Neuropsychiatric systemic lupus erythematosus: pathophysiology and the future of treatment

Systemic lupus erythematosus (SLE) is characterized by the presence of several autoantibodies, including anti-dsDNA. Among types of SLE, neuropsychiatric (NP)-SLE accounts for significant morbidity and mortality. Cerebrovascular disease, which could account for most of the serious permanent neurological damage, is a common presentation of NP-SLE. The pathophysiology of NP-SLE involves several factors, including vasculitis, thrombosis, and inflammation and/or apoptosis of neuronal and glial cells. The current treatment strategy is immunosuppressive therapy, which is occasionally insufficient for patients with NP-SLE. Recent studies have revealed that autoantibodies, such as anti-NR2, pass from the peripheral blood to the brain through the blood–brain barrier, cross-react with human brain tissue and cause increased intracellular Ca^{2+} in SLE. Regulating blood–brain barrier permeability, inhibiting autoantibody deposition in tissues and modulating intracellular Ca^{2+} may be new concepts for the treatment with NP-SLE.

KEYWORDS: anti-NR2 ▪ antiphospholipid ▪ antiribosomal P ▪ autoantibodies ▪ blood–brain barrier permeability ▪ cross-reactivity ▪ intracellular Ca^{2+} signaling ▪ neuropsychiatric symptoms ▪ systemic lupus erythematosus

Takahisa Gono*[1], Takeshi Takarada[2], Yasuhiro Katsumata[1], Yasushi Kawaguchi[1], Yukio Yoneda[2] & Hisashi Yamanaka[1]

[1]Institute of Rheumatology, Tokyo Women's Medical University, 10-22 Kawada-cho, Shinjuku-ku, Tokyo 162-0054, Japan
[2]Laboratory of Molecular Pharmacology, Division of Pharmaceutical Sciences, Kanazawa University Graduate School of Natural Science & Technology, Kanazawa, Japan
**Author for correspondence: Tel.: +81 3 5269 1725 Fax: +81 3 5269 1726 tgono@ior.twmu.ac.jp*

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is characterized by the presence of several autoantibodies, including anti-dsDNA antibodies [1,2]. Patients with SLE are affected with the following conditions: skin rash, arthritis, serositis, such as pericarditis and pleurisy, cytopenia, nephritis and neuropsychiatric (NP) symptoms. The prevalence of SLE ranges from 20 to 200 cases per 100,000 people worldwide, and the frequency appears to be increasing as SLE becomes more readily recognized and the survival rate increases [1,3]. Females between the ages of 15 and 50 years frequently suffer from SLE. Genetic, environmental, hormonal and epigenetic factors are involved in the onset of SLE. These factors cause the generation and activation of autoreactive T, B and plasma cells [4]. These cells cause inflammation and injury of several organs through cytokines, antibodies, immune complexes and the infiltration of cytotoxic cells. Thus, the current treatment strategy for SLE is primarily the regulation of exacerbated autoimmunity using immunosuppressive therapy. Recently, biological targeting B-cell therapies, including rituximab (anti-CD20), epratuzumab (anti-CD22) and belimumab (anti-B-cell activating factor), have been developed for patients with SLE. The development of immunosuppressive therapy has improved the prognosis for patients with SLE compared with previous treatments during the last decade. However, the 10-year survival rate is approximately 70–80% lower in patients with lupus nephritis or NP complications compared with patients without those complications [5]. Moreover, regardless of these treatments, refractory or relapsing cases are occasionally (30–40%) found in NP-SLE, which is defined not as a type of SLE, but as a list of disparate NP manifestations of SLE. As NP-SLE contributes to the morbidity and mortality of patients with SLE, it is important for clinicians to manage NP-SLE appropriately and specifically.

Here, we describe the pathophysiology of NP-SLE and discuss future treatments of patients with NP-SLE, with reference to recently published reports.

Neuropsychiatric-systemic lupus erythematosus

NP-SLE refers to NP symptoms that are directly related to SLE and are not secondary complications. The prevalence of NP-SLE among patients with SLE ranges from 14 to 90% according to previously published reports [6–9]. NP events are frequent complications in patients with SLE. However, fewer than 40% of these NP events are directly associated with SLE. The remaining events are related to complications of the disease, such as drug effects and infections [2]. These cases should not be classified as NP-SLE. NP-SLE often occurs at the onset of the disease or within the first 2 years after diagnosis [2]. The complication of NP-SLE is commonly associated

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with systemic disease activity [10]. Furthermore, NP-SLE can be present even when the overall disease activity is stable or improving after treatment for SLE-related symptoms, such as lupus nephritis, cytopenia or arthritis. NP-SLE encompasses a wide variety of clinical courses and NP symptoms. Thus, NP-SLE remains a diagnostic and therapeutic challenge.

