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REVIEW ARTICLE

The role of autoantibodies in neuropsychiatric systemic lupus erythematosus: mechanisms, biomarkers and clinical correlations

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ABSTRACT

Introduction. Neuropsychiatric lupus erythematosus is still a disease with a very challenging diagnostic process, lacking high specificity and sensitivity assays. Autoantibodies can change this perspective, and because of their pathogenetic involvement, can become a very powerful tool for early detection and disease activity tracking. However, their biomarker potential still needs further evaluation. In this study, we focused on the pathogenetic mechanisms of neuropsychiatric lupus erythematosus and the involvement of brain-specific and systemic autoantibodies in the development of neuropsychiatric manifestations.

Material and methods. Medical articles addressing the correlation of autoantibodies concentrations in serum and cerebrospinal fluid and their potential pathogenetic mechanism, were reviewed. More than 100 articles were identified from databases such as PubMed, ScienceDirect, Frontiers, and Wiley, using keywords such as "neuropsychiatric lupus erythematosus", "autoantibodies", "pathogenesis", "biomarker" and "neuropsychiatric manifestations". From these, 47 articles were selected for the current review.

Results. Autoantibodies truly are indeed a tool in the diagnostic process of neuropsychiatric lupus erythematosus, and many researchers have obtained statistically valid correlations between their presence and specific neuropsychiatric manifestations. Variations in their concentration not only reflect the disease activity but also the fact that they are involved in its development through interactions with neuronal and vascular targets. Besides autoimmunity, brain-blood barrier dysfunction is also another key part of the pathogenetic mechanism, with markers of this injury also being useful in the diagnostic methodology. With future research, specific combinations of these markers can be linked to distinct clinical manifestations by creating multi-biomarker panels, a robust framework for diagnosing neuropsychiatric lupus erythematosus.

Conclusions. Neuropsychiatric lupus erythematosus remains a condition that highly challenging to diagnose and manage due to the heterogeneity of symptoms and the lack of standardized diagnostic tools. Autoantibodies, along with other markers of vascular and inflammatory injury can aid specialists in dealing with this disease, but further research is needed to validate these biomarkers in diverse patient populations and to standardize assays for clinical application to improve the early detection and management of NPSLE, ultimately enhancing patient outcomes and quality of life.

Keywords: neuropsychiatric lupus erythematosus, pathogenesis, autoantibodies, brain-blood barrier, neuro-inflammation, biomarker.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

Despite extensive research, the precise pathogenetic role and diagnostic utility of many brain-specific autoantibodies in neuropsychiatric systemic lupus erythematosus remain unclear. Additionally, there is limited understanding of how disruptions in the blood-brain barrier and its interaction with these autoantibodies can be reliably measured and integrated into personalized therapeutic strategies.

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The research hypothesis

Specific brain-targeted autoantibodies and disruptions in the blood-brain barrier play a pivotal role in the pathogenesis of neuropsychiatric systemic lupus erythematosus, offering potential as biomarkers and therapeutic targets for personalized management.

The novelty added by the manuscript to the already published scientific literature

The manuscript highlights the potential of specific brain-targeted autoantibodies and blood-brain barrier disruptions as combined biomarkers for neuropsychiatric systemic lupus erythematosus, emphasizing their role in symptom-specific pathogenesis and paving the way for personalized diagnostic and therapeutic strategies.

Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by a loss of immune tolerance, the production of autoantibodies against self-antigens, and the formation of immune complexes that contribute to inflammation and tissue damage [1, 2]. Affecting multiple organ systems, SLE commonly involves the skin, joints, kidneys, and serosal membranes. The disease's considerable heterogeneity, influenced by genetic, environmental, and immunological factors, has earned the title "the disease with a thousand faces". Among its many manifestations, involvement of the central and peripheral nervous systems represents a unique and complex aspect of the disease, known as neuropsychiatric systemic lupus erythematosus (NPSLE).

NPSLE is defined as a set of neuropsychiatric manifestations that can affect both the central and peripheral nervous system and encompasses a spectrum ranging from mild cognitive impairments and anxiety to severe manifestations, including stroke, seizures, and psychosis [2-4]. These symptoms can be classified as primary, if the manifestation is a result of the autoimmune inflammatory processes from the nervous system, or secondary due to the treatment or infections of the nervous system from chronic immunosuppression. Also, they can be divided into focal or diffuse manifestations, and central or peripheral, depending on what part of the nervous system is affected [2].

The clinical manifestations can vary from patient to patient, ranging from headaches and subtle cognitive dysfunction to more severe manifestations, including psychosis, acute confusion, and epilepsy. According to the American College of Rheumatology nomenclature and classification criteria, scientists identified 12 neuropsychiatric manifestations associated with the central nervous system (CNS) and 7 associated with the peripheral nervous system [3-5] (Table 1). Some of these symptoms are seen more frequently (cognitive dysfunction, mood disorders, anxiety headaches, seizures) whereas others remain infrequent or very rare (acute confusional status, aseptic meningitis, autonomic disorders, plexopathy) [3].

Table 1. Classification of neuropsychiatric and neurological syndromes in NPSLE according to ACR criteria [4].

Category	Central Nervous System	Peripheral Nervous System
Neurological Syndromes	Focal Manifestations Seizure disorders Aseptic meningitis Demyelinating syndromes Myelopathy Cerebrovascular disease Headache Movement disorders	Focal Manifestations Autonomic disorders Myasthenia gravis Polyneuropathy Cranial neuropathy Guillain-Barré syndrome (GBS) Mononeuropathy Plexopathy
Neuropsychiatric Syndromes	Diffuse Manifestations Anxiety disorders Psychosis Acute confusional state Cognitive dysfunction Mood disorders	

***Note**: This table presents the classification of neuropsychiatric and neurological manifestations in neuropsychiatric systemic lupus erythematosus (NPSLE) as defined by the American College of Rheumatology (ACR). The manifestations are categorized based on their association with the central nervous system (CNS) or peripheral nervous system (PNS), and are further divided into focal and diffuse syndromes. While some manifestations, such as cognitive dysfunction and mood disorders, are commonly observed, others like acute confusional states and plexopathies are infrequent or rare.*

One of the major challenges in dealing with NPSLE patients is determining whether the neuropsychiatric manifestations are attributable and result directly from SLE, or are consequences of factors such as treatment, comorbid conditions, or non-organic psychological diseases that mimic the neuropsychiatric symptoms of the SLE. Along with the American College of Rheumatology definitions, Bortoluzzi *et al.* proposed and validated an algorithm based on lupus activity assessment, imaging techniques, and cerebrospinal fluid analysis to better differentiate the primary NPSLE manifestations from those caused by other factors [6, 7]. Also based on different SLICC inception cohort studies, researchers have also developed additional criteria to consider in the evaluation of NPSLE manifestations. These criteria take into account critical factors such as the temporal relationship between the interval of the

onset of neuropsychiatric symptoms and the diagnosis of SLE, the presence of secondary causes for the NPSLE-like manifestations, and the frequency of particular neuropsychiatric events in the general population. Also, according to these criteria, symptoms such as isolated headaches, mild anxiety or depression, and cognitive impairment affecting fewer than three cognitive domains are less likely to be attributed to SLE [3-5].

Despite advancements in understanding NPSLE, significant challenges remain in its recognition, diagnosis, and treatment due to the heterogeneity of symptoms, the absence of standardized diagnostic criteria, and the limited reliability of conventional markers [4, 6, 8]. Among the promising avenues for addressing these gaps is the exploration of autoantibodies as biomarkers for NPSLE. Brain-targeting autoantibodies, such as anti-NMDA receptor and anti-ribosomal P protein antibodies, have been implicated in both serum and cerebrospinal fluid (CSF) of NPSLE patients, with their presence often correlating with specific neurological manifestations and blood-brain barrier (BBB) disruption [2, 5, 9]. These autoantibodies, along with others targeting phospholipids or unidentified CNS antigens, provide a potential window into the mechanisms of NPSLE and its clinical variability. This research aims to explore their role as biomarkers, highlighting their diagnostic and prognostic utility while investigating the underlying pathogenesis, particularly the role of BBB leakage.

Material and methods

A comprehensive literature review was conducted to analyze the role of antibodies in the pathogenesis, diagnosis, and prognosis of NPSLE, with a specific focus on their utility as biomarkers and their involvement in the neuroinflammatory process. This section describes the methodological approach used to identify, analyze, and synthesize relevant studies, ensuring a thorough and critical examination of the existing knowledge base.

Data sources and search strategy. The systematic search spanned multiple databases, including PubMed, Frontiers, Springer Nature Link, and Science Direct. The literature search covered publications from 1998 to 2024, ensuring the inclusion of both foundational studies and the latest advancements. To maximize search efficiency and coverage, a combination of keywords was used: "NPSLE," "autoantibodies," "pathogenesis," "biomarker," "neuropsychiatric manifestations," "BBB," and "choroid plexus," as well as Boolean operators and truncations to account for variations in terminology.

Studies were selected based on predefined inclusion and exclusion criteria to ensure relevance and quality. *The inclusion criteria were*: original research articles, systematic reviews, meta-analyses, and clinical trials; studies explicitly addressing the role of antibodies in NPSLE pathogenesis, their potential as diagnostic or prognostic biomarkers, and their involvement in the disruption of the BBB and the BCB; publications in English that provided detailed methodology and specific data relevant to the research objective. *Exclusion criteria included*: studies lacking explicit data on antibodies or their role in NPSLE; case reports and editorials, as they were less likely to provide comprehensive or generalizable insights; studies focusing solely on lupus nephritis, cutaneous lupus, or other non-neuropsychiatric manifestations of systemic lupus erythematosus.

Data extraction and analysis. Data was systematically extracted using a structured template, focusing on study design, population characteristics, antibody roles in NPSLE pathogenesis, and their diagnostic or prognostic utility. Studies employing advanced techniques like immunohistochemistry, cytokine profiling, and neuroimaging received particular attention for their insights into antibody-CNS interactions. Each study was critically assessed for methodological rigor and relevance. The extracted data were synthesized narratively, emphasizing the heterogeneity in antibody profiles, their mechanistic roles in NPSLE, and their clinical implications. Trends and gaps in the literature were identified, highlighting areas requiring further research. Where available, quantitative data were incorporated to provide context for the significance of findings, such as correlations between antibody titers and clinical outcomes or imaging abnormalities.

Ethical considerations. Given the nature of the study as a review of existing literature, ethical approval was not required.

Limitations. This review is limited by its reliance on published literature in English, which may have excluded relevant studies available in other languages. Nonetheless, the comprehensive search strategy and the critical appraisal of the included studies provide a solid foundation for understanding the antibody-mediated mechanisms in NPSLE.

Results

Pathogenetic mechanisms of NPSLE

According to recent perspectives, NPSLE is a multifactorial process involving numerous pathogenetic pathways, ranging from the integrity of the BBB to the interaction of the immune cells with the brain tissue [7, 8]. Some scholars consider the integrity of the neuroimmune interfaces to be one of the key elements in NPSLE pathogenesis, which consist of the meningeal barrier, glymphatic circulatory system, BBB, and blood-CSF barrier (choroid plexus; BCB), neuroinflammation and interaction of brain tissue with different cytokines, autoantibodies and immune complexes, cerebrovascular lesions and direct interactions between central and peripheral nervous system cells (microglia activation, abnormal endothelial-immune cell interactions) [6]. However, there is no consensus on the activation and progression of this cascade of changes.

It is known that during the homeostatic state, the BBB, composed of specialized endothelial vessels surrounded by pericytes, astrocytic end-feet, and microglial cells, represents a very selective and robust barrier that limits the entry of several types of immune cells or inflammatory molecules into the brain parenchyma. The endothelial cells (EC), that reassemble the blood vessel wall, maintain robust tight junctions that effectively seal

the intercellular spaces and are characterized by diminished transcytosis, which is a consequence of a very specific set of transporters (GLUT1, MCT1, L1, γ^+, EAAT etc.) that regulates the entry and the afflux of different types of molecules and ions, what is very important, according to some authors, for the progression of immune reactions [5, 8]. The BCB operates using quite the same architectonics, the capillaries that form choroid plexus have fenestrations, but also serve as an educational gateway, allowing memory T cells to access and perform immunosurveillance on antigens and pathogens drained from the CSF [7, 8]. Conforming to specialized literature, the alteration in the permeability of the BBB and the BCB are one of the key parts of the neuroinflammatory process and the pathogenesis of the neuropsychiatric manifestations of NPSLE [5, 9]. Furthermore, as some authors suggest, due to the hyperactivity of both innate and adaptive immune systems, the homeostatic mechanisms of regulatory systems become impaired, and different immunological mechanisms and systems such as cytokine formation, the complement system, and autoreactivity from the immune cells for self-antigens start to modulate the permeability of the BBB [2, 4, 8]. The cytokines formed in vast quantities, such as tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and fibroblast growth factor-inducible 14 (Fn14) when bonded together induce the formation of different pro-inflammatory molecules such as IL-6, IL-8 and INCAM-1 (Intracellular adhesion molecule-1) in astrocytes [9]. Due to the large secretion of these substances, the production of tight junction proteins (occludin-5, JAM-A, ZO-1, etc.) is diminished, but the expression of such proteins as matrix metalloproteinases (MMPs) (MMP2, MMP9) is elevated in ECs, astrocytes, microglial cells, monocytes and macrophages, therefore disturbing the BBB permeability and its function, and allowing transmigration of inflammatory cells into the CNS parenchyma [7, 10]. Some studies have been published indicating that, in addition to the above-mentioned molecules, in large concentrations were found inflammatory cytokines like B-cell activating factor (BAAF), interferon-γ (IFN-γ), and interferon-α (IFN-α) [8, 11]. The concentration of these inflammatory cytokines is independent of their serum value, indicating that the hyperproduction site of these molecules occurs in the CNS [6]. Recent studies show that there is a very strong correlation between the serum concentration of IL-6 and NPSLE manifested with acute confusion states, the authors, Hirohata et al. 2021 stating that serum IL-6 concentration can be used as a biomarker for the severity of the NPSLE, the damage of the BBB being measured using the cerebrospinal fluid/serum albumin quotient (Qalb) [11]. Another route through which cytokines, autoantibodies, and immune cells can reach the brain tissue is the choroid plexus. In their study, Gelb et al. showed that sometimes the BBB can remain intact, and the gate through which the neuroinflammation starts is the dysfunctional choroid plexus, mainly its EC. Using the immunofluorescence technique, they showed that in some epithelial cells, the transcytosis process from the choroid plexus was elevated, leading to increased deposition of antibodies into the central nervous system at the choroid plexus and infiltration of lymphocytes through transepithelial migration creating a tertiary lymphoid structure [12, 13].

There is growing evidence that CNS cells are also influenced by all these inflammatory disturbances and play a key role in the pathogenesis of the NPSLE manifestations [7, 10, 11]. Microglial cells, which are long-lived resident macrophages, are classified into two types of population, M1 which is involved in the production of the proinflammatory cytokines, reactive oxygen species, and nitric oxide, and M2, with an inhibitory effect over the inflammatory processes. In the case of NPSLE, it is thought that the M1 polarized microglial cells are more active, a phenomenon called microgliolisis, leading to increased phagocytic activity and an intensified reactive state. Also, these cells exhibit functional alterations, such as increased internalization of synaptic materials leading to synapse loss [14, 15]. In mouse models, scientists identified microglial cells with a distinct transcriptional profile, termed "NP-SLE signature". These macrophages had downregulated or depleted genes that control the negative regulation of cytokine production, a positive regulator of cell motility, cell-cell adhesion, regulation of neurogenesis, angiogenesis, and upregulated and enriched with genes that control antigen processing and presentation of exogenous peptide antigen, immune effector process, complement activation of