headache" [175, 176]. Additionally, no specific mechanism for headache in SLE patients exists, and there is no link between headache and disease activity or cumulative organ damage [175, 177]. Pooled prevalence in this meta-analysis was 50.2%, in contrast to a much lower 12.2% in a more recent meta-analysis [96]. The estimate is closer to 30% if only prospective and elicited studies are included [96], suggesting that there is either underreporting in retrospective reviews or perhaps a component of recall bias in prospective studies. Additionally, it has been observed that headache prevalence can vary considerably with cultural differences, as Asian populations tend to report headache less frequently [178].

A recent prospective study of an international cohort found no link between headache and specific autoantibodies at time of study enrollment [177]. Although headaches negatively impacted quality of life, most headaches resolved independently of lupus-specific therapies [177], further supporting the lack of evidence for "lupus headache." There is inconsistency in diagnosing headache associated with SLE, even by physicians who specialize in SLE, and it remains unclear whether headache in SLE patients exists as an entity independent of other NPSLE events, such as meningitis, seizure, and cerebrovascular disease, and whether it warrants measurement as included in ACR criteria [175, 177].

The International Headache Society (IHS) has established criteria for the classification of all headaches, and in a 2008 study, they were found to be more exhaustive than current ACR criteria and include categories such as chronic headache disorders, which were not included in the ACR criteria [176]. Thus, some headache disorders may not be classified [176]. Discrepancies in headache classification may also explain prevalence variance. Additionally, cluster headaches are included in the criteria but evidence for its existence in NPSLE is sparse. This weakness suggests that ACR criteria may be in need of revision, especially given that IHS criteria is already used as the basis for clinical trials of headache treatments.

4.12 Summary

In conclusion, the clinical syndromes of NPSLE are varied and each presents with challenges in diagnosis and classification. The ACR criteria are in need of an update to offer more specificity, as pathogenetic mechanisms cannot be elucidated if there is no consensus about which patients have the syndrome. Because none of the syndromes discussed above are unique to NPSLE, there are often already pre-existing classification criteria, such as those for headaches and psychosis. As such, it is important in future studies to adhere to more stringent and consistent criteria rather than using inconsistent classification or evaluation methods. This approach would likely also limit the high variability in prevalence estimates of all NPSLE syndromes, notwithstanding the already subjective nature of many of these syndromes as well as differences in population characteristics. Many of these syndromes, such as seizures, myelopathy, and psychosis, present early on and can be the initial manifestation of NPSLE. Thus, as is the case with any disease, successful diagnosis of NPSLE starts with its inclusion on the list of differentials, although it remains a diagnosis of exclusion due to the lack of consistent biomarkers. A recent review detailed a diagnostic algorithm incorporating ACR case definitions and results from other studies suggesting modifications [94], and use of this may likely improve diagnostic accuracy and precision of prevalence estimates for future studies.

5. Evaluation and diagnosis

5.1 Imaging

A variety of imaging modalities are available for use in patient evaluation, including both anatomical imaging, such as CT, MRI, and magnetization transfer imaging, as well as functional imaging, such as functional MRI, PET, and SPECT imaging [97]. For a review of the most prevalent findings in NPSLE for each modality, see the review by Jeltsch-David and Muller [97]. As expected, the focal neurologic syndromes, namely seizures, cerebrovascular disease, myelopathy, and demyelinating syndrome, have the most identifiable imaging manifestations. MRI is perhaps the most commonly used technique due to its availability and popularity as an anatomical imaging modality, despite its poor sensitivity and specificity for NPSLE [97]. Additionally, MRI is often used in the workup of primary neurological diseases and is necessary to exclude these in the etiology of symptoms. For example, MRI can help to exclude infection and malignancy [131], and since NPSLE is a diagnosis of exclusion, MRI is a necessary part of the evaluation. Additionally, specific MR sequences with fluid attenuated inversion recovery and diffusion weighted imaging are recommended to improve sensitivity and specificity [93].

5.2 Biomarkers

Patient evaluation consists of first collecting a detailed medical history and ensuring exclusion of more common etiologies of NPSLE symptoms prior to chasing a diagnosis of neurolupus [97]. Only then, it is worthwhile to pursue broad laboratory investigation, such as CSF analysis, complement levels, erythrocyte sedimentation rate, as well as autoantibody panels. Identification of reliable biomarkers remains elusive, hence the continued need for pathogenetic inquiry [97]. Mechanisms are complex, and due to the diversity of presentations, no single pathway has been identified as a sole marker of disease. However, some commonalities include BBB dysfunction, vascular occlusion, neuroendocrine-immune imbalance, tissue damage mediated by autoantibodies and proinflammatory cytokines, and direct neuronal cell death [97]. Additionally, it is important to consider the heterogeneity of the studied population and assays used to assess antibody levels [179].