As shown in Box 1, NP-SLE is divided into 19 NP syndromes, as classified by the ACR [11]. The focal CNS form is defined as neurological syndromes such as headache, meningitis, seizure, paralysis and chorea. The diffuse CNS form is defined as diffuse psychiatric/neuropsychological syndromes such as confusional state, cognitive dysfunction, mood disorder and psychosis. NP symptoms associated with infection, drug effects or other factors should not be diagnosed as NP-SLE. Physicians should exclude non-SLE-related factors that are involved with NP symptoms. Headache, mood disorder, anxiety and mild cognitive dysfunction are common in the general population without SLE, so clinicians will need to assess whether these NP symptoms are directly related to SLE. By excluding these NP symptoms and polyneuropathy without electrophysiological confirmation, the frequency of NP-SLE decreases by half, and the specificity of the diagnosis increases from 46 to 93% [12]. A gold standard for diagnosis has not been established for NP-SLE. Thus, it is occasionally difficult for clinicians to correctly diagnose patients with NP-SLE.

Box 1. Classification of neuropsychiatric symptoms in neuropsychiatric-systemic lupus erythematosus.

CNS

- Focal symptoms:
  - Aseptic meningitis
  - Cerebrovascular disease
  - Demyelinating syndrome
  - Headache
  - Movement disorder
  - Myelopathy
  - Seizure
- Diffuse symptoms:
  - Acute confusional state
  - Anxiety disorder
  - Cognitive dysfunction
  - Mood disorder
  - Psychosis

PNS

- Acute inflammatory demyelinating polyradiculoneuropathy
- Autonomic disorder
- Mononeuropathy (single/multiplex)
- Myasthenia gravis
- Neuropathy (cranial)
- Plexopathy
- Polyneuropathy

Pathophysiology of NP-SLE

The pathophysiology of NP-SLE involves several factors, including vasculitis, thrombosis, inflammation and/or apoptosis of neuronal and glial cells [2,13]. Its mechanisms are mediated through autoantibodies, complement components, cytokines, chemical mediators and infiltration of inflammatory cells, such as neutrophils, lymphocytes and plasma cells. We classified the pathophysiology of NP-SLE into the three subsets as described below.

Vasculopathy

The complication of cerebrovascular disease or systemic thrombosis is involved with antiphospholipid syndrome (APS), atherosclerosis or vasulitis. It has been reported that vasuculitis is rare in SLE [12]. However, it is difficult to discriminate between vasculitis and nonvasculitis thrombosis as cerebral vessel biopsy is not conducted in daily clinical practice. In fact, the mechanism of vasculopathy may be occasionally involved with both vasculitis and thrombosis.

Focal or diffuse nervous inflammation

Aseptic meningitis, myelitis, neuropathy or polyradiculoneuropathy are associated with focal nervous inflammatory mechanism. These NP symptoms are involved in vasculitis or nonvasculitis inflammation through complement proteins, autoantibodies and cytokines. On the other hand, acute confusional state or psychosis could be associated with diffuse nervous inflammation accompanied with the global disease activity of SLE.

Noninflammatory/nonthrombotic antibody-mediated apoptosis

Cognitive dysfunction or depression is caused by the injection of autoantibodies such as antiribosomal P and anti-*N*-methyl-D-aspartate (NMDA) receptor in model mice. This mechanism is associated with apoptosis of neuronal cells via a noninflammatory/nonthrombotic process. These autoantibodies affect some signaling of cell viability.

Incidence of NP-SLE

The cumulative incidence of NP-SLE symptoms is shown in Box 2. Common manifestations of

NP-SLE are cerebrovascular disease and seizures [6,12]. The incidence of cerebrovascular disease is 7–10% in white/African–American individuals and 2–5% in Asian individuals [2]. Seizures occur in 7–10%. Most seizures represent a single isolated attack in patients with SLE [12]. This phenomenon is usually associated with global SLE disease activity. Mild cognitive dysfunction, mild depression, headache and polyneuropathy without electrophysiologic confirmation, are common. However, these NP symptoms are not usually related to SLE. Severe cognitive dysfunction, neuropathy, myelopathy, aseptic meningitis and psychiatric symptoms such as major depression and psychosis, are uncommon or rare in NP-SLE.

Box 2. Estimated cumulative incidence of neuropsychiatric systemic lupus erythematosus symptoms.

Common (5–10%)
- Cerebrovascular disease
- Seizure

Relatively uncommon (~5%)
- Severe cognitive dysfunction
- Major depression
- Peripheral nervous disorders
- Acute confusional state

Rare
- Psychosis
- Myelopathy
- Cranial neuropathies
- Aseptic meningitis
- Movement disorder (chorea)

Diagnosis of NP-SLE

NP-SLE is diagnosed on the basis of comprehensive investigations, such as a neurological examination, MRI of the brain and spinal cord, EEG, analysis of the cerebrospinal fluid (CSF), a nerve conduction examination, a psychiatric interview and a short battery of neuropsychological tests recommended by the ACR [11]. The sensitivity of MRI is 57% in active NP-SLE, 76 and 51% in focal CNS form and diffuse CNS form, respectively [12]. These findings suggest that MRI is not sensitive enough to detect the diffuse CNS form in NP-SLE. In EEG, the frequency of abnormal findings are 70–80% in the active phase, epileptiform in 50–70% and diffuse slow wave in 30–50% [2]. For CSF, mild abnormalities, including pleocytosis and mild elevation of protein level, are commonly (40–50%) found in active NP-SLE. However, these results are not specific to the manifestations of NP-SLE. No diagnostic gold standard tools have been established in NP-SLE. However, these diagnostic tools are available for differential diagnosis such as infection and tumor.

