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The role of B cells and Autoantibodies in Neuropsychiatric Lupus

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Abstract

The central nervous system manifestations of SLE (neuropsychiatric lupus, NPSLE) occur frequently, though are often difficult to diagnose and treat. Symptoms of NPSLE can be quite diverse, including chronic cognitive and emotional manifestations, as well as acute presentations, such as stroke and seizures. Although the pathogenesis of NPSLE has yet to be well characterized, B-cell mediated damage is believed to be an important contributor. B-cells and autoantibodies may traverse the BBB, promoting an inflammatory environment consisting of glia activation, neurodegeneration, and consequent averse behavioral outcomes. This review will evaluate the various suggested roles of B-cells and autoantibodies in NPSLE, as well as therapeutic modalities targeting these pathogenic mediators.

Keywords

SLE; Neuropsychiatric lupus; B cells; Autoantibodies

1. Introduction

1.1 SLE and NPSLE

Systemic lupus erythematous (SLE) is a chronic autoimmune disease that predominantly affects women, with onset typically occurring during reproductive years (15–44 years old) [1]. SLE is characterized by high titers of autoantibodies and systemic inflammation, which ultimately culminates in various end organ pathologies [1]. Brain involvement, or neuropsychiatric SLE (NPSLE), affects approximately 40% of SLE patients. NPSLE presents with a diverse array of manifestations which can be sorted into two distinct categories: focal and diffuse [2]. Focal symptoms include cerebrovascular events and seizures that are generally attributable to coagulopathies such as the anti-phospholipid syndrome. Diffuse manifestations, which will be the focus of this review, are associated with

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the activation of various inflammatory pathways and consist of a broad spectrum of neuropsychiatric symptoms including headache, cognitive dysfunction, and depression [3].

The diagnostic criteria for NPSLE, as defined by the American College of Rheumatology (ACR) in 1999, include 19 neuropsychiatric conditions (12 central nervous system (CNS) and 7 peripheral nervous system (PNS) symptoms), as listed in Table 1 [3]. However, these conditions may arise from multiple causes, and therefore cannot distinguish NPSLE from other non-SLE associated neurological diseases. Between the heterogeneous nature of NPSLE and the limited utility of current diagnostic modalities (such as imaging), it can be difficult to accurately diagnose NPSLE.

Moreover, even when accurately diagnosed, the management of NPSLE is less than ideal. Current regimens for the treatment of primary NSPLE consist of corticosteroids and immunosuppressive agents, which are therapies known to have unfavorable side effects, including psychiatric ones [4]. Symptomatic treatment tends to be empirical (e.g. anticoagulation therapy, cognitive rehabilitation, and anti-depressant medications), tailored to the individual needs of each patient [2]. Evidence from large controlled clinical trials highlight the relative ineffectiveness of the current treatment modalities for NPSLE [2]. In addition, the prognosis of NPSLE patients has only been investigated in a relatively small number of studies that produced inconsistent observations, which may be due to initiation of treatment at different stages of disease [5, 6]. Nevertheless, it is believed that early treatment should lead to better outcomes in NPSLE patients [2]. More importantly, patients would benefit from the advent of more targeted therapies, which would require a better understanding of the pathogenesis of NPSLE.

1.2 The pathogenesis of NPSLE

While the mechanisms underlying NPSLE pathogenesis remains somewhat obscure, B cells, autoantibodies, and cytokines [2, 7] are cited as key mediators of disease. Aberrant regulation of cytokines such as IFN-α, TNF, and IL-6 is a characteristic feature in SLE [7]. In NPSLE, cytokines either from the periphery or the CNS may trigger blood brain barrier (BBB) disruption, thus allowing the passage of autoantibodies into the CNS. Autoantibody deposition leads to neurotoxicity and glial cell activation, which can in turn produce abundant, locally enriched cytokines in the CNS, ultimately resulting in behavioral abnormalities. Further, elevated cytokines within the CNS, such as TWEAK, are able to induce neuropsychiatric manifestations directly by mediating inflammatory responses of brain resident cells [8]. It should also be noted that some systemically elevated cytokines can alter behavior directly through the vagus nerve, without ever passing through the BBB [9]. For example, when IL-1β is injected peripherally in animals, it binds to the IL-1 receptor on the sensory neurons of the vagus nerve, leading to overt “sickness behavior”, which can be reversed by vagotomy [10].