Antibodies to consider measuring include those targeting phospholipids, ribosomal P peptides, glial fibrillary acidic protein (GFAP), NMDA receptor, microtubule-associated protein 2 (MAP-2), and matrix metalloproteinase 9 (MMP-9). As outlined above, many of these have also been identified in animal models of NPSLE, further supporting potential causative and/or diagnostic relationships. Details on the specificity and association of each of these antibody specificities with each NPSLE syndrome were recently summarized [97]. In a recent meta-analysis of 41 studies of serum and CSF autoantibodies in NPSLE, significantly more NPSLE patients demonstrated positivity for serum aCL Abs, LA Abs, anti-RP Abs, antineuronal Abs, and CSF antineuronal antibodies as compared to SLE patients [50]. Thus, they suggest that measurement of these antibodies may help to identify patients at the risk of developing NPSLE.

It is important to note that multiple measurements of antibodies are needed for the most complete assessment, as antibody levels have been shown to fluctuate with time and disease activity (flares) [179]. Specific testing recommended for each syndrome is detailed elsewhere [131]. Measurement of aPL antibodies is warranted particularly if patients present with cerebrovascular disease, seizures, myelopathy, or cognitive dysfunction, as aPL-induced thrombosis is implicated in the

pathogenesis of these conditions. Positivity for aPL also influences management, as discussed further below.

Importantly, none of these antibodies have an adequately consistent association to qualify as a reliable biomarker, with even the most studied antibodies peaking at around 50% for prevalence in patients with NPSLE [97]. For example, antiribosomal P antibodies generated a great deal of interest, due to its early discovery in patients with lupus psychosis [41]. However, although early studies found diagnostic value, more recent studies shed doubt on its accuracy for NPSLE diagnosis [20]. A handful of cytokines, however, do show promise as being consistently elevated, among which is the aforementioned IFNα [73, 97]. Thus, more research is needed to determine if IFNα or other cytokines, such as IL-6, IL-8, and IL-10, would be suitable biomarkers or markers of disease activity.

6. Management

Due to the dearth of controlled trials for NPSLE therapy, current clinical practice is still defined by either addressing inflammation with immunosuppressive medication or ischemia and thrombotic events with anticoagulants [180]. Immunosuppression, which is still currently the mainstay of treatment for NPSLE, consists of corticosteroids alone or in combination with a second immunosuppressive agent [131]. Options for additional immunosuppression include cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, cyclosporine, rituximab, intravenous immunoglobulins, therapeutic plasma exchange, and hematopoietic stem cell transplant as a last resort [131]. Because corticosteroids have the most immediate antiinflammatory effect, they are often used in treatment of SLE disease flares, although dosing is still often empirical [181]. In addition to the previously discussed side effects of mood disturbances and psychosis, glucocorticoids can also cause hypertension, dyslipidemia, and increase the already elevated risk for cerebrovascular events in SLE [182]. Keeping doses <7.5 mg/day as well as the use of methylprednisolone pulses rather than long-term steroid therapy may help to mitigate the long-term adverse effects [183]. Thus, steroid therapy for NPSLE should be administered judiciously, and it may be prudent to use the minimum effective dose and titrate up as needed, reserving the higher doses for the acute setting.

Of the other immunosuppressive agents, cyclophosphamide was the only one tested in a randomized controlled clinical trial in acute, severe NPSLE, which found that treatment response was higher in the cyclophosphamide group versus the methylprednisolone group [184]. However, a subsequent Cochrane review categorized this study as low quality evidence due to its small size and high risk of allocation concealment, blinding, and selective reporting [185], thus highlighting the need for more high-quality randomized controlled trials evaluating the different immunosuppressive agents. Of the remaining options, azathioprine is most often used clinically as maintenance therapy following cyclophosphamide induction due to its milder side effect profile, and rituximab is used as a second-line therapy for severe, refractory NPSLE, although none of these agents have sufficient high-quality evidence to support their use [131].