Despite the occasional existence of NP symptoms, there are no specific findings for NP-SLE in comprehensive investigations, including MRI, CSF and EEG. In patients with psychiatric symptoms associated with SLE, such as an acute confusional state or psychosis, corticosteroids and immunosuppressive agents tend to ameliorate these symptoms even though an MRI of the brain detects no obvious findings. This phenomenon suggests that the pathophysiology involves inflammation and diffuse small lesions, which MRI cannot detect in the CNS. Similarly, in the early stage of Parkinson's disease or Alzheimer's disease, NP symptoms are evident in patients before MRI can detect findings in the brain. In SLE, neurodegeneration may result from autoimmunity. Clinicians should remember that diffuse small lesions or degenerative changes of the CNS cannot be detected by conventional MRI.

Recent advances in autoantibodies associated with NP-SLE

Other than APS, several autoantibodies that affect neuronal cells or glial cells have been discovered in patients with NP-SLE. The pathophysiology associated with these autoantibodies in NP-SLE has been gradually clarified and understood. We describe recently identified associations between autoantibodies and NP-SLE. Table 1 lists the associations between autoantibodies, NP-SLE symptoms and pathophysiology.

Antiphospholipid antibodies

APS is characterized by both presence of antiphospholipid antibodies (aPL) and arterial/venous thrombosis, and is sometimes present as a complication of SLE. aPL target anionic phospholipids and protein–phospholipid complexes. aPL are found in 20–55% of patients with SLE [6]. Additionally, aPL are associated with the occurrence of seizures and cognitive dysfunction [14]. The 'two-hit' model of thrombosis is proposed in the mechanism of APS [15]. The 'first hit' is initiation of endothelial damage. The 'second hit' is thrombus formation. Thrombosis is not caused by injection of aPL obtained from patients with APS into mice in the absence of vessel-wall injury [16,17]. Moreover, β2-glycoprotein I does not bind the unstimulated endothelium *in vivo* [18]. The stimulation of oxidative stress and decreased nitric oxide are involved with the injury of endothelium in APS. aPL upregulate

Table 1. Association between autoantibodies, neuropsychiatric systemic lupus erythematosus symptoms and pathophysiology.

Autoantibody	NP-SLE symptoms	Pathophysiology
Anti-PL	Cerebrovascular disease Seizure Cognitive dysfunction	Endothelium injury and thrombosis Anti-PL activates complement consumption and p38 MAPK–NF-κB in monocytes and endothelial cells
Antiribosomal P	Psychosis Depression	Apoptosis of neuronal cells Antiribosomal P binds to olfactory and limbic areas, and increases intracellular Ca^{2+} influx
Anti-AQP4	Optic neuritis Myelitis	Intracellular edema and inflammation Anti-AQP4 binds the water transporter AQP4 and injures astrocytes
Anti-NR2	Acute confusional state Cognitive dysfunction	Apoptosis of neuronal cells Anti-NR2 inhibits the zinc-binding site of NR2 and decreases cell viability by increasing Ca^{2+} influx

NP-SLE: Neuropsychiatric-systemic lupus erythematosus; NR2: N-methyl-D-aspartate receptor subunit 2; PL: Phospholipid.

intercellular adhesion molecule-1, vascular cell adhesion molecule-1, E-selection and tissue factor by activating p38 MAPK–NF-κB in monocytes and vascular endothelial cells, which lead to an enhanced inflammatory response and subsequent thrombotic events [13,19,20]. Hypocomplementemia (C3 and C4) and elevation of anaphylatoxins (C3a and C4a) are also found in primary APS [21]. Complement activation and consumption are also associated with anticoagulant activity. The regulation of APL-induced activating p38 MAPK–NF-κB in monocytes and vascular endothelial cells or complement activation may become a treatment strategy for APS in the future.

Antiribosomal P antibody

Antiribosomal P antibodies are found in 6–46% of patients with SLE [22,23]. Antiribosomal P antibodies recognize the P0 (38 kDa), P1 (19 kDa) and P2 (17 kDa) proteins located on the 60S subunit of eukaryotic ribosomes. Antiribosomal P antibodies are associated with disease activity in patients with SLE [22,24]. Moreover, NP symptoms, especially psychosis and depression, are related to the presence of antiribosomal P antibodies [25,26]. Antiribosomal P targets a neuronal surface protein, which has remained unidentified, causing calcium (Ca^{2+}) influx and apoptosis [27]. Antiribosomal P specifically binds to neurons in the hippocampus, cingulate cortex and piriform cortex. Moreover, in model mice, these autoantibodies induce depression. These results implicate the olfactory and limbic areas in the pathogenesis of depression in patients with SLE [28]. The inhibition of antiribosomal P deposition on neuronal cells or the regulation of intracellular Ca^{2+} may prevent or improve the status of antiribosomal P-associated NP-SLE. However, there are few studies regarding the mechanism of antiribosomal P-induced NP symptoms. Additional investigations should address the biological function of antiribosomal P.