Onset of NPSLE may occur at any point during the SLE disease course, including as the presenting symptom at diagnosis, before the onset of systemic manifestations [11–13]. Similarly, in one murine lupus prone model (MRL/lpr), depression-like behavior occurs as early as 5 weeks of age, which precedes autoantibody production and kidney damage which peak around 16 weeks of age [12,13]. In addition, transplantation of bone marrow from

healthy control mice to lupus prone mice does not attenuate the behavioral phenotype but did ameliorate systemic disease, thus indicating that CNS damage can occur independently. Consequently, NPSLE may be primarily driven by brain intrinsic factors rather than systemic inflammation [14].

The MRL/lpr mouse is a classic murine model of SLE that closely mimics human lupus. MRL/lpr mice exhibit a disease predominance in females and develop glomerulonephritis at 3–4 months of age, concomitant with high titers of autoantibodies, immune complex deposition, and cytokine dysregulation. The disease phenotype in this strain is caused by a mutation in the Fas (CD95) gene, compromising Fas-FasL signaling and resulting in defective lymphocyte apoptosis and lymphoproliferation [15]. Importantly, this strain has been validated as a useful model for studying NPSLE [7,16]. MRL/lpr mice exhibit robust depression-like behavior as early as 5 weeks of age [12], and cognitive dysfunction, such as spatial memory deficits, at 16 weeks of age, a phenotype consistent with human NPSLE [17].

In addition to the MRL/lpr strain, NZB/W and BXSB are two additional murine models commonly use to study SLE, both of which develop delayed onset of lupus nephritis at 6 months of age [18]. However, while BXSB mice do display certain spatial deficits consistent with NPSLE in mice [19], contrary to human disease, they have a disease predominance in males [20]. Moreover, in the context of studying NPSLE, neither of these strains are as useful as the MRL/lpr mouse. Both NZB/W and BXSB mice display a lower incidence of neuropsychiatric disease compared with MRL/lpr mice [21]. Additionally, they both possess congenital brain abnormalities characterized by atypically localized collections of neurons in layer I of the cerebral cortex, introducing confounding factors to the analysis [22].

1.3 The role of B cells in SLE and NPSLE

Generally, it is believed that there are three major potential roles for B cells in SLE. First, autoreactive B cells produce autoantibodies, leading to immune complex deposition in various organs [23]. These immune complexes can then further activate the complement system and attract inflammatory cells, such as macrophages and neutrophils, into the tissue resulting in abundant cytokine production and subsequent organ injury [23]. As a specific example, it was shown that an injection of hybridoma clones that secrete anti-dsDNA antibodies into SCID mice was sufficient to induce glomerulonephritis, thus directly supporting a role of autoantibodies in the pathogenesis of kidney damage [24]. Another important role of B cells in SLE is their ability to serve as antigen presenting cells (APC) to T cells, facilitating T cell activation [23]. Giles *et al.* recently showed that MHC II specific deletion in B cells, which blocked T and B cell interactions, results in substantially ameliorated symptoms as a consequence of decreased T-cell activation [25], suggesting the importance of B cells in antigen presentation in lupus nephritis. Finally, B cells secrete various cytokines, such as TNF and IL-6, which contribute to local inflammation and mediate leukocyte infiltration [25].

While several studies have examined the roles of B cells and autoantibodies in NPSLE, these studies have not been entirely consistent, largely due to the unique and multifactorial nature of this disease presentation. In this review, we summarize the research to date focusing on B

cells in murine NPSLE models and NPSLE patients. We also discuss classic autoantibodies associated with NPSLE and their possible pathogenic mechanisms. Finally, we highlight some of the advances made in targeting B cells, both in murine and human CNS lupus.