Symptomatic therapy, which does not address the underlying pathology of NPSLE, is often the first treatment for SLE patients presenting with NP symptoms due to a lack of recognition of NPSLE [131]. Examples include antidepressive and antipsychotic agents for mood disturbances and psychosis, antiepileptics for seizures, dopamine agonists for movement disorders, and NSAIDs for headache [131]. These agents can be sufficient for symptomatic control in those with mild NPSLE disease. In those experiencing cognitive dysfunction or mood disturbances

secondary to the psychological burden of disease, psychoeducational group interventions may be beneficial [186, 187].

Primary prevention strategies, defined as preventing the onset on NPSLE, have been suggested with the use of hydroxychloroquine [144, 188], which is advantageous since hydroxychloroquine is a widely used and safe therapy for SLE [131]. As discussed previously, antimalarials are associated with less damage accrual [189] and have been shown to reduce mortality [118, 190], reduce cardiovascular disease and thrombotic risk [122, 123], and protect against seizures [106]. Statins may affect the regulation of inflammatory processes leading to atherosclerosis [191] and thus would be a reasonable agent to consider in the primary prevention of cerebrovascular events in NPSLE. However, a 2-year trial of statin therapy showed no benefit in primary or secondary atherosclerosis outcomes in SLE patients [192]. Accordingly, statins should be started in NPSLE patients with hyperlipidemia who meet criteria based on current cardiovascular disease guidelines [131]. Lastly, antiplatelet agents and anticoagulants are crucial for primary and secondary prevention of thrombotic complications in NPSLE patients [131]. Recommendations from a task force published in 2011 state that SLE patients with medium-high titers of aPL-antibodies should receive primary thromboprophylaxis with hydroxychloroquine and low-dose aspirin [193]. In a more recent randomized controlled trial of 166 SLE patients with aPL, no difference in thrombosis rate was found between those that received low-dose aspirin versus low-dose aspirin plus low-intensity warfarin [194]. Those with aPL-antibodies should also receive low-molecular-weight heparin for prophylaxis during high-risk situations, such as surgery or prolonged immobilization [193]. Low-dose aspirin is still recommended in patients with aPL even if they do not have SLE [193]. Patients diagnosed with APS following a thrombotic event should receive heparin followed by long-term anticoagulation with warfarin [193]. It is worth noting that the newer direct oral anticoagulants (DOACs), such as thrombin inhibitor dabigatran and antifactor Xa inhibitors rivaroxaban and apixaban, may be advantageous due to their fixed dosing and more predictable anticoagulant effects as compared to warfarin. Currently, insufficient evidence exists to recommend their use in APS, SLE and NPSLE, although ongoing trials are investigating their efficacy in APS specifically [195].

6.1 Potential future therapies

In addition to the lack of evidence for the use of broad immunosuppression in NPSLE, many of the drugs described above have an array of adverse and potentially debilitating side effects [131]. This emphasizes the need for more targeted therapies that may have greater efficacy in additional to minimizing the side effect profile. Some future candidates include factors implicated in BBB dysfunction, such as TWEAK, a pro-inflammatory cytokine in the TNF superfamily, as well as eculizumab, a humanized monoclonal antibody that blocks terminal complement generation, which again interferes with BBB integrity [131].

Of the potential future targets, perhaps the most promising is IFNα. Treatment with anti-IFNα antibodies has been shown to reduce SLE disease activity [196], and as previously discussed, IFNα has been consistently implicated in mouse models [68, 74, 197] and patients [73, 198] with NPSLE. More recently, anifrolumab, a type I IFN-receptor antagonist, was explored as a treatment option for moderate to severe SLE [199]. Unfortunately, patients with CNS syndromes were excluded in this study. Given the evidence for a pathogenic role of IFNα in mouse models of SLE and the identification of elevated IFNα levels in NPSLE patients, it will be important to study the response to anifrolumab therapy in NPSLE patients [74].

7. Conclusion

In summary, NPSLE is a debilitating disease that affects a number of SLE patients. Due to diverse presentations and overlap with other diseases, it is a particularly challenging entity to characterize and study. Here, we have reviewed the basic science, including commonly used mouse models, the involvement of the BBB, autoantibodies, cytokines, and microglial activation. We have also covered the various clinical phenotypes, emphasizing the wide range in reported prevalence, lack of suitable biomarkers, and steps in evaluation and management. The information presented herein calls for further research into the basic mechanisms driving NPSLE to ultimately improve quality of life for patients with this disease.

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Conflict of interest

The authors declare no conflict of interest.

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