Anti-AQP4 antibody

The detection of anti-AQP4 antibodies in neuromyelitis optica (NMO) has been reported [29]. NMO is characterized by optic neuritis and transverse, longitudinally extensive myelitis. Wingerchuk *et al.* reported that clinical, laboratory and imaging features generally distinguish NMO from multiple sclerosis [30]. In general, NMO is also a separate syndrome from SLE. However, NMO has been reported as a complication of autoimmune diseases, such as thyroiditis, SLE or Sjögren's syndrome [31,32]. In some patients with these autoimmune diseases, including SLE, anti-AQP4 antibodies were detected. Thus, NMO is occasionally a complication of SLE. However, anti-AQP4 negative-myelitis/optic neuritis is also a complication of SLE. The mechanism of myelitis/optic neuritis with SLE might be heterogeneous.

The mechanism of NMO is intracellular odema and inflammation caused by anti-AQP4 binding to AQP4, which is a channel that transports water across the cell membrane. The blood–brain barrier (BBB) is surrounded by astrocytes. AQP4 is expressed highly on the cell membrane of astrocytes, especially in the optic nerve and spinal cord. Anti-AQP4 could affect the function of astrocytes; damage the BBB; and induce inflammation of the optic nerve, spinal cord and brain. In NMO, the response to corticosteroid therapy is effective. Immunosuppressive agents such as calcineurin inhibitors and

rituximab are also effective for relapsing cases with NMO.

Anti-NMDA antibody

Some anti-dsDNA antibodies cross-react with NMDA receptor subunit 2 (NR2) in patients with SLE [33]. The NMDA receptors are ligand-gated ion channels that play crucial roles in synaptic transmission and CNS plasticity. NMDA receptor dysfunction has been implicated in multiple brain disorders, including stroke, chronic neurodegeneration, epilepsy and schizophrenia. Anti-NMDA receptor encephalitis is one of the paraneoplastic syndromes. This disease is associated with ovarian teratoma. The characteristics of clinical manifestations are refractory seizures and psychosis [34]. In anti-NMDA receptor encephalitis, the anti-NMDA receptor antibodies recognize NMDA receptor subunit 1 (NR1) and NR2 heteromers [35]. Moreover, critical epitopes are present in NR1. The main therapy is immunosuppressive therapy and resection of the teratoma.

The anti-NR2 autoantibodies are found in 30% of patients with SLE [36]. It has been reported that the epitopes recognized by the autoantibodies differ between anti-NMDA receptor encephalitis and SLE. The presence of anti-NR2 antibodies in the CSF is associated with diffuse psychiatric/neuropsychological SLE, such as acute confusional state, depression and cognitive dysfunction [37]. Whether anti-NR2 is associated with seizures in patients with SLE has not been confirmed. If the anti-NR2 antibodies breach the BBB, it can cause neuronal damage via an apoptotic pathway [38,39]. In non-neuronal tissues, significant inverse correlations have been found between the anti-NR2 antibody titers and both the leukocyte count and the hemoglobin level [36]. The NMDA receptors are located in neuronal and non-neuronal tissues, such as pancreas, bone and blood cells. The anti-NR2 antibodies might damage non-neuronal tissues, such as blood cells, through the NMDA receptor. Additionally, human anti-NR2 antibodies decrease cell viability by increasing Ca^{2+} influx in the NMDA receptor-transfected HEK 293 cells. The anti-NR2 antibodies bind the zinc-binding site of NR2 and inhibit modulation of the intracellular Ca^{2+} influx [39]. In the brains of mice injected with anti-NR2 antibodies, there was minimal local activation of astrocytes and microglial cells and there was no lymphocytic inflammation [33]. The anti-NR2-induced injury of neuronal cells might involve a noninflammatory mechanism, such as modulation of cell viability signaling. The inhibition of anti-NR2 deposition on neuronal cells or the regulation of BBB permeability or intracellular Ca^{2+} influx may be a potent therapy for anti-NR2-positive NP-SLE.