2. B cells and autoantibodies in murine NPSLE

2.1 B cells in murine NPSLE

The CNS is considered to be immune privileged, with tight regulation of movement of immunomodulatory macromolecules and leukocytes across brain endothelial cells [26]. However, during neuroinflammation, leukocytes from systemic circulation can penetrate the blood-brain barrier (BBB) and/or the blood-cerebrospinal fluid barrier (BCSFB), which consists of choroid plexus epithelia [27]. One prominent histopathological feature in the brains of MRL/lpr mice is gross leukocytic infiltration. By 4 months of age, infiltrates occupy the choroid plexus of the third and fourth ventricles, as well as the periventricular regions adjacent to these ventricles, while isolated leukocytes are observed in the lateral ventricle [27, 28]. The infiltrating population is mixed, predominantly composed of B and T lymphocytes, as well as macrophages [27, 28]. Although the appearance of extensive infiltrates in the CNS coincides with the peak of anti-dsDNA autoantibody titers at 4 months of age [27], cellular infiltration in the brains of MRL/lpr mice persists after bone marrow transplantation from healthy control background matched (MRL/mpj) mice [14], indicating that peripheral immune dysregulation may be associated with, but not a direct cause of, the cellular infiltration in the brain. At 6 months, MRL/lpr mice exhibit immune cell infiltration in the meninges in addition to the choroid plexus [27]. Similarly, at 14 months of age, NZB/W mice undergo an infiltrative process, though this occurs adjacent to blood vessels, as well as in the choroid plexus [29]. In addition, immune complex deposition is observed in the basal lamina of brain parenchymal capillaries at the same time [29]. In contrast, BXSB mice do not show evidence of cellular infiltration in the brain at 4 months of age [27].

Several potential mechanisms may account for the cellular infiltration in the CNS during NPSLE development. First, elevated expression of the adhesion molecules ICAM-1 and VCAM-1 are detectable both in the choroid plexus and the endothelium in periventricular areas, both of which are associated with CNS infiltration [30]. Secondly, immune complex deposition occurs primarily within the choroid plexus and vasculature [31], leading to endothelial activation and chemotactic factor secretion, and, ultimately the recruitment of immune cells. Finally, elevated cytokines, such as TNF, can disturb the integrity of BBB and BCSFB, facilitating the leukocyte transmigration [32].

Currently, the exact role of the infiltrating cells in murine NPSLE is unknown. However, it has been suggested that infiltrating B cells may produce autoantibodies *in situ*, and thereby induce neurotoxicity [27]. Whether infiltrating B cells can function as professional APCs to activate T cells in the pathogenesis of NPSLE remains to be determined. In addition, despite MRL/lpr mice displaying early depression-like behavior, cognitive dysfunction does not appear until later (around 16 weeks of age), which is around the same time the cellular infiltration occurs. Whether the cellular infiltrates can have a negative impact on hippocampal function resulting in cognitive deficits is another interesting question that demands further exploration.

2.2 Autoantibodies in murine NPSLE

Gao *et al.* reported that MRL/lpr mice display robust depression-like behavior as early as 5 weeks of age, as demonstrated by increased immobility in the Porsolt swim test [12]. In addition, immobility scores significantly correlated with the elevated serum titers of anti-ds DNA IgG and anti-NMDAR IgG [12]. Zameer *et al.* described the presence of brain reactive autoantibodies in the brains of various murine NPSLE models, including the MRL/lpr, BSXB, and NZB/W strains [33]. Given that the BBB is thought to be breached in NPSLE [26, 34], deposited autoantibodies in the CNS may arise by traversing the disrupted BBB [17], though they may originate through *in situ* secretion by plasma cells [33]. Recent studies have investigated the association between specific subtypes of autoantibodies and neuropsychiatric manifestations, amongst which anti-ribosomal P, anti-NMDAR, and anti-phospholipid antibodies are the most commonly studied [7,35] and further discussed below.

