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Neuropsychiatric lupus: new mechanistic insights and future treatment directions

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Abstract

Patients with systemic lupus erythematosus (SLE) frequently show symptoms of central nervous system (CNS) involvement, termed neuropsychiatric SLE (NPSLE). The CNS manifestations of SLE are diverse and have a broad spectrum of severity and prognostic implications. Patients with NPSLE typically present with nonspecific symptoms, such as headache and cognitive impairment, but might also experience devastating features, such as memory loss, seizures and stroke. Some features of NPSLE, in particular those related to coagulopathy, have been characterized and an evidence-based treatment algorithm is available. The cognitive and affective manifestations of NPSLE, however, remain poorly understood. Various immune effectors have been evaluated as contributors to its pathogenesis, including brain-reactive autoantibodies, cytokines and cell-mediated inflammation. Additional brain-intrinsic elements (such as resident microglia, the blood–brain barrier and other neurovascular interfaces) are important facilitators of NPSLE. As yet, however, no unifying model has been found to underlie the pathogenesis of NPSLE, suggesting that this disease has multiple contributors and perhaps several distinct aetiologies. This heterogeneity presents a challenge for clinicians who have traditionally relied on empirical judgement in choosing treatment modalities for patients with NPSLE. Improved understanding of this manifestation of SLE might yield further options for managing this disease.

The nervous system is one of the major organs affected in patients with systemic lupus erythematosus (SLE). Research interest in neuropsychiatric SLE (NPSLE; formerly termed lupus cerebritis) has seen major growth during the past 5 years, which is largely attributable to the understanding that NPSLE develops along unique pathogenetic pathways compared with other SLE manifestations. One challenge that clinicians often face in the diagnosis and

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management of patients with NPSLE is that its presentation can be highly variable, ranging from common and nonspecific features, such as headache, cognitive abnormalities and mood disorders, to rare presentations including Guillain–Barré syndrome and autonomic dysfunction¹.

The true prevalence of NPSLE is unknown, but published estimates suggest that it affects between 12% and 95% of patients with SLE^{1–4} (Table 1). This wide range is probably due to differences in study design, inclusion and exclusion criteria and inconsistency in the attribution of neuropsychiatric presentations to SLE. For example, the protocols of some studies exclude headache because it is essentially ubiquitous in the general population. Nevertheless, even when minor neuropsychiatric symptoms are excluded, CNS disease can be conservatively estimated to occur in >20% of patients with SLE³. In fact, NPSLE is a major source of morbidity in the SLE population, and its mortality is second only to that of lupus nephritis.

Our understanding of NPSLE is confounded by several complexities: its presentation is diverse and often elusive; it probably encompasses a variety of pathogenetic mechanisms (including thrombosis, autoantibodies, cytokines and cell-mediated inflammation); and its management options are still inadequately optimized. Nevertheless, SLE research in general has greatly benefited from extraordinary progress in the understanding of its immunological mechanisms over the past decade, as well as from advances in investigational techniques that have accelerated our ability to study this complex and multifactorial disease. NPSLE in particular, owing to its heterogeneous and intricate pathogenetic mechanisms, has experienced a resurgence of interest and renewed investigational efforts.

In this Review, we present the current understanding of NPSLE and explore new ideas and directions in the study and management of this complex condition.

Clinical manifestations

NPSLE encompasses a variety of neurological and psychiatric signs and symptoms that are often hard to distinguish from SLE-unrelated events. The central nervous system (CNS) manifestations of SLE range from subtle cognitive dysfunction, which occurs in up to 50% of patients with SLE (even in those with mild disease and without overt NPSLE manifestations⁵), to acute confusional states, psychosis, seizure disorders and stroke¹. In 1999, an ad hoc committee of the ACR released a consensus statement in which 19 neuropsychiatric syndromes that can occur in patients with SLE were defined⁶. Of these, 12 syndromes were related to the CNS and 7 were peripheral nervous system manifestations. These were further classified into diffuse psychiatric or neuropsychological syndromes and focal neurological syndromes (Table 1).

Focal NPSLE represents localized CNS involvement, which is generally attributable to episodes of either venous thrombosis or arterial ischaemia. These events are thought to account for ~20% of NPSLE cases^{7,8}, but reported rates range from 3% to 43%, probably because of differences in the stringency of attribution models for NPSLE in the various studies^{9,10}. These events are predominantly attributable to thromboembolic phenomena that

occur in the context of SLE-related hypercoagulable states and are clearly correlated with the presence of anti-phospholipid (aPL) antibodies^{4,7-16}. True vasculitis as an underlying cause of cerebrovascular disease, however, is a rare cause of focal or diffuse NPSLE manifestations¹⁷.

Although headache, mood disorders, anxiety and mild cognitive dysfunction are the most frequent neuropsychiatric complaints in patients with SLE, they typically do not reflect disease activity in the CNS⁷. Cerebrovascular disease, seizure disorders, acute confusional states and neuropathies are the most common presentations of NPSLE^{7,9,18}. These myriad presentations and their varying intensities suggest that multiple pathogenetic mechanisms are involved in NPSLE, similar to our current understanding of the extracranial manifestations of SLE¹².

Attribution

Linking neuropsychiatric manifestations directly to SLE can often present a challenge, as the symptoms themselves can be mild and nonspecific (such as headaches and 'brain fog' or mild cognitive dysfunction) and no specific objective histological, laboratory or imaging findings can confirm the diagnosis. Many of the neuropsychiatric presentations found in patients with SLE also occur frequently in the general population. Moreover, risk factors for these features are associated with conditions that are frequently comorbid with SLE, such as cerebrovascular disease in patients with hypertension, diabetes or hyperlipidaemia. Some NPSLE manifestations, primarily the affective ones, can be explained by either the emotional burden of having a chronic disease or the adverse effects of commonly used medications such as corticosteroids. Many SLE-related neuropsychiatric events occur at disease onset or within the first 1–2 years after diagnosis^{10,19}. Similarly, although neuropsychiatric presentations occurring in close proximity to SLE diagnosis or flare are probably a primary manifestation of SLE (that is, directly caused by the disease rather than being attributable to secondary causes), they can occur independently of overt SLE activity, which again complicates the diagnostic process.

Neuroimaging has inconsistent utility in identifying primary CNS involvement in SLE. The current standard of care is MRI, which can identify intracranial abnormalities and assess their chronicity and evolution in addition to ruling out other causes of the neuropsychiatric symptoms such as abscesses, infectious meningitis and mycotic aneurysms. MRI is especially sensitive for identifying haemorrhagic and ischaemic infarction and transverse myelitis but does not currently have the spatial resolution needed to detect microvascular involvement (which is known to be present in up to 42% of patients with SLE who have neurological manifestations)^{20,21}. In circumstances when conventional MRI is insufficient to identify a suspect lesion, we recommend the use of advanced imaging modalities if available, such as quantitative MRI, single photon emission computed tomography (SPECT) or PET¹⁹. The radiological modalities in current use or in development that have shown potential in NPSLE have been reviewed in depth elsewhere²². However, the specificity of neuroimaging for NPSLE (60–82% for MRI¹⁹) remains inadequate even for these advanced modalities, and this circumstance, along with the not-infrequent absence of overt CNS lesions in patients with suspected NPSLE, relegates the current utility of neuroimaging to

adjunct use. Neuroimaging is helpful mostly to rule out other possible causes of the presentation but cannot be the sole arbiter of NPSLE diagnosis, which still greatly relies on the skilled clinician.

Establishing whether particular neuropsychiatric symptoms are primary manifestations of SLE (which would suggest a need for increased immunosuppression) or secondary to other factors (such as high-dose corticosteroid treatment or psychological disease burden) certainly has implications for the treatment of affected patients. Several models have been devised to improve the attribution of neuropsychiatric symptoms to SLE (reviewed elsewhere)²³. These models take into account factors that have been identified as associated with NPSLE, such as a temporal relationship between the neuropsychiatric syndrome onset and diagnosis or change in activity of SLE, minor versus major syndrome (minor syndromes, such as headaches, are common in the general population, whereas major syndromes are rare but more specific for NPSLE), viable alternative explanations and risk factors specific to SLE, such as aPL antibodies or anti-ribosomal P protein antibodies^{7,12,19,24–26}. However, despite providing a fairly reliable bedside diagnostic tool (positive and negative predictive values are both in the range 70–85%)^{12,13,23–26}, these models are based on statistical predictions and correlation with expert opinion as the gold standard as opposed to objective evidence of NPSLE, which leaves room for persistent diagnostic uncertainty. Therefore, until more reliable and specific diagnostic tools are available, the attribution of neuropsychiatric symptoms to SLE remains a moving target reliant on the clinician's assessment, index of suspicion and clinical reasoning. Importantly, a careful multidisciplinary approach, including neuropsychological, radiological and laboratory evaluations in addition to the rheumatology work-up, increases the specificity of NPSLE diagnosis and is an important avenue to consider^{22,27}.