16/6 idiotype antibody

The 16/6 idiotype (Id) antibodies are one of the anti-DNA Id antibodies that are associated with SLE. Immunizing naive mice with the human 16/6 Id monoclonal antibody induces an SLE-like disease characterized by serological, clinical and pathological findings. These antibodies cross-react with cytoskeletal proteins, pathogens (such as *Mycobacterium tuberculosis*), glycoproteins and brain glycolipids [40]. 16/6 Id antibodies can be deposited in human tissues, such as the skin, kidney and brain [41], and this deposition is found in patients with active SLE or NP-SLE. Thus, the 16/6 Id antibodies are also one of the potential factors that cause NP-SLE. A recent study evaluated the cognitive function and behavioral performance of C3H female mice that had been injected with the human 16/6 Id IgG antibodies (16/6 Id mice subset) and compared them with mice that were injected with a commercial human IgG (control mice subset) [42]. Compared with the control mice, visual recognition memory and spatial memory were impaired in the 16/6 Id mice subset. Additionally, compared with the control mice, the brain tissue of 16/6 Id mice showed increased microglial activation in the hippocampus and amygdala, but not in the neocortex or piriform cortex. An increased number of astrocytes was found in the hippocampus of the 16/6 Id mice. Together, these results demonstrate that the 16/6 Id antibodies impair visual and spatial memory through hippocampal inflammation and injury in mice and might selectively cross-react with some antigens in the hippocampus. Other than the suppression of synthesising autoantibodies by immunosuppressive therapy, the inhibition of autoantibodies deposition on neuronal cells, such as using a small peptide, which could bind to autoantibodies and may be a key treatment for NP-SLE.

Current treatment for NP-SLE

The general management of patients with NP symptoms and SLE is aggravated by factors such as adverse drug effects, infection or metabolic abnormalities [12]. If NP symptoms, including acute confusional state, psychosis, cranial and peripheral neuropathies and myelitis, are

associated with inflammation and autoantibodies induced by SLE-related autoimmunity, the treatment strategy for SLE should include immunosuppressive therapy using corticosteroids or immunosuppressive agents, such as cyclophosphamide (CY), calcineurin inhibitors or mycophenolate mofetil (Table 2).

Previously, a controlled clinical trial of intravenous (iv.) CY versus iv. methylprednisolone (MP) was conducted in NP-SLE [43]. After randomization, each patient was received MP 1 g daily for 3 days as induction therapy. Oral prednisone, 1 mg/kg/day, was started on day 4 of treatment in each patient, for no more than 3 months and tapered according to disease activity. In the MP subset (n = 13), MP was given 1 g daily for 3 days every month for 4 months, then bimonthly for the next 6 months and, subsequently, every 3 months for another year. In the CY subset (n = 19), CY 0.75 g/m^2 was given monthly for 1 year and every 3 months for another year. The results demonstrated that the response to treatment was found in 54% among the MP subset and 95% among the CY subset, respectively. In another study, the frequency of improvement for NP-SLE was higher in patients receiving prednisone and low-dose (200–400 mg/monthly) iv. CY than in patients receiving prednisone alone or with antimalarials [44]. In severe cases of NP-SLE, such as optic neuritis, myelitis, peripheral neuropathy, psychosis and acute confusional state, the combination therapy of corticosteroid and CY could be considered. Moreover, plasma exchange, rituximab and iv. immunoglobulin are also used in refractory cases of NP-SLE. Anticoagulation or antiplatelet therapy is indicated when thrombosis is associated with aPL/APS. In the pathophysiology of NP-SLE, the differentiation between the thrombotic process and inflammatory process is not always obvious, even if anti-aPL are present. In some patients with NP-SLE, both thrombotic and inflammatory pathophysiologies are involved. In NP-SLE patients who do not respond to anti-inflammatory therapy and have positive aPL, anticoagulation or antiplatelet therapy might be considered.

In anticoagulation therapy, warfarin, a vitamin K antagonist, is commonly used. Recently, new oral coagulants have been developed. New oral coagulants include dabigatran etexilate, a direct thrombin inhibitor, and rivaroxaban, apixaban and edoxaban, which are direct anti-Xa inhibitors [45]. Both rivaroxaban and dabigatran have been approved by the European Medicines Agency and the US FDA for the prevention of stroke in patients with nonvalvular atrial fibrillation. These agents may be also effective for APS. A prospective, randomized, controlled trial of warfarin versus rivaroxaban is scheduled in patients with APS.

For chronic headache, mood disorders and anxiety disorder that are not associated with global SLE disease activity, symptomatic therapies, such as painkillers, antidepressants or antipsychotic medications, are administered. However, NP-SLE can be refractory to these treatments and is therefore challenging.

Table 2. Current therapy and perspective directions for neuropsychiatric systemic lupus erythematosus.

Treatment	Agents	Pharmacological effect
Current therapies		
Immunosuppressive therapy	Corticosteroid Cyclophosphamide MMF Rituximab	Regulation of lymphocytes and synthesis of autoantibodies and cytokines
Anticoagulation/antiplatelet	Warfarin Aspirin	Antithrombosis
Perspective directions		
Small peptide	DWEYS peptide FISLE-412	Inhibition of autoantibody deposition in tissue
Modulation of Ca^{2+} influx	Memantine Dipyridamole	Noncompetitive NR antagonist Inhibitor of calcineurin/NF-AT
Zinc supplement	Zinc	Regulation of Ca^{2+} influx via NR
Modulation of BBB permeability	Anticytokine mAb Anti-CD88 mAb	Inhibition of cytokine, autoantibody and inflammatory cell penetration into CNS