2.2.1 Anti-ribosomal P autoantibodies—Anti-ribosomal P autoantibodies recognize a C-terminal, 22 amino acid antigenic determinant that is shared by three phosphorylated ribosomal proteins (P0, P1, and P2) located in the large ribosomal subunit [36]. Although intracellular ribosomal antigens are inaccessible to anti-ribosomal P antibodies, there are several potential cell surface proteins which may represent the antigenic targets of anti-ribosomal P antibodies. Neuronal surface P antigen (NSPA) may be one such antigenic determinant recognized by anti-ribosomal P antibodies. NPSA is an integral membrane protein expressed on neuron cell surfaces that are distributed in brain regions involved in emotion, cognition, and memory, such as the hippocampus and amygdala [37]. The binding of anti-ribosomal P antibodies to this antigen results in a rapidly increased calcium influx in neurons, leading to apoptosis. Neuron loss in these regions may result in some of the characteristic emotional and behavioral deficits of NPSLE, and provides some insight into how anti-ribosomal P antibodies mechanistically contribute to NPSLE [37]. Importantly, *in vivo* injection of anti-ribosomal P antibodies similarly triggered neuronal apoptosis when injected into the rat primary motor cortex [37]. Additionally, Katzav *et al.* reported that when anti-ribosomal P antibodies purified from the serum of NPSLE patients were intracerebroventricularly injected into C3H mice, they deposited in the limbic system (hippocampus, cingulate cortex, and the piriform cortex) and induced depression-like behavior [38], further supporting the possibility that anti-ribosomal P antibodies are effectors of NPSLE symptomatology.

2.2.2 Anti-NMDAR autoantibodies—NMDA receptor (NMDAR) autoantibodies are a subtype of anti-dsDNA autoantibodies, which primarily recognize the NR2 subunit of the NMDAR [39]. NMDARs are glutamate receptors, a major excitatory neurotransmitter controlling cognitive and emotional abilities. In particular, NMDAR signaling in the hippocampus is an important regulator of fear responses in rodents, including anxiety like behavior, aberrations of which are routinely found in NPSLE [40]. Over activation of the NMDAR (such as by excessive glutamate) results in neuronal excitotoxicity, and subsequent neuron death. Kowal *et al.* reported that when the blood-brain barrier is otherwise breached, intravenous injection of anti-NMDAR autoantibodies into C57/B6J mice induces neuron cell death in the hippocampal CA1 region and consequent cognitive impairment [39]. This mechanism is reminiscent of glutamate mediated excitotoxicity, thus suggesting that anti-

NMDAR antibodies are receptor hyperactivating autoantibodies [41]. Interestingly, autoantibody-mediated neurotoxicity is concentration dependent; at low concentrations, anti-NMDAR autoantibodies promote excitotoxicity by enhancing excitatory postsynaptic potentials, while at high concentrations, cell death is predominantly triggered by the increased mitochondrial permeability transition [42], suggesting that studies of neuropathic autoantibodies in patients should stratify outcomes by immunoglobulin concentrations both in serum and CSF.

2.2.3 Anti-phospholipid autoantibodies—Anti-phospholipid autoantibodies are a group of antibodies, including anti-cardiolipin antibodies (aCL), anti-β2 glycoprotein I (β2GPI) antibodies, and lupus anticoagulant antibodies (LAC), which are directed against cell surface phospholipids or phospholipid-binding proteins, classically leading to the activation of coagulation pathways and thrombosis formation [43]. Mice immunized with TIFI, a phospholipid-binding peptide that is structurally similar to the phospholipid-binding site of β2GPI, produced high levels of anti-phospholipid antibodies which act similarly to aCL, β2GPI, and/or LAC [44]. *In-vivo* infusion of monoclonal anti-phospholipid antibodies that have both aCL and LAC activity results in significantly increased vascular leukocyte adhesion, as well as enhanced thrombus formation [44]. A recent study further indicates that anti-phospholipid antibodies induced thrombus formation through the activation of Toll-like receptor 4 [45]. Interestingly, anti-phospholipid antibodies appear to exert cognitive abnormalities in mice independent of coagulopathy mediated focal disease. For example, Katzav *et al.* found diminished conditioned memory responses in mice injected with aPL antibodies intracrebroventricularly, as well as short term memory deficits [46]. However, no study to date has identified emotional abnormalities in association with aPL antibodies, such as depression-like behavior, which are hallmark features of NPSLE.