Pathogenesis

Animal models of NPSLE

As in many neurological conditions, animal models are the mainstay of basic research in NPSLE because human brain tissue is difficult to come by. Several mouse models are used to study NPSLE, each with its own strengths and weaknesses (Table 2). Most of these models recapitulate diffuse but not focal symptoms of NPSLE alongside a lupus phenotype of varying severity. Additionally, in adoptive transfer studies, neuropathic antibodies introduced into the CNS of otherwise healthy non-autoimmune mice have been used to demonstrate the direct pathogenic effects of specific autoantibodies associated with human NPSLE^{28–30}.

The two leading animal models of NPSLE are the New Zealand black/New Zealand white F1 (NZB × NZW F1) and MRL/MpJ-*Fas*^{lpr/lpr} (MRL/lpr) mice. NZB × NZW F1 mice manifest systemic and serological features resembling SLE, such as high titres of anti-nuclear and anti-double-stranded DNA (dsDNA) antibodies³¹. These mice also develop lupus-like behavioural manifestations along with a CNS cellular infiltrate that peaks between 10 and 18 months of age³². The first major study of neuropsychiatric disease in NZB × NZW F1 mice evaluated postural response and placing reflex behaviours. These behaviours correlate with thalamic and limbic brain regions, consistent with the anatomical structures

associated with affective symptoms in patients with diffuse NPSLE³². Subsequently, NZB × NZW F1 mice were shown to develop an aberrant neuroprogenitor cell population in the corpus callosum, along with accelerated immunopathology in the same region³³.

MRL/lpr mice are similar to NZB × NZW F1 mice in that both models develop neuropsychiatric features as well as systemic (non-neurological) manifestations of SLE. One disadvantage of the NZB × NZW F1 mouse model, however, is the late onset and slow progression of overt neuropsychiatric disease. By contrast, MRL/lpr mice, which develop SLE as a consequence of a loss-of-function mutation in the *Fas* gene superimposed on a complex MRL background, show an accelerated course of disease, which peaks at a median of 16 weeks of age³⁴. The MRL/lpr mouse consistently exhibits a range of cognitive and affective manifestations, including memory deficits and depression-like behaviour, both of which resemble traits observed in patients with NPSLE. Moreover, MRL/lpr mice develop many lupus-associated anti-nuclear³¹ and brain-reactive³⁵ autoantibodies. Although both MRL/lpr and NZB × NZW F1 mice have prominent serological phenotypes, their circulating autoantibody profiles have not been directly compared to assess differences in brain-reactive antibody specificities or neuropathic potential.

Several other, less frequently employed, models of NPSLE are useful for exploring the contribution of individual pathways to disease development. One such mouse is the 564Igi strain, which has an invariant immunoglobulin G (IgG) knock-in with RNA auto-reactivity leading to the development of a lupus-like phenotype, albeit one with slow disease progression^{36–38}. Behavioural deficits and increased neuronal death also occur in B6 mice carrying the same *Fas* mutation found in MRL/lpr mice (B6-lpr/lpr mice), although this phenotype is probably attenuated compared with that of the MRL/lpr strain³⁹. Of note, none of the mutations and genetic risk factors seen in the above models of NPSLE commonly occur in patients with SLE. Rather, these models recapitulate key clinical manifestations and potential immunological effectors of this disease, which enable the study of specific underlying pathways and therapeutic targets.

Neuroimmune interfaces

The CNS has long been thought to be an immune-privileged site owing to the presence of a highly restrictive and tightly regulated blood–brain barrier (BBB) that prevents passive transfer of most immune mediators from the circulation to the CNS. Therefore, a question (and one that remains to be fully answered) of importance to the discussion of CNS pathology in SLE is whether breach of the BBB is truly central to the pathogenesis of NPSLE, as it has long been considered. Although focal NPSLE is most frequently a consequence of cerebrovascular disease^{40,41}, in which BBB damage results from the mechanical disruption of brain vascular integrity, reperfusion and/or local inflammation^{42–47}, the mechanisms underlying increased BBB permeability in diffuse NPSLE are not yet clear.

Much of what is believed about the loss of BBB integrity in SLE is based on empirical inference and surrogate markers. The presence of serum albumin within the CNS (the cerebrospinal fluid (CSF) serum albumin quotient, or Q_{alb}) has long been employed as the gold-standard surrogate marker of serum leakage into the CNS^{48,49}. Serum and CSF

positivity for autoantibodies that might mediate direct neuronal damage, such as anti-N-methyl-D-aspartate receptor (NMDAR)^{50–52}, anti-Smith⁵³ and anti-ribosomal P protein antibodies^{54–56}, correlate with the development of diffuse NPSLE, as well as with an elevated Q_{alb} in some patients^{52,53}, suggesting that these antibodies do penetrate the BBB (which is typically antibody impermeable). As seropositivity for these autoantibodies does not reliably predict NPSLE development⁵⁷, an additional ‘hit’, such as excessive stress or an underlying infection, might induce temporary BBB disruption and thereby facilitate brain injury by serum-derived auto antibodies. Similarly, in animal models, the pathogenicity of neuropathic autoantibodies has been demonstrated, although always in the context of BBB disruption or bypassing; for example, injections of either adrenaline or lipopolysaccharide (LPS) are used to model stress or infection, respectively^{29,58–60}. Thus, increased permeability of the BBB remains a strong candidate for the mechanism and route by which pathogenic antibodies reach the brain in human NPSLE.

Despite the logical inference that BBB disruption occurs in NPSLE, and the long history of the finding of an elevated Q_{alb} in patients with NPSLE as described above, few studies have specifically probed the matter. Albumin exits from the brain vasculature into the parenchyma by diffusion as well as active and vesicular transport⁶¹, which potentially increases its intrathecal concentration without necessarily indicating vascular leakage per se (accordingly, this mechanism remains speculative at this time). Additionally, although brain-reactive autoantibodies within the CNS of patients with SLE might have originated in serum, their presence could also indicate direct intrathecal antibody production by plasma cells. Furthermore, the cerebral vasculature is not the only perfused site within the skull; the meningeal barrier and the choroid plexus (the site of the blood–CSF barrier) also warrant attention as potential sites of neuroimmune interactions. Finally, two fluid-transport mechanisms have been identified in the CNS in the past 5 years: the glymphatic pathway, a perivascular conduit running along the cerebral vasculature that enables coordinated movement of interstitial fluid and CSF⁶², and the intradural lymphatic network⁶³. Both these systems represent previously under-recognized potential avenues for leukocyte transport into and out of the CNS. The roles of these fluid channels in neuro-immunity in general (and NPSLE in particular) have yet to be fully explored but are promising avenues of investigation (Fig. 1).

In addition to disruption of the BBB, which can enable serum-borne effectors to penetrate the CNS, other brain structures might serve as locations of serum–CSF interactions. For example, the meningeal barrier can be disrupted in patients with aseptic meningitis either as a primary manifestation of SLE^{64,65} or by NSAID use, which is common in patients with SLE⁶⁶. Patients with SLE are also at an increased risk of infectious meningitis owing to the frequent need for corticosteroids and other immunosuppressive treatments in the management of SLE⁶⁷.

The choroid plexus is another potential site of immune penetrance into the CNS. This structure is regionally situated deep within the CNS, floating within the ventricles and bathed in CSF. The choroid plexus is a secretory epithelial structure surrounding a highly vascularized capillary plexus; uniquely, its endothelium is fenestrated and includes interepithelial tight junctions that serve a barrier function. Additionally, the choroid plexus is

the site of CSF production and is the default source of any solutes therein⁶¹. The choroid plexus is thought to be the site through which inflammation is initiated in multiple sclerosis⁶⁸ and is implicated in age-related inflammatory changes associated with cognitive decline⁶⁹. Studies of the choroid plexus in patients with SLE have revealed evidence of disease involvement, particularly immune complex deposition^{70–73}, although this finding might be nonspecific. Anecdotal evidence in the form of case reports have associated MRI enhancement of the choroid plexus with the onset of cognitive dysfunction⁷⁴. Of note, in MRL/lpr mice, the choroid plexus epithelium has been identified as a route of entry into the CSF for pathogenic autoantibodies and leukocytes and is a primary site of neuropathology^{75–79}. The contributions of the various brain barriers to the pathogenesis of NPSLE has been extensively reviewed elsewhere⁸⁰.