BBB: Blood–brain barrier; mAb: Monoclonal antibody; MMF: Mycophenolate mofetil; NR: N*-methyl-*D*-aspartate receptor.*

Future treatment for NP-SLE

In patients with NP-SLE, brain tissue-reactive antibodies may be synthesised in the CNS or peripheral organs, such as the lymph nodes and bone marrow [46]. Therefore, if NP-SLE is associated with antibodies that reach the CNS through the BBB, then treatments that not only eliminate brain tissue-reactive antibodies but also protect the integrity of the BBB should be considered. Moreover, the anti-NR2 and antiribosomal P antibodies increase intracellular Ca^{2+} influx and cause neuronal cells to undergo apoptosis. Thus, one treatment option is to modulate the intracellular Ca^{2+} levels and use antiapoptosis therapy. Future treatment directions are described in TABLE 2. These therapies mentioned below could be theoretical. However, the efficacies of these new therapies remain unproven in patients with NP-SLE.

Small peptide therapy

Some anti-dsDNA antibodies cross-react with the DWEYS peptide, which is part of the NMDA receptor sequence. The D-isoform of the DWEYS peptide can block the deposition of anti-dsDNA/NMDA receptor antibodies in the kidney and brain in lupus model mice [38,47]. In humans, serum anti-dsDNA reactivity was inhibited by an octameric form of the DWEYS peptide in ten patients with SLE. This peptide may be harmless to humans as it is a small peptide and nonimmunogenic. However, the peptide could not be administered orally due to its short half-life [48]. Diamond *et al.* designed a unique small molecule, FISLE-412, that imitates the structure of DWEYS to overcome the lack of molecular stability and oral availability [49]. FISLE-412 blocks the antigen and tissue destructive activity of dsDNA/DWEYS-reactive autoantibodies. *In vitro*, *ex vivo* and *in vivo* assays revealed that FISLE-412 neutralises the activities of the DWEYS peptide. Pathogenic human SLE autoantibodies were injected intracerebrally into a mouse hippocampus with or without preincubation with FISLE-412. Neuronal toxicity was observed in the mouse hippocampus without FISLE-412. By contrast, the neuronal cells were protected in the mouse hippocampus with FUSLE-412. Small peptides, such as FISLE, are a potent therapy that can inhibit antibody deposition in tissues and protect organs in patients with autoantibody-associated NP-SLE or lupus nephritis.

Modulation of intracellular Ca^{2+} influx

Although the appropriate intracellular Ca^{2+} level is important for cell survival, excessive Ca^{2+} load can trigger cell death programs, such as the activation of protease, caspase and other catabolic processes [50]. Intracellular Ca^{2+} is stored in the endoplasmic reticulum and mitochondria. The intracellular Ca^{2+} level in unstimulated cells is maintained at less than 100 nM by both uptake into the endoplasmic reticulum and extrusion into the extracellular space by the plasma membrane Ca^{2+}-ATPase [51]. Excessive Ca^{2+} influx into cells, which is triggered by several agents (e.g., Ca^{2+} ionophores), promotes the opening of the mitochondrial permeability transition pore, resulting in the release of cytochrome c and other proapoptotic proteins from the mitochondria and the induction of apoptosis [51].

Regarding the pathophysiology of SLE, an increased intracellular Ca^{2+} level is also associated with the injury of neuronal cells or blood cells, and activation of T cells [39,52]. Thus, modulating the intracellular Ca^{2+} level might be a potent therapy for SLE.

Memantine

Memantine is a noncompetitive NMDA receptor antagonist and is one of the medications used to treat Alzheimer's disease. Memantine acts on the glutamatergic system by blocking the NMDA receptor and modulating the intracellular Ca^{2+} influx. In BALB/c mice that were immunized with a multimeric form of the DWEYS peptide and developed a high anti-NR2 titer, memantine protected against neuronal damage [53]. Neuronal damage occurs due to an increase in Ca^{2+} influx caused by anti-NR2 antibodies. Therefore, memantine modulates Ca^{2+} influx and protects neuronal cells via the NMDA receptor in the mouse model. In humans, a randomized, double-blinded, placebo-controlled trial with memantine was conducted on 51 patients with SLE and cognitive impairment. However, the patients who were treated with memantine did not exhibit significant improvement in cognitive function compared with the placebo group. In this trial, anti-NR2 was detected in only five out of 51 patients. In the future, it is necessary to evaluate whether memantine is effective for patients with SLE who are anti-NR2 positive [54].

Dipyridamole

Dipyridamole, which is a phosphodiesterase inhibitor, increases the intracellular cAMP level. Recently, dipyridamole has been recognized as an inhibitor of calcineurin/NF-AT [55]. In patients with SLE, T cells display a hyperactive calcineurin/NF-AT pathway. Dipyridamole inhibits SLE human T-cell function, the production of

cytokines such as interferon-γ, IL-17 and IL-6, and T-cell-dependent B-cell immunoglobulin secretion. Additionally, it improves pathological changes in lupus-prone mice [52]. Dipyridamole may protect neuronal cells by inhibiting the hyperactive calcineurin/NF-AT pathway induced by the increased intracellular Ca^{2+} levels, which are caused by antiribosomal P or anti-NR2 antibodies, in patients with NP-SLE.