Although autoantibodies with diverse antigenic targets may induce neuropsychiatric manifestations through distinct mechanisms, all autoantibodies have the capacity to contribute to disease via formation of immune complexes, activation of complement pathways, and the induction of inflammatory mediator expression, ultimately culminating in end organ pathology. Nevertheless, despite the aforementioned data suggesting a pathogenic role of autoantibodies *in vivo*, whether B cells are ***obligate*** in the murine model of NPSLE is yet undefined and needs further investigation. It is noteworthy that most murine studies assessing the role of autoantibodies employ non-autoimmune mice instead of commonly used spontaneous lupus strains. While this is a necessary reductionist approach which has been very informative in studying the renal manifestations of SLE, such studies likely minimize the multifactorial pathogenesis underlying autoimmunity in general, and NPSLE in particular. Consequently, it becomes necessary to extend B cell studies into a spontaneous murine NPSLE model.

2.3 Targeting B cells in murine NPSLE

Given that hyperactive B cells play an important role in many manifestations of SLE, and that autoantibodies can induce NPSLE symptoms, exploring B cell depletion may provide for a therapeutic avenue for treating the disease. Interestingly, the MRL/lpr strain is resistant to B cell depletion [47] by anti-CD20 antibodies, especially in the spleen. This is likely due

to the B cell-intrinsic defect in the apoptotic pathway, as well as elevated expression of B cell activating factor (BAFF) which enhances B cell survival [47]. To overcome this difficulty and better assess whether B cells are required for murine NPSLE, several genetic approaches for B cell depletion have been developed. The JhD/MRL/lpr mouse strain is a constitutively B cell deficient strain created by knocking out the Jh region of IgG heavy chain [48]. In a study of lupus nephritis, constitutively B cell deficient (JhD/MRL/lpr) mice displayed a significantly attenuated disease phenotype, as demonstrated by reduced proteinuria and suppressed immune cell infiltration in the kidney [48]. Additionally, by taking advantage of the Cre/Lox system, conditionally B cell depleted mice (Cre-human CD20 MRL/lpr × Rosa26-Flox-STOP-DTA MRL/lpr, referred to as hCD20-DTA MRL/lpr, inducible by tamoxifen) can be generated [49]. To date, however, the effects of B-cell depletion on NPSLE in lupus prone mice have yet to be reported, which is an avenue of investigation currently being pursued.

3. B cells and autoantibodies in human NPSLE

3.1 B cells in human NPSLE

Past studies of human NPSLE have mainly focused on analysis of patient CSF and serum samples [35], as well as brain MRI and other imaging techniques [50,51]. Only a few studies have investigated the histopathology in the brain of NPSLE patients, largely due to the scarcity of CNS tissue samples. In these studies, the most common histopathological change is vasculopathy, including widespread microinfarcts and perivascular lymphocytic infiltration [52]. In addition, cortical atrophy, microhaemorrhages, gross infarction, and ischemic neuron demyelination are also observed, but vasculitis is rare [52]. An autopsy case report of a patient with fatal NPSLE revealed the occlusion of small blood vessels triggered by leukocyte aggregates [53]. While no studies to date have specifically identified the presence of B cells in the CNS of NPSLE patients, intrathecal production of IgG indicated by an elevated IgG index and oligoclonal bands are viewed as an indirect indication of their presence [54].

Cytokines and chemokines are also important modulators of B cell function. BAFF and APRIL are cytokines that belong to the TNF family and promote B-cell activation and differentiation. A recent study reported elevated levels of BAFF and APRIL in the CSF of NPSLE patients, and suggested that antagonism of APRIL and BAFF may be beneficial to NPSLE patients [55]. In addition, CXCR4, a 7-transmembrane–domain G protein–coupled receptor located on B cells and T cells with CXCL12 serving as its ligand, is an important mechanism of leukocyte recruitment [56]. Wang *et al.* found increased CXCR4 expression on B cells in patients with increased disease activity, especially in patients with active NPSLE [56]. They suggest the blockade of CXCR4/CXCL12 interactions may represent a potential therapeutic target for NPSLE [56].