Autoantibodies

A hallmark of SLE is the formation of autoantibodies, several of which are implicated in NPSLE manifestations. Indeed, a substantial number of the autoantibodies identified in patients with NPSLE are believed to contribute to the pathogenesis of the disease. Of these, aPL antibodies are thought to be directly (although not exclusively) related to focal NPSLE via autoantibody-mediated thrombosis; others, such as anti-NMDAR and anti-ribosomal P protein antibodies, are considered to target specific brain parenchymal structures and might explain diffuse NPSLE presentations (Table 3).

Anti-phospholipid antibodies.—Anti-phospholipid syndrome (APS) is characterized by thrombosis of the venous or arterial circulation and/or adverse pregnancy outcomes in the presence of persistently elevated titres of one or more aPL antibodies, including lupus anticoagulant (which represents multiple antibodies that inhibit phospholipid-dependent coagulation), anti-cardiolipin antibodies and anti- β 2-glycoprotein 1 antibodies. Although this syndrome can occur in isolation, it is much more prevalent in patients with SLE than in the general population (10–44% versus 0.1–5.0%)⁸¹. The specific role of aPL antibodies in thrombus formation is still not fully characterized, although they are known to activate endothelial cells, platelets and monocytes, which are then thought to shed prothrombotic microparticles^{81,82}.

The CNS is more susceptible than most tissues to thrombus formation, which accounts for the increased risk of stroke and transient ischaemic attack seen in aPL-antibody-positive patients⁸³. In addition, aPL antibodies accelerate atherosclerosis⁸⁴, which is an independent risk factor for cerebrovascular ischaemia. The risk of stroke in individuals aged <50 years is about eightfold higher in aPL-antibody-positive than in aPL-antibody-negative individuals⁸⁵. Among patients with SLE, those with aPL antibodies are about twice as likely as aPL-antibody-negative people to develop NPSLE⁹. Indeed, the presence of these antibodies has long been considered a strong risk factor for NPSLE^{11,15,19}. Interestingly, aPL antibody positivity has also been linked with NPSLE syndromes that are not necessarily directly related to thrombosis, such as seizures, chorea, cognitive dysfunction and myelopathy^{16,86–91}, which suggests that these autoantibodies have a pathogenic role beyond their prothrombotic effects. In vitro, aPL antibodies bind to neurons and other CNS cells, and intrathecal transfer of immunoglobulins from aPL-antibody-positive patients induces

cognitive deficits in recipient mice⁹², thereby supporting a direct effect of these antibodies on the brain. Nevertheless, most of the NPSLE manifestations attributed to aPL antibody seropositivity are thought to be the sequelae of ischaemic events in brain regions such as the amygdala, hippocampus and frontal cortex⁴. In addition, local vascular injury caused by a thrombotic event can damage the integrity of the BBB, enabling peripheral effectors (such as circulating neuropathic autoantibodies and leukocytes) to enter the CNS^{44,93}.

Anti-NMDAR antibodies.—Autoantibodies mediate several pathological manifestations of SLE. The most well-known association relates to anti-dsDNA antibodies, which are important mediators of lupus nephritis^{94,95}. A subset of anti-dsDNA antibodies cross-reacts with the NR2A and NR2B subunits of NMDARs; binding of these autoantibodies to NMDARs leads to neuronal death, primarily via increased neuronal calcium influx, which mimics glutamate excitotoxicity^{96,97}. These cross-reactive anti-NMDAR antibodies occur in patients with SLE and are frequently associated with NPSLE^{50,51,60,98}. Although serum levels of anti-NMDAR antibodies are not consistently correlated with NPSLE activity^{25,99–101}, CSF titres of these antibodies are higher in patients with active diffuse NPSLE than in individuals with focal NPSLE or non-inflammatory CNS disease^{99,102}. However, a substantial population of patients with non-neuropsychiatric SLE is also anti-NMDAR antibody positive¹⁰³.

Passive transfer of sera containing anti-NMDAR antibodies from patients with SLE to healthy BALB/c mice induced features of NPSLE, although only after additional disruption of the BBB²⁹. Similarly, immunization of healthy BALB/c mice with the NMDAR-derived DWEYS pentapeptide induced the development of anti-NMDAR antibodies, although these autoantibodies were likewise unable to induce CNS symptoms unless the mice also underwent pharmacological BBB disruption⁵⁹. Interestingly, LPS treatment (which induces inflammation mimicking a response to infection) led to localization of anti-NMDAR antibodies within the hippocampus, where they caused cognitive impairment, whereas administration of adrenaline (which mimics a stress response) resulted in localization of the antibodies to the amygdala, where they caused affective disturbances^{29,58,59}. These studies collectively indicate that some method by which anti-NMDAR antibodies can enter the CNS is required to induce pathology.

Beyond direct neuronal excitotoxic effects, an intriguing report has described a novel pathogenic effect of anti-NMDAR antibodies in a passive transfer mouse model. Anti-NMDAR antibodies impaired dendritic arborization, which induced deficiencies in spatial recognition; this effect was dependent on locally activated microglia and the presence of complement component C1q. Interestingly, this particular pathogenic mechanism could be attenuated by angiotensin-converting enzyme inhibitors, which deactivate microglia¹⁰⁴.

Anti-ribosomal P protein antibodies.—Anti-ribosomal P protein antibodies are highly specific for SLE and are present in up to 46% of patients with SLE¹⁰⁵. High titres of these autoantibodies are associated with psychosis^{54–56,106} and a wide range of NPSLE syndromes, including depression, seizure, coma, transverse myelopathy and aseptic meningitis^{107,108}. Adoptive transfer studies of anti-ribosomal P protein antibodies from patients with SLE in non-autoimmune mice models support a role for these antibodies in

depression¹⁰⁹ and memory impairment³⁰. Immunohistochemical evaluation of brains from mice injected with anti-ribosomal P protein antibodies found that these antibodies bind to the hippocampus, cingulate cortex and piriform cortex, which are all part of the limbic system and are implicated in mood^{107,109}. Interestingly, binding of anti-ribosomal P protein antibodies to olfactory structures caused a reduced sense of smell^{92,110}, which might represent another mechanism by which anti-ribosomal P protein antibodies cause depression^{111,112}. This observation suggests that interconnectivity exists between the environment (smell), immunity and mental health.

Anti-ribosomal P protein antibodies bind to the carboxy-terminal regions of three ribosomal P proteins, P1, P2 and P0, at a binding site termed the P epitope¹¹³. These autoantibodies cross-react with a P epitope found on neuronal surface P antigen (NSPA), a large integral plasma membrane protein found exclusively in neurons that acts as an ubiquitin ligase that regulates the function of NMDAR at the synaptic region. NSPA is also involved in synaptic transmission and plasticity related to memory in the hippocampus and mediates the deleterious effects of anti-ribosomal P protein antibodies on these processes¹¹⁴.

In vitro, anti-ribosomal P protein antibodies bind directly to human peripheral blood monocytes to induce TNF production¹¹⁵. The release of TNF could promote local CNS inflammation and result in BBB impairment, which enables infiltration of the antibodies into the CNS where they cause direct neuronal damage.

Anti-aquaporin 4 antibodies.—Aquaporin 4 (AQP4) is a water channel protein that is expressed on astrocytic foot processes surrounding blood vessels, thereby controlling the flow of water into and out of the brain¹¹⁶. Anti-AQP4 antibodies cause astrocyte toxicity, particularly in the optic nerve and white matter structures of the spinal cord, and are thought to underlie the pathogenesis of neuromyelitis optica (NMO)^{116–118}. The diagnoses of NMO and SLE overlap to some extent, as some patients with NMO eventually develop SLE, and a minority of patients with SLE develop the demyelinating lesions typical of NMO. Anti-AQP4 antibodies occur in 70–90% of patients with NMO^{119,120}. In one study, anti-AQP4 antibodies were detected in 3% of all patients with NPSLE¹²¹. However, they were present in 27% of patients with NPSLE who had demyelinating lesions¹²¹. Similar to other circulating neuronal antibodies, anti-AQP4 antibodies must penetrate the BBB to induce injury (in Lewis rats)¹²². Interestingly, and specifically in patients with NMO, an additional autoantibody directed against glucose-regulated protein 78 (which is a component of the brain cerebral vasculature) can disrupt the BBB, allowing the penetration of anti-AQP4 antibodies into the CNS¹²³. Importantly, some patients with SLE remain positive for anti-AQP4 antibodies for many years without developing NMO or any other neurological symptoms¹²⁴.