Zinc supplements

Each NR2 subunit (NR2A, NR2B) consists of a large extracellular amino-terminal domain (ATD), a bilobed agonist-binding domain (ABD), a transmembrane domain and an intracellular C-terminal domain. The ATD is composed of approximately the first 350 amino acids of the protein [56]. Residues 283–287 are DWDYS in NR2A and DEWDY in NR2B. These sequences are recognized by anti-NR2. Asp 283 in NR2A and Glu 284 in NR2B are considered zinc-binding sites. Zinc binding to the NR2A/2B ATD modulates Ca^{2+} influx and NMDA receptor-mediated synaptic responses [57]. We reported that anti-NR2 decreases cell viability by increasing Ca^{2+} influx in SLE because it inhibits the binding capacity of zinc [39]. Anti-NR2 can increase the intracellular Ca^{2+} level in a dose-dependent manner. When the concentration of zinc increases, the levels of intracellular Ca^{2+} decrease in NR1/NR2A-transfected-HEK 293 cells treated with an anti-NR2 antibody. These results suggest that supplementing zinc in the CSF might modulate intracellular Ca^{2+} and protect neuronal cells that express NMDA receptors in patients with NP-SLE who have anti-NR2.

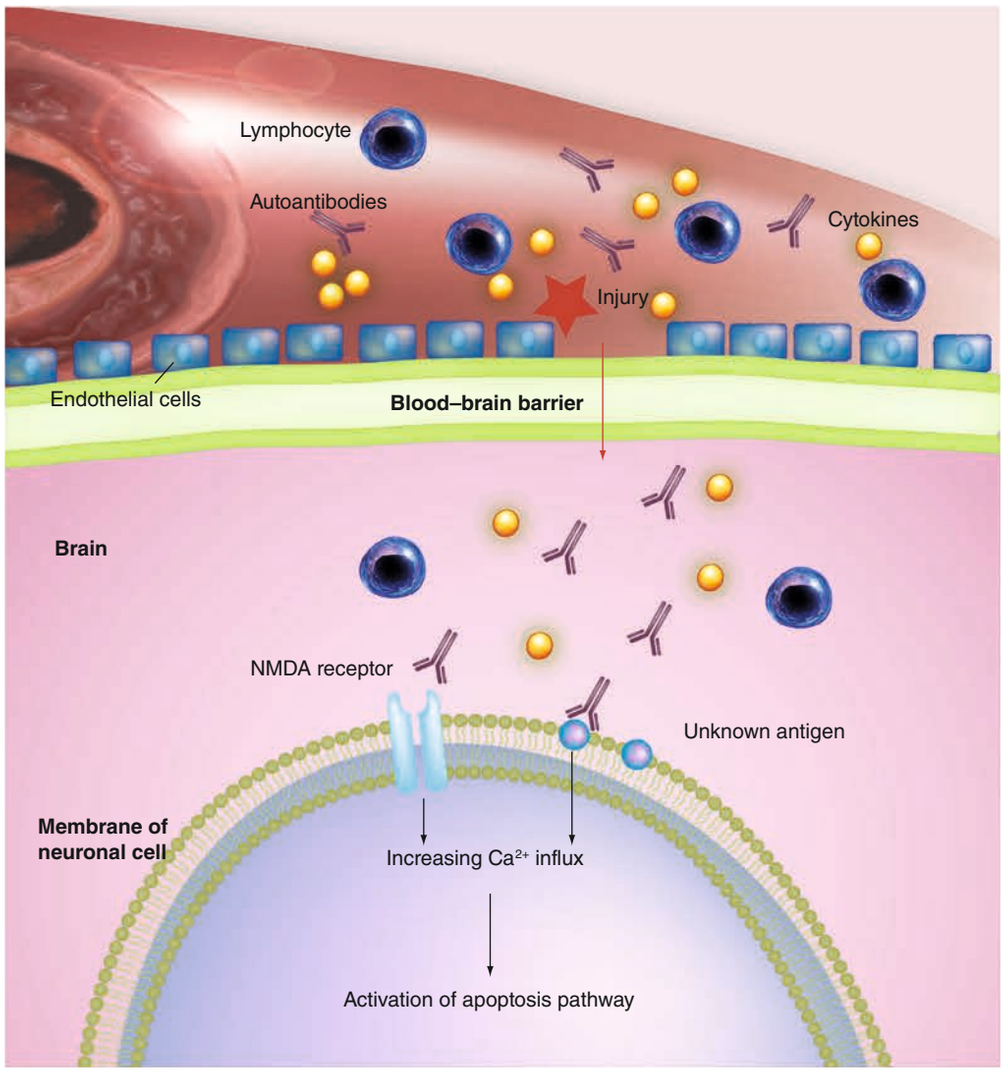

Figure 1. Hypothesis for the pathophysiology of neuropsychiatric systemic lupus erythematosus.
NMDA: *N*-methyl-D-aspartate.