3.2 Autoantibodies in NPSLE patients

As described above in mice, it is believed that autoantibodies in serum and/or cerebrospinal fluid (CSF) from NPSLE patients may be potential biomarkers for disease diagnosis and prognosis. Here, we focused on the most thoroughly studied ones, including anti-NMDAR,

anti-ribosomal P, and anti-phospholipid autoantibodies. Other neuropathic autoantibodies have been comprehensively reviewed elsewhere [43].

3.2.1 Anti-NMDAR autoantibodies—Similar to murine studies, anti-NMDAR autoantibodies have been demonstrated to correlate with cognitive dysfunction in human NPSLE [43]. Kowal *et al.* inferred the presence of anti-NMDAR autoantibodies in the brain of NPSLE patients based upon the evidence that the eluted IgG from the frozen brains of NPSLE patients could bind to DNA and DWEYS peptide, a consensus sequence present in the NR2A and NR2B subunits of the NMDA receptor [41]. Furthermore, in human brain sections, the eluted IgG from patients co-localized with a commercial antibody against the NMDA receptor on neurons [41]. In addition, Gono *et al.* performed multiple linear regression analyses on serum samples from a cohort of 107 SLE patients, and found that anti-NR2A antibody titers were significantly correlated with CNS involvement of SLE patients [57]. Despite these important findings, others could not confirm an association between NMDAR autoantibodies and NPSLE [43, 58].

3.2.2 Anti-ribosomal P antibodies—Anti-ribosomal P antibodies are linked with psychosis [43], and anti-ribosomal P seropositivity has long been thought to be associated with increased likelihood of developing NPSLE [59]. However, a meta-analysis of a large cohort of lupus patients demonstrated that antiribosomal P antibodies were not related to any diffuse manifestations and possessed limited diagnostic value for focal elements of NPSLE [60]. Interestingly, the prevalence of anti-ribosomal P antibody in pediatric lupus (20–42%) is twice as that of adult patients (10–20%), indicating that the sensitivity of this biomarker may be age dependent [61]. Overall, as in the case of anti-NMDAR antibodies, the exact role of anti-ribosomal P antibodies in NPSLE remains inconclusive.

3.2.3 Anti-phospholipid autoantibodies—There is a strong association between anti-phospholipid antibodies, (in particular, anti-cardiolipin and lupus anticoagulant antibodies), and focal NPSLE manifestations including cerebrovascular diseases, such as stroke, seizure, epilepsy, and migraine [43]. Interestingly, as is the case with anti-ribosomal P antibodies, anti-phospholipid antibodies are more prevalent in children with NPSLE compared to adults [61]. However, most of these studies fail to show a significant association between anti-β2 glycoprotein I antibodies and neuropsychiatric symptoms [62].

Overall, the association of autoantibodies and NPSLE manifestations remains controversial. Considering that NPSLE is a complex autoimmune disease with diverse manifestations, it is perhaps unlikely that a single autoantibody would be responsible for all the varied neuropsychiatric manifestations. In addition, the inconsistent results when comparing studies may be a consequence of the diagnostic criteria for NPSLE, and the asynchrony between clinical manifestations and serum evaluation [2]. Therefore, brain reactive autoantibodies may represent a contributing factor requiring other concurrently active disease mechanisms, such as BBB disruption and/or cytokine mediated inflammation.

3.3 Targeting B cell in human NPSLE

3.3.1 Rituximab (Rituxan, Mabthera)—Rituximab, a chimeric monoclonal antibody targeting the CD20 antigen on the surface of B cells, has been shown to be effective in the depletion of B cells and therefore is routinely used in the treatment of B-cell mediated autoimmunity [63]. Based on the known pathogenic roles of B cells in SLE, the efficacy of rituximab in SLE patients has been evaluated as well. Two randomized controlled trials including large numbers of SLE patients failed to show any significant differences in clinical improvement between the rituximab and placebo treated groups [64,65], suggesting initially that the utility of rituximab as a therapy for SLE is limited.