Anti-endothelial cell antibodies.—Anti-endothelial cell antibodies (AECAs) are found in >60% of patients with NPSLE (compared with ~30% of patients with SLE who do not have neuropsychiatric involvement) and are associated with psychosis and depression^{125,126}. AECAs induce the expression of adhesion molecules in endothelial cells, which enhances leukocyte rolling and adhesion to vessel walls, in addition to inducing endothelial cell secretion of various cytokines, such as IL-6 and IL-8 (reF.¹²⁷). This activation of endothelial

cells might contribute to cerebral vasculopathy, which, in turn, mediates the neuropsychiatric symptoms of SLE. Finally, molecular cloning studies have shown that some AECAs cross-react with the ribosomal P epitope¹²⁸, although other studies have not found any such association between AECAs and anti-ribosomal P protein antibodies¹²⁵.

Anti-microtubule-associated protein 2 antibodies.—Microtubule-associated protein 2 (MAP2) is a cytoskeletal protein found exclusively in neurons. Anti-MAP2 antibodies have been found in the sera of patients with NPSLE, and, although NPSLE can occur in their absence, their presence in the CSF of patients with SLE correlates closely with the presence of neurological symptoms^{129,130}. However, the pathogenic roles and biomarker capabilities of these antibodies need to be further explored.

Anti-suprabasin antibodies.—Suprabasin is a protein secreted specifically in stratified epithelium and is thought to be an epidermal differentiation marker^{131,132}. The CSF of patients with NPSLE was compared with that of patients with non-neuropsychiatric SLE, multiple sclerosis and normal-pressure hydrocephalus in a proteomic study that aimed to identify the target antigens of circulating immune complexes. Titres of anti-suprabasin antibodies were higher in the patients with NPSLE than in any of the other groups. In vitro, exposure of astrocytes to anti-suprabasin antibodies activated senescence and autophagy pathways, which might provide some insight into the pathogenesis of the neuropsychiatric symptoms mediated by these antibodies¹³³.

Cell-mediated inflammation

Evidence obtained in both mouse models and humans, albeit preliminary, indicates that cell-mediated inflammation is involved in NPSLE. MRL/lpr mice show increased rolling and adhesion of leukocytes in the cerebral vasculature, which is attenuated by α -integrin and vascular cell adhesion molecule 1 (VCAM1) blockade¹³⁴. The leukocyte population within the cerebral vasculature (although not that in the brain parenchyma) contained substantial numbers of double-negative T cells^{76,134}. This T cell subset is important in SLE, particularly in renal disease activity^{135,136}, but its role in NPSLE has not been defined. In addition, MRL/lpr mice show prominent cellular infiltration through the choroid plexus, including of CD4⁺ T helper cells and plasma cells that can mediate CNS inflammation^{79,80,137}. These observations could explain the presence of intrathecal pathogenic autoantibodies, even without major damage to the BBB^{79,80,137}.

Macrophages are instrumental in SLE¹³⁸, and activated macrophages are found in affected organs (such as the skin and kidneys) of MRL/lpr mice^{139,140}. Within the brain, resident microglia are the predominant immune cells of the CNS and are potent cytokine producers. Levels of type I interferons are elevated in the serum and hippocampus of patients with SLE and induce microglial activation and aberrant synaptic pruning in mouse models of NPSLE³⁸. Indeed, activated microglia are a feature of several mouse models of lupus^{49,141,142}, and we and others have shown that inhibition of microglial activation attenuates the phenotype of NPSLE in these mice^{38,104,143}.

Information on the nature of the inflammatory process in human NPSLE is scarce, mainly owing to the difficulty of obtaining sufficient brain tissue samples. In the few studies that did

evaluate brain pathology in patients with NPSLE, the most striking feature was vasculopathy rather than robust cellular infiltration^{17,20,144}. However, inflammation-like changes were seen in ~7% of patients with NPSLE who underwent brain MRI²⁰, whereas in a different MRI study, selective contrast enhancement of the choroid plexus, seen in two patients with NPSLE¹⁴⁵, was reminiscent of the local inflammation found in the choroid plexus of the MRL/lpr mice described above. These MRI findings point to the presence of local CNS inflammatory processes, which are presumably driven by immune cells, but the extent of this cellular inflammation in human NPSLE needs to be further explored.

Cytokine-mediated inflammation

In the MRL/lpr mouse model, early neuropsychiatric changes are accompanied by increased serum levels of multiple cytokines, including IFN γ , IL-10, CXC-chemokine ligand 10 (CXCL10; also known as IP10) and CC-chemokine ligand 2 (CCL2; also known as MCP1), to name several¹⁴⁶. Similarly, patients' serum and intrathecal cytokine environments have been extensively characterized in the search for potential biomarkers. As in SLE itself, IFN α has been implicated as a leading effector of NPSLE pathogenesis. In early work, increased CSF levels of IFN α were found in patients with NPSLE, as well as evidence of IFN α production within the CNS^{147,148}. Additionally, antibodies obtained from the CSF of patients with SLE induce IFN α expression in vitro¹⁴⁹. Moreover, therapeutic administration of type I interferons induces psychiatric symptoms, including sickness behaviour associated with depression^{150,151}.

Although studies that looked for associations between IFN α expression and NPSLE have reported equivocal results^{5,152,153}, IFN α is directly involved in aberrant synaptic pruning in a lupus-prone mouse model. Neuropsychiatric manifestations observed in this model were reversible with IFN α inhibition, indicating that IFN α is important in the pathogenesis of NPSLE³⁸. TNF-like weak inducer of apoptosis (TWEAK) has shown promise in mouse models of NPSLE^{49,154,155}, although this cytokine seems to be elevated in the CSF of patients with SLE regardless of whether they have neuropsychiatric symptoms¹⁵⁶. Elevated intrathecal levels of IL-6 have been demonstrated in patients with conditions linked to diffuse NPSLE, such as acute confusional state and psychosis; this cytokine could be an interesting diagnostic tool once infection and stroke have been ruled out^{157–159}. Increased levels of various other cytokines are also correlated with the development of NPSLE, including IL-8 (reF.¹⁵²) and IFN γ ^{160,161}, which warrant additional study (Table 4).

Each of the aforementioned cytokines might prove to be promising targets in the treatment of neuropsychiatric and systemic manifestations of SLE. However, the need to measure cytokine levels in CSF is a major obstacle to the identification of appropriate targets. CSF solute levels are subject to exquisitely complicated regulation⁶¹ that results in considerable fluctuation, which makes it challenging to derive accurate CNS levels of any given solute from CSF analyses. Additionally, the additional routes of fluid movement described above (namely, the glymphatic¹⁶² and CNS lymphatic systems) further confound CSF analysis as the sole method of evaluating intrathecal molecular composition. The development of new and creative means of evaluating intrathecal solute levels is required.

Complement activity

The role of complement activation in NPSLE is another area of exciting developments in both mouse models and human SLE¹⁶³. In MRL/lpr mice, complement blockade decreased the expression of inflammatory cytokine and adhesion molecule genes and diminished caspase-mediated apoptosis¹⁶⁴. A histopathological evaluation of brain tissue from patients with NPSLE found, in addition to increased vascular pathology and ischaemic changes, strong evidence of local activation of the complement cascade in at least some patients²⁰. The levels of complement components in the CSF probably represent both intrathecal production and leakage from the systemic circulation. After correction for Q_{alb} (to assess intrathecal complement production), the available studies report conflicting results as to whether complement activity is increased in patients with NPSLE^{165,166}. A subsequent study that evaluated CSF levels of C3 indicated an increase specifically in C3 of systemic origin in patients with an acute confusional state, compared with patients who had other diffuse and focal presentations of NPSLE, or SLE without neuropsychiatric features¹⁵⁹. Similarly, CSF levels of C5a and C5 were closely correlated with Q_{alb} in patients with NPSLE¹⁶⁷. Thus, BBB integrity might be a major driver of CSF complement levels, but whether the observed increases in levels of complement components derived from the systemic circulation are involved in the pathogenesis of NPSLE is yet to be elucidated. C5a itself has been postulated to be involved in disruption of the BBB, which could explain its apparent serological consumption when the BBB is breached in NPSLE¹⁶⁷. However, this hypothesis needs to be further studied.

As mentioned above, the importance of C1q in synaptic pruning by microglia has been demonstrated in a mouse model of NPSLE mediated by passive transfer of anti-NMDAR antibodies, but this mechanism has yet to be explored in human disease¹⁰⁴. Of note, no clinical trials of complement-related therapies for SLE are currently included in the [ClinicalTrials.gov](https://clinicaltrials.gov) database; nevertheless, anecdotal evidence suggests the potential efficacy of a complement-targeted approach, particularly using eculizumab (a recombinant monoclonal antibody that targets complement component C5), in patients with catastrophic APS^{168–170} and recurrent NMO¹⁷¹, perhaps hinting at a potential therapeutic role of complement inhibition in specific manifestations of NPSLE.

Brain structural changes

An intriguing area of investigation is the structural changes that occur in the brains of patients with SLE. These changes might explain why neurological manifestations are often discrepant with disease activity, as chronic structural changes would be expected to persist during disease quiescence. Furthermore, some patients with SLE experience cognitive impairment even in the absence of a diagnosis of NPSLE or evidence of active inflammation, suggesting that this symptom is associated with an underlying SLE-related chronic neurological pathology⁵. Local scarring or damage from a thrombotic event can explain manifestations such as seizures, chorea, myelopathy and cognitive decline. However, these and other manifestations might also occur in patients without a history of microvascular or macrovascular thrombosis and at times when the systemic, non-neurological disease is well controlled.

Although this observation of temporal discrepancy is still unexplained, a number of published findings are of interest and perhaps relevant. Synaptic loss in the brains of patients with SLE might be due to increased IFN α -induced microglial activation³⁸. A similar neuronal deficit in patients with NPSLE might be related to increased CSF levels of the neurite outgrowth inhibitor reticulon 4 (also known as nogo protein); CSF levels of nogo are also elevated in MRL/lpr mice, and nogo inhibits neuronal recovery following damage in the adult CNS¹⁷². Inhibition of this pathway promoted myelin repair, in addition to improving cognition and memory, in the MRL/lpr mouse model¹⁷². A fascinating study published in 2018 showed (in mouse models) that microglia might retain the 'memory' of prior systemic inflammatory stimuli, which alters their subsequent responses to local pathology such as ischaemia or amyloid plaque accumulation¹⁷³. This memory is generated by epigenetic changes in the microglia that persist for at least 6 months following the systemic trigger. In this study, the aberrant microglial response was shaped by acute systemic inflammatory events, but we consider that similar processes might be relevant to the chronic inflammation associated with SLE.

In patients with rheumatoid arthritis, functional studies of neuronal networks have shown changes in network association patterns that correlated with the degree of inflammation and with pain and fatigue¹⁷⁴. Although this evaluation was not performed in patients with SLE, the results suggest that chronic inflammation leads to functional changes in brain connectivity and function, which could explain some manifestations of NPSLE or contribute to their severity. In addition, an elegant MRI study showed disturbed white matter microstructure in the brains of patients with SLE that correlated with disease duration and fatigue but not with SLE disease activity or damage, white matter intensities or depression¹⁷⁵.

SLE often manifests at an early age, while the brain is still maturing. During this time, brain structural changes are likely to be particularly devastating, even life-trajectory-altering. Therefore, it is imperative that the pathogenic mechanisms behind these processes are further elucidated (and, if possible, halted) as soon as they are diagnosed. In addition, increased understanding of these changes would improve our ability to recognize and differentiate between acute inflammation-related neuropsychiatric manifestations of SLE, which can be treated with immunosuppressive agents, and chronic processes that might occur independently of systemic disease activity.

Genetic contribution to disease

Although SLE is thought to possess a strong genetic component, SLE is definitely not subject to Mendelian inheritance in the large majority of patients seen in clinical practice. In addition, the considerable variability in its presentation, together with the variety of environmental factors that are probably important in triggering the disease, its manifestations and its severity, make the genetic drivers of SLE hard to trace. NPSLE, with its sometimes vague presentations and difficulty in diagnosis, is similarly challenging to pin down. Nevertheless, several studies of SLE risk alleles identified in genome-wide association studies have found evidence of several single-nucleotide polymorphisms (SNPs) that occur more frequently in patients with NPSLE than in the general SLE population.

Several of these polymorphisms are associated with specific NPSLE syndromes. *TREX1* (which encodes 3' repair exonuclease, also known as DNase III) is linked to Aicardi–Goutières syndrome and increased expression of type I interferons, and SNPs in this gene are associated with NPSLE, particularly with seizures^{176–178}. Similarly, the *HLA-DRB1*04/*13* genotype and the SNP rs10181656 in *STAT4* (encoding signal transducer and activator of transcription 4) have both been associated with strokes in SLE, independently of aPL antibody status and traditional cardiovascular risk factors^{179,180}. Finally, the cumulative effect of SNPs in several genes associated with SLE (including *HLADRBI*, *IRF5*, *STAT4*, *BLK*, *TNFAIP3*, *TNIP1*, *FCGR2B* and *TNFSF13*) has been evaluated in Japanese patients with SLE. Having ten or more SNPs increased these patients' risk of developing neurological manifestations twofold¹⁸¹.

Management

Management of NPSLE can be challenging on many levels, including diagnosis based on obscure symptoms, challenges in attributing them to SLE and the fairly limited and nonspecific treatment armamentarium currently available. Initially, a thorough investigation for alternative causes, such as infection, malignancy, metabolic disorders or adverse effects of medication, should be undertaken. Once these confounders and mimics have been ruled out and the symptoms are considered primary to SLE, the goals of management are twofold. First, symptomatic treatment should be provided: correction of hypertension and metabolic derangements; anti-epileptics for seizures; and anxiolytics, antidepressants, mood-stabilizers or antipsychotics for psychiatric manifestations, as appropriate. At the same time, treatment of the underlying SLE process should be administered according to whether the neuropsychiatric symptoms are attributable to a diffuse, inflammation-driven syndrome or a focal (localized) thromboembolic process¹⁹.

Inflammation-induced manifestations

Other than belimumab, no specific targeted biologic treatments are available for SLE. End-organ involvement in patients with SLE is usually treated with high doses of corticosteroids, cyclophosphamide, mycophenolate mofetil and azathioprine. A similar treatment strategy is also used in patients with NPSLE, in which the specific choice of the steroid-sparing agent is based on the clinician's assessment of disease severity and their clinical experience. Unfortunately, high-level clinical evidence regarding the optimization of NPSLE treatment is strikingly absent. Only a single randomized controlled trial has compared intravenous cyclophosphamide infusions with bimonthly intravenous methylprednisolone in treating patients with severe NPSLE, and this study showed a much better response rate in the cyclophosphamide arm¹⁸². In addition, oral cyclophosphamide for 6 months followed by azathioprine maintenance therapy was effective in the treatment of lupus psychosis¹⁸³. Although the evidence in favour of this approach is still anecdotal, the addition of rituximab (or another anti-CD20 monoclonal antibody) to the NPSLE treatment algorithm warrants consideration. The efficacy of rituximab was evaluated in ten patients with refractory NPSLE, who experienced substantial and rapid improvement in their clinical signs and symptoms, as well as in radiological findings¹⁸⁴. Rituximab was also effective and fairly safe in a retrospective study of paediatric patients with NPSLE¹⁸⁵. Perhaps of relevance is

the observation that rituximab can be beneficial in other inflammatory neurological conditions, such as NMO, anti-NMDAR encephalitis and opsoclonus–myoclonus syndrome^{186–188}. Of note, belimumab has not been evaluated in the treatment of major CNS manifestations¹⁸⁹.

Thromboembolic manifestations

As with all aPL-antibody-related thrombosis, lifelong anticoagulation with warfarin is the mainstay of therapy¹⁹⁰. The recommended international normalized ratio (INR) target in patients with APS is 2.5–3.0, and in patients with recurrence of thrombosis despite optimal warfarin therapy INR should be kept at 3.0–4.0 (reF.¹⁹¹). Statins can prevent endothelial cell activation secondary to aPL antibodies¹⁹², and antimalarial agents are protective against thrombosis in patients with SLE¹⁹³. As the safety profile of these two medications is favourable, they should be considered in addition to warfarin treatment, especially in patients with recurrent thrombosis.

Low-dose aspirin is recommended in patients with cardiovascular risk factors. Of note, although randomized clinical trials are ongoing, currently the data are insufficient to recommend the use of direct oral anticoagulants (also known as novel oral anticoagulants) to prevent aPL-antibody-mediated thromboembolic events¹⁶⁸. In patients with NPSLE and catastrophic APS, pulse corticosteroids, intravenous immunoglobulin infusions and/or plasmapheresis are recommended¹⁹⁴. The addition of eculizumab to these treatments was effective in several case reports and small series^{168–170}.

Future directions

The human brain tissue used for research into NPSLE is almost exclusively obtained post-mortem, usually after long-term treatment directed towards both systemic and neuropsychiatric manifestations of SLE, and shows in addition typical age-related neuropathology. Only limited systematic efforts have been made to include brain tissue from patients with NPSLE in brain tissue repositories, which typically focus on primary and CNS-limited disease processes. However, given our evolving understanding of NPSLE and the advances in model organisms, increased efforts to promote the specific recruitment of SLE brain tissue for translational research purposes, beyond local efforts that are already in place, would be useful.

A pressing need remains for additional targeted therapies for SLE, but the varied and complex underlying pathogenic pathways complicate the development of such therapies. Studies of drug treatments for NPSLE in particular, with its challenges in symptom attribution and often severe manifestations, are difficult to execute and therefore have been few and far between. However, a number of agents are currently being studied that might prove promising (Fig. 2).

Anifrolumab, a type I interferon receptor antagonist, has shown some success in a phase IIb trial in patients with SLE: this treatment led to a substantial reduction in moderate-to-severe disease activity, especially in patients who had a strong type I interferon signature at baseline¹⁹⁵. Patients with severe NPSLE were excluded from this study; therefore, these data

do not support the efficacy of this drug in NPSLE. However, as previously mentioned, type I interferon receptor inhibition decreased microglia-related synaptic loss and attenuated anxiety-like behaviour and cognitive deficits in 564Igi lupus-prone mice³⁸. Therefore, type I interferon inhibition might have a future role in the treatment of NPSLE, most likely in patients with a strong type I interferon signature.

Macrophage colony-stimulating factor 1 receptor (CSF1R) is an important regulator of both macrophage and microglia function. Signalling through this receptor is crucial for macrophage and microglia development, survival and activation¹⁹⁶. In MRL/lpr mice, inhibition of CSF1R signalling reduced the brain expression of pro-inflammatory cytokines and attenuated depression-like behaviour, although no improvement was seen in abnormal spatial recognition¹⁹⁷.

Tyrosine-protein kinase BTK (also known as Bruton tyrosine kinase) is important in B cell development, survival and function and in crystallizable fragment (Fc) receptor and Toll-like receptor (TLR) signalling in macrophages and macrophage polarization^{198–200}. Inhibition of BTK improves nephritis in several mouse models of lupus^{201–203}. In addition, treatment with a highly selective BTK inhibitor (BI-BTK-1) decreased microglial activation, reduced choroid plexus cellular infiltration and improved cognitive functioning in MRL/lpr mice¹⁴³. Of note, the BTK inhibitor ibrutinib is already approved for clinical use in haematological indications such as chronic lymphocytic leukaemia²⁰⁴. Results from ongoing early phase clinical trials of BTK inhibitors in patients with SLE are eagerly awaited.

In addition to the above investigational therapies, most of which are still in preliminary stages of development, other tools are being developed to aid the management and personalized treatment of NPSLE. For example, a multi-modal imaging-based approach for diagnosis of NPSLE has been developed that takes into account both structural and functional information²⁰⁵. Furthermore, biomarkers, mostly in the form of cytokine levels in serum or CSF, are still being pursued for diagnosis and surveillance purposes. Genetic investigations, including gene expression analyses, are also ongoing to accurately characterize the risk of NPSLE and its specific manifestations.

Conclusions

Neuropsychiatric disease is a major cause of morbidity and mortality in patients with SLE, yet many knowledge gaps remain in our basic understanding of NPSLE and its clinical management. As the signs and symptoms of NPSLE vary greatly and can often be nonspecific, it is often challenging to confidently attribute them to SLE; indeed, no 'gold-standard' diagnostic method exists. In addition, the pathogenesis of neuropsychiatric disease in patients with SLE is probably multifaceted, complex and possibly unique to specific individuals or subsets of patients. Creation of a unified treatment algorithm for specific syndromes therefore seems unlikely to be possible, further highlighting the importance of a skilled clinician in management of these presentations. Many important questions are still unanswered, such as the mechanisms through which particular autoantibodies exert pathogenic effects, the route or routes through which neuropathic antibodies penetrate the brain, the role of infiltrating leukocytes, the contributions of specific cytokines and

chemokines to the neuropathological process and, importantly, the relationship between particular pathogenic factors and specific presentations of NPSLE. Promising research efforts into novel targeted therapies and improved diagnostic tools are continuing, but much work remains to be done to optimize our ability to diagnose, prognosticate and treat NPSLE.

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Competing interests

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Key points

- Management of neuropsychiatric symptoms in patients with systemic lupus erythematosus (SLE) remains challenging as evidence-based regimens are not generally available.
- A pressing need in the management of neuropsychiatric SLE (NPSLE) is the appropriate attribution of symptoms to either primary inflammatory pathology or secondary consequences of the general SLE disease burden.
- Research efforts are aggressively pursuing the identification of pathways involved in NPSLE development, along with new therapeutic targets.
- Mechanisms at the neuroimmune interface are being studied and might extend beyond the cerebral circulation and the blood–brain barrier to include the blood– cerebrospinal fluid barrier and/or the meningeal barrier.
- Novel therapies, including small-molecule inhibitors and biologic agents that target inflammatory pathways, are currently being explored to target NPSLE specifically.

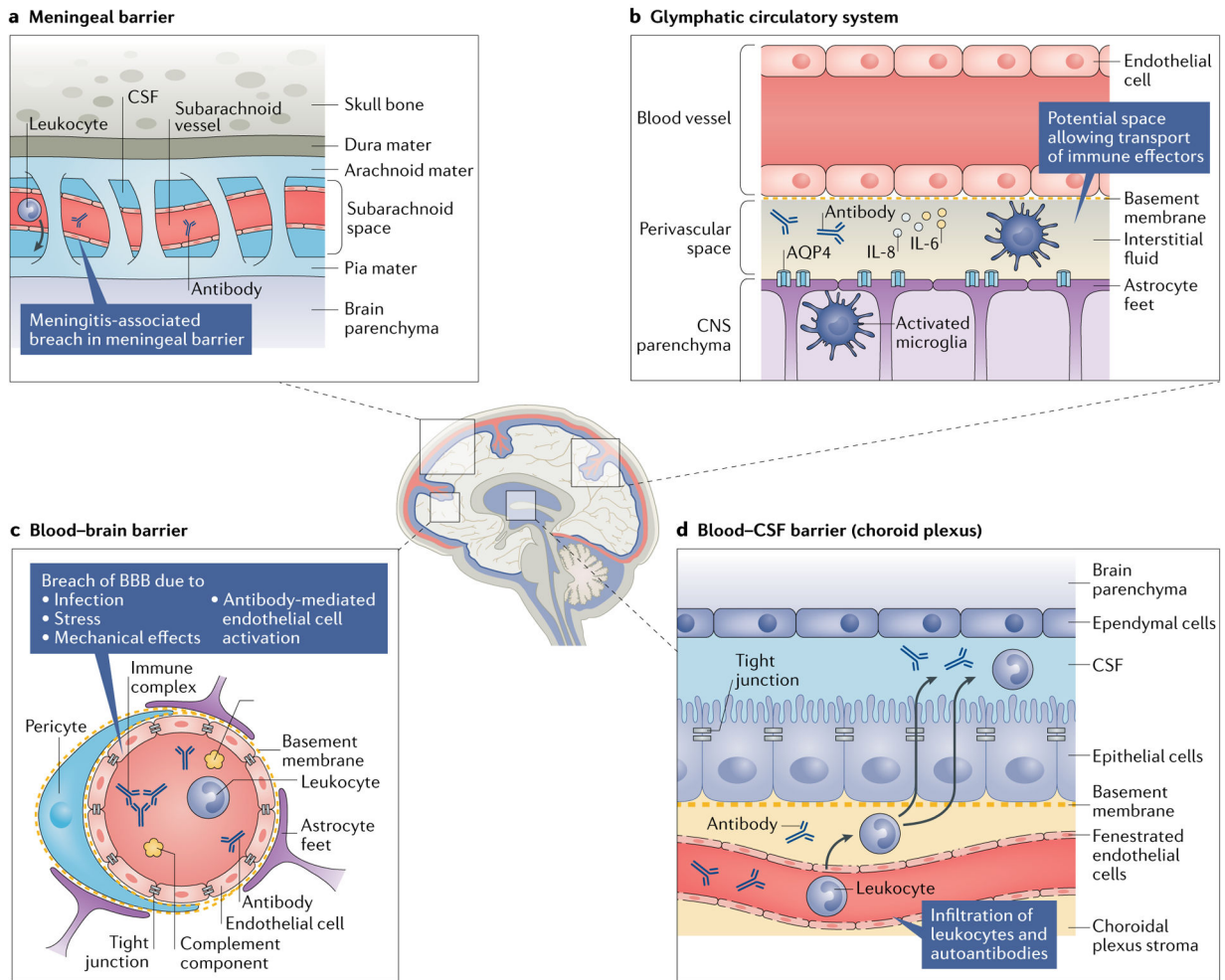


Fig. 1 | Neuroimmune interfaces and postulated mechanisms by which they can be breached. Damage to the blood–brain barrier (BBB) might enable neuropathic antibodies in the serum of patients with systemic lupus erythematosus to enter the central nervous system (CNS); however, several other interfaces could also serve as sites of leukocyte and pathogenic antibody transfer into the CNS. **a** | The arachnoid epithelium serves as the meningeal barrier between the cerebrospinal fluid (CSF) in the subarachnoid space and the blood in cerebral veins. Meningitis (both aseptic and infectious) can cause inflammation in the subarachnoid space, potentially leading to a breach of this barrier that enables circulating pathogenic antibodies, leukocytes and pro-inflammatory cytokines to enter into the CSF. **b** | The glymphatic pathway is a perivascular pseudolymphatic system that provides a conduit for interstitial fluid in the brain parenchyma. Brain antigens (such as microtubule-associated protein 2) might be recognized by indwelling antigen-presenting cells in the perivascular space, which can migrate to the cervical lymph nodes and initiate an adaptive response. **c** | Breach of the BBB has been observed under several circumstances, including infection (simulated by lipopolysaccharide administration), stress (simulated by adrenaline infusion), the mechanical and inflammatory sequelae of vascular occlusion and antibody-mediated endothelial cell activation. **d** | The fenestrated capillary plexus within the choroid plexus enables ready access of antibodies and leukocytes to the choroidal plexus stroma (a

previously characterized site of immunosurveillance) and potentially into the CSF. AQP4, aquaporin 4.

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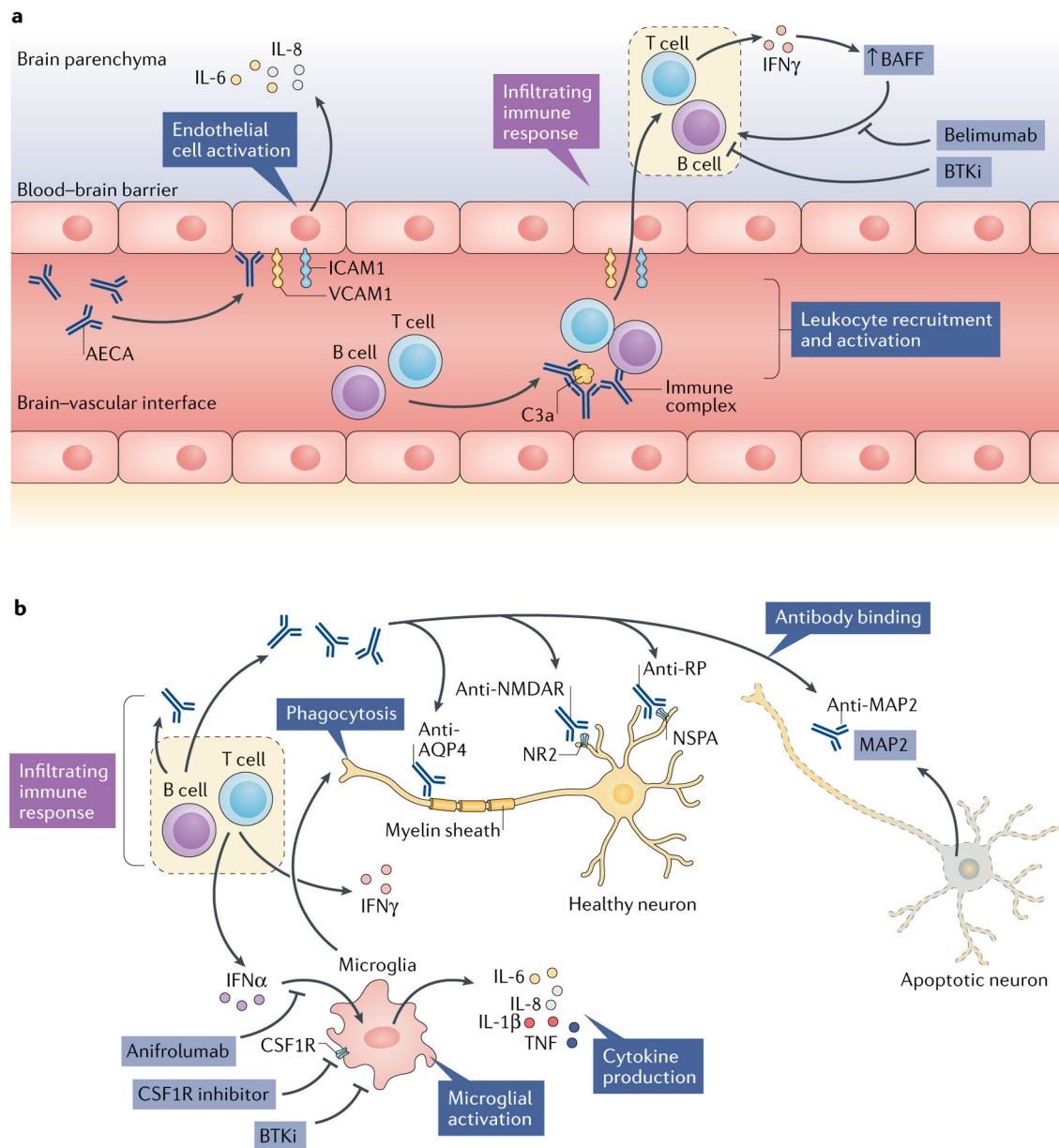


Fig. 2 | Pathogenetic mechanisms and potential treatment targets in diffuse NPSLE.

Several different but potentially complementary pathways and effectors in the central nervous system (CNS) microenvironment might be involved in the pathogenesis of neuropsychiatric systemic lupus erythematosus (NPSLE). **a** | Endothelial cells connected by tight junctions comprise the blood–brain barrier and are subject to activation by autoantibodies such as anti-endothelial cell antibodies (AECAs). Activated endothelial cells show upregulated expression of adhesion molecules (such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecule 1 (VCAM1)), which facilitate leukocyte infiltration into the CNS parenchyma. In addition, these activated endothelial cells secrete pro-inflammatory cytokines, including IL-6 and IL-8. Concurrently, immune complexes in the cerebral vasculature activate the complement system, which further promotes

chemotaxis. The locally infiltrating leukocytes secrete pro-inflammatory cytokines, such as IFN γ , which in turn promotes B cell survival and activation via increasing local levels of B cell activating factor (BAFF). **b** | Microglia are consequently activated, most notably by interferons, the elevated intrathecal levels of which are commonly seen in patients with NPSLE. Activated microglia further propagate local cytokine and chemokine signalling cascades, in addition to direct phagocytic activity focused on neuronal surface signalling domains and synaptic termini. Finally, several neuropathic autoantibodies have been implicated in NPSLE, including antibodies to the NR2 subunit of the anti-*N*-methyl-D-aspartate receptor (NMDAR), anti-ribosomal P protein (RP; targeting neuronal surface P antigen (NSPA)) and anti-microtubule-associated protein 2 (MAP2) antibodies, which might have direct neurotoxic effects and provide a source of intrathecal immune complexes. Anti-aquaporin 4 (AQP4) antibodies, directed against the myelin sheath, are found in some patients with SLE who have demyelinating disease. The above pathogenetic mechanisms, along with studies in animal models, suggest that several drugs might prove to be effective in treating NPSLE, including belimumab (a BAFF inhibitor), anifrolumab (a type I interferon receptor antagonist), macrophage colony-stimulating factor-1 receptor (CSF1R) inhibitors (which block activation of microglia and infiltrating macrophages) and tyrosine-protein kinase BTK (also known as Bruton tyrosine kinase) inhibitors (BTKis), which interrupt inflammatory activation of B cells and macrophages or microglia.

Table 1 |

Prevalence of neuropsychiatric features in patients with SLE

| Feature | Source | Prevalence (%) | Refs |
|--|--------|----------------|-------------------|
| <i>Diffuse psychiatric or neuropsychological syndromes</i> | | | |
| Psychosis | CNS | 0.6–11.0 | 1,6,7,206 |
| Anxiety disorder | CNS | 6.4–40.0 | 1,6,206,207 |
| Acute confusional state | CNS | 0.9–7.0 | 1,6,7,206 |
| Mood disorder | CNS | 7.4–65.0 | 1,6,7,206,207 |
| Cognitive impairment | CNS | 6.6–80.0 | 1,6,7,206 |
| <i>Neurological syndromes</i> | | | |
| Headache (including migraine and benign intracranial hypertension) | CNS | 12.2–28.3 | 1,6,7,206 |
| Seizure disorders | CNS | 7.0–20.0 | 1,6,7,206 |
| Cerebrovascular disease | CNS | 8.0–15.0 | 1,6,7,206 |
| Movement disorder (chorea) | CNS | 0.9 | 1,6,206,208 |
| Myelopathy | CNS | 0.9–3.9 | 1,6,7 |
| Demyelinating syndrome | CNS | 0.9–2.7 | 1,6,7,206,209,210 |
| Aseptic meningitis | CNS | 0.3–2.7 | 1,6,7,206 |
| Acute inflammatory demyelinating polyradiculopathy (Guillain–Barré syndrome) | PNS | 0.08–1.20 | 1,6,7 |
| Autonomic disorder | PNS | 0.08–1.30 | 1,6,7 |
| Mononeuropathy, single or multiplex | PNS | 0.9–6.9 | 1,6,7 |
| Plexopathy | PNS | NR | 6,7 |
| Polyneuropathy | PNS | 1.5–5.4 | 1,6,7 |
| Myasthenia gravis | PNS | 0.2 | 1,6 |
| Cranial neuropathy | PNS | 1.0 | 1,6,7 |

Some central nervous system (CNS) and most peripheral nervous system (PNS) manifestations are uncommonly studied, with uncertain and/or rare prevalence. NR, not reported; SLE, systemic lupus erythematosus. References cited here discuss the particular presentation and/or its prevalence in SLE.

Table 2 |

Animal models of NPSLE

| Mouse model | Advantages | Disadvantages |
|--|--|---|
| MRL/MpJ- <i>Fcγ2b</i> ^{flpr} /lpr | <ul style="list-style-type: none"> • Rapid onset, multisystemic presentation akin to SLE in patients • Available congenic controls | Complex pathogenic contributors |
| NZB × NZW F1 offspring | <ul style="list-style-type: none"> • Neuropsychiatric disease occurs before systemic disease • Slow progression is an approximation of human disease • Appropriate brain regions are affected | <ul style="list-style-type: none"> • Delayed progression limits feasibility of certain studies • Unclear contribution of neuroprogenitor cells in the corpus callosum |
| 564Igi | Emphasizes the contribution of a particular anti-nuclear antibody (directed against RNA) and increased type I interferon activity to disease development | Minimizes effects of the adaptive immune response due to an invariant IgG clone |
| C57Bl/6- <i>Fcγ2b</i> ^{flpr} /lpr | The same <i>Fas</i> mutation as in MRL/lpr mice, but on the C57Bl/6 background, which allows for more effective genetic manipulation using existing mutant strains | Disease develops in an attenuated fashion and with incomplete penetrance compared with that in MRL/lpr mice |

IgG, immunoglobulin G; NPSLE, neuropsychiatric systemic lupus erythematosus; NZB, New Zealand black; NZW, New Zealand white; SLE, systemic lupus erythematosus. Other models of SLE with neuropsychiatric disease exist but are less often employed owing to various confounding variables, such as anatomical abnormalities or technical considerations.

Table 3 |

Autoantibodies in NPSLE

| Antibody | Effects in humans | Data from preclinical models | Refs |
|--|---|---|------------------|
| Anti-phospholipid antibodies: | | | |
| • Anti-cardiolipin antibodies | • Focal and diffuse disease due to medium-vessel and small-vessel vasculopathy | Intracerebroventricular injection causes neurobehavioural deficits in mice | 16,81–92 |
| • Anti-β ₂ -glycoprotein I antibodies | • Evidence of involvement in diffuse neuropsychiatric symptoms | | |
| • Lupus anticoagulant | | | |
| Anti-N-methyl-D-aspartate receptor antibodies | CSF positivity is correlated with NPSLE in some patients | Induce cognitive and affective symptoms in mice when introduced intrathecally | 50,58–60,96–103 |
| Anti-ribosomal P protein antibodies | Seropositivity has long been correlated with NPSLE | <ul style="list-style-type: none"> • Bind to limbic system brain regions, thereby affecting mood and memory • Induce TNF production in vitro, promoting inflammation and BBB impairment | 30,54–56,105–115 |
| Anti-aquaporin 4 antibodies | Associated with demyelination in neuromyelitis optica, found not only in NPSLE but also in SLE without neuropsychiatric features | ND | 116–124 |
| Anti-endothelial cell antibodies | Present in a majority of patients with NPSLE and in many with SLE | Might induce endothelial cell activation and expression of adhesion molecules or cytokines | 125–128 |
| Anti-MAP2 antibodies | <ul style="list-style-type: none"> • 100% correlated with CNS disease when found in the CSF • Intracellular antigen, which suggests that neuron death might be required before they develop | MAP2 is exclusively found in neurons | 129,130 |
| Anti-suprabasin antibodies | <ul style="list-style-type: none"> • Occur in high titres in patients with NPSLE • Unclear mechanistic role in pathogenesis | <ul style="list-style-type: none"> • Bind to an epidermal differentiation marker secreted by stratified epithelium • In vitro, activate astrocyte senescence and autophagy | 131–133 |

BBB, blood–brain barrier; CNS, central nervous system; CSF, cerebrospinal fluid; MAP2, microtubule-associated protein 2; ND, not discussed; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus.

Table 4 |

Cytokines in NPSLE

| Cytokine | Effects | Refs |
|--------------|--|-----------------|
| TNF | <ul style="list-style-type: none"> • Conflicting data regarding elevated CSF levels in NPSLE • Treatment with TNF inhibitors can induce SLE-like symptoms • Increased levels can impair the BBB via increased local inflammation | 115,211–214 |
| BAFF | <ul style="list-style-type: none"> • Mediates B cell survival and promotes immunoglobulin class switching (important in SLE pathogenesis) • Anti-BAFF (belimumab) antibody treatment is approved for the treatment of SLE, but efficacy in NPSLE has not been established | 215,216,189 |
| IFN α | <ul style="list-style-type: none"> • Important in SLE pathogenesis • Strong systemic interferon signature in patients with NPSLE • Induced in vitro by CSF from patients with NPSLE • Activates microglia leading to synaptic pruning • Can induce depression (most common adverse effect), psychotic features, confusion, focal neurological deficits and seizures | 149–151,217–219 |
| TWEAK | <ul style="list-style-type: none"> • Mediates BBB disruption, choroid plexus cellular infiltration and neuronal damage • Elevated in the CSF of patients with SLE | 49,156,220 |
| IFN γ | <ul style="list-style-type: none"> • Mainly produced by T cells and found in high levels in sera from patients with SLE • Elevated in the CSF of patients with NPSLE, which can distinguish NPSLE from demyelinating neurological conditions | 160 |
| IL-6 | <ul style="list-style-type: none"> • Secreted primarily by myeloid cells, activated astrocytes and endothelial cells • Stimulates B cells, promotes immunoglobulin secretion by plasma cells, promotes differentiation of T_H17 cells and inhibits differentiation of regulatory T cells • Elevated in the CSF of patients with NPSLE, but similarly elevated in CSF from patients with demyelinating neurological conditions and septic meningitis | 152,160,211,221 |
| IL-8 | <ul style="list-style-type: none"> • Secreted by several cell types, including activated endothelial cells • Elevated in the CSF of patients with NPSLE, but similarly elevated in CSF from patients with demyelinating neurological conditions and septic meningitis | 152,160,211 |

BAFF, B cell activating factor; BBB, blood–brain barrier; CSF, cerebrospinal fluid; NPSLE, neuropsychiatric systemic lupus erythematosus; SLE, systemic lupus erythematosus; T_H17 cell, T helper 17 cell; TWEAK, TNF-like weak inducer of apoptosis.