Modulation of BBB permeability

The BBB is a dynamic interface that separates the brain from the circulatory system and protects the CNS from harmful chemicals. A tight junction between each vascular endothelial cell plays a role in restricting the passage of solutes [58]. Even if anti-NR2 is present in the peripheral blood, then NP-SLE is not definitely complicated with anti-NR2-positive SLE patients [36,48]. In a mouse model, NP symptoms could not occur even if anti-NR2 was injected into the peripheral blood. However, when the mouse model was treated with lipopolysaccharide, which increases BBB permeability, NP symptoms appeared [38]. Therefore, autoantibodies harboring cross-reactivity against neuronal surface proteins must reach the CNS through the BBB for NP-SLE to occur. In general, humoral factors, such as IL-β, TNF-α, IFN-γ and VEGF, disrupt the tight junction and increase the permeability of the BBB [58]. This disruption is occasionally found in patients with SLE [59,60]. The mechanism of increased BBB permeability may involve cytokines, complement or autoantibodies, although the mechanism has not been established. C5a and CD5a receptor (CD88) signaling is associated with altered BBB integrity in patients with lupus. Signaling through CD88 regulates BBB integrity in an NF-κB-dependent manner. CD88 might be a therapeutic target that will reduce NF-κB signaling cascades during inflammation [60]. Taken together, the development of new agents that protect BBB permeability might be useful for the treatment and the prevention of NP-SLE.

Conclusion

A wide variety of NP syndromes are caused directly by SLE-associated disease activity or secondary factors, including drug effects, infection, hypertension and social stress. Additionally, NP-SLE comprises diverse pathophysiologies, such as vasculopathy, inflammation or degeneration of neuronal cells and glial cells. Each autoantibody, such as antiribosomal P, anti-NR2 and anti-16/6 Id, may recognize different brain tissue antigens and cross-react with the nervous system. Together, clinical manifestations might be different and diverse in NP-SLE. The identification and evaluation of such differences would be useful for developing more selective and specific therapies for patients with NP-SLE.

Future perspective

Over the next 10 years, specific target therapy, such as biologics and small-molecule agents, will be developed for patients with SLE. These new agents will hopefully improve the prognosis of patients with NP-SLE. Accordingly, we should

Executive summary

Systemic lupus erythematosus

- Systemic lupus erythematosu (SLE) is a multisystem inflammatory disorder that is characterized by the presence of several autoantibodies, including anti-dsDNA.
- Lupus nephritis and neuropsychiatric (NP)-SLE contribute to the prognosis of patients with SLE.

Neuropsychiatric-systemic lupus erythematosus

- NP-SLE refers to NP symptoms that are directly related to SLE and are not secondary complications, caused for example, by drugs or infection.
- NP-SLE accounts for substantial morbidity and mortality in patients with SLE.
- NP-SLE is divided into 19 NP syndromes, as classified by the ACR.
- Cerebrovascular disease and seizures are common presentations of NP-SLE.

Pathophysiology of NP-SLE

- Antiphospholipid antibodies are associated with arterial/venous thrombosis.
- Psychosis is related to antiribosomal P antibodies. The mechanism might be intracellular Ca^{2+} influx and apoptosis induced by the autoantibody binding a neuronal surface protein.
- Anti-AQP4 antibodies cause myelitis and optic neuritis by injuring AQP4 channels on astrocytes.
- Anti-*N*-methyl-D-aspartate receptor subunit 2 antibodies are associated with acute confusional state, depression or cognitive dysfunction. Anti-*N*-methyl-D-aspartate receptor subunit 2 antibodies bind the zinc-binding site of *N*-methyl-D-aspartate receptor subunit 2, inhibit modulation of intracellular Ca^{2+} influx and cause neuronal apoptosis.

Current treatment & future perspective

- The current treatment strategy is immunosuppressive therapy, such as corticosteroids or immunosuppressive agents, including cyclophosphamide. However, the efficacy of these treatments is occasionally insufficient for refractory cases or relapsing cases with NP-SLE.
- Regulating blood–brain barrier permeability, inhibiting autoantibody deposition in tissues and modulating intracellular Ca^{2+} may be new concepts for the treatment of patients with NP-SLE.

more precisely clarify the pathophysiology and identify a new diagnostic gold standard tool for NP-SLE. Figure 1 shows our hypothesis for the pathophysiology of NP-SLE. Regulating the BBB permeability, inhibiting autoantibody deposition in tissues and modulating intracellular Ca^{2+} may be new concepts for the treatment of patients with NP-SLE. Although immunosuppressive therapy is a basic treatment for NP-SLE, the addition of these putative new agents may not only improve the prognosis for NP-SLE, but also be effective for refractory or relapsing cases with NP-SLE. These concepts should be useful for the development of therapies for NP-SLE. Investigators and clinicians should consider not only immunosuppressive therapy but also protection of the BBB, vascular endothelial cells, neuronal cells and glial cells, when devising treatment strategies for NP-SLE.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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