However, Tokunaga *et al.* reported that in patients with intractable NPSLE, treatment with rituximab was effective in attenuating disease manifestations, including seizures, cognitive dysfunction, and psychosis [66]. The improved clinical response was maintained for more than 1 year in half of the patients [66]. The most recent study conducted in 2015 by Tsanyan *et al.* demonstrated that after the treatment with rituximab, 86% of patients with refractory NPSLE displayed greatly improved neuropsychiatric profiles during the 15 months of follow-up [67]. Although these studies are based on limited cases and lack controls, rituximab has been recommended as an off-label alternative in patients refractory to conventional immunosuppressive treatment [68].

3.3.2 Belimumab—Belimumab is a monoclonal antibody which inhibits BAFF, and has been approved by the FDA for the treatment of SLE. In two randomized controlled clinical trials (BLISS-52 and BLISS-76), treatment with belimumab reduced SLE disease activity and flares [69, 70]. However, in both studies, patients with active NPSLE were excluded [69, 70]. Nonetheless, post hoc analysis performed for both of these phase III trials demonstrated overall clinical improvements in most common organ domains with a low prevalence at baseline, including the CNS [71]. Thus, the potential for belimumab as a promising treatment modality for NPSLE remains to be determined.

4. Conclusion

NPSLE is a complex autoimmune disease mediated by multiple factors including B cells, autoantibodies, and cytokines. The disruption of the blood brain barrier triggered by cytokines is a prerequisite for B cells and autoantibodies to gain access to the brain, inducing neurotoxicity and subsequent negative behavioral outcomes. Although it is obvious that in murine experimental models autoantibodies can induce neuropsychiatric symptoms consistent with human lupus, whether B cells and autoantibodies are ***required*** for the development of murine NPSLE is still unknown and needs to be further addressed by B cell depletion studies in MRL/lpr and other experimental lupus strains. In human NPSLE, the exact roles of autoantibodies in pathogenesis are still under debate, which may be due to the heterogeneous nature of the disease. Despite the promise of B cell targeting strategies for refractory cases, more clinical trial data with features of NPSLE as directed endpoints need to be collected in order to determine the efficacy of rituximab, belimumab, and novel B-cell and autoantibody targeting experimental drugs in the treatment of human neuropsychiatric lupus.

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Take home messages

- Patients with neuropsychiatric lupus can be afflicted with a variety of NPSLE manifestations, among which headache, cognitive dysfunction, and depression are the most common.
- Disruption of the blood brain barrier allows B cells and autoantibodies to gain access to the CNS, inducing inflammation, neurotoxicity, and consequent neuropsychiatric symptoms.
- The role of specific subtypes of autoantibodies in neuropsychiatric manifestations is controversial.
- While B cell targeting therapy in the MRL/lpr strain has not been extensively investigated, treatment of NPSLE with rituximab, a monoclonal anti-CD20 antibody, has been proposed as alternative therapy for refractory cases in human disease.

Table 1

Neuropsychiatric syndromes in SLE *

Central Nervous System		Peripheral Nervous System	
1	Aseptic meningitis	**1**	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain–Barré syndrome)
2	Cerebrovascular disease	**2**	Autonomic neuropathy
3	Demyelinating syndrome	**3**	Mononeuropathy
4	Headache	**4**	Myasthenia gravis
5	Movement disorder	**5**	Cranial neuropathy
6	Myelopathy	**6**	Plexopathy
7	Seizure disorders	**7**	Polyneuropathy
8	Acute confusional state		
9	Anxiety disorder		
10	Cognitive dysfunction		
11	Mood disorder		
12	Psychosis		

* Defined by ACR nomenclature and case definitions for neuropsychiatric SLE syndromes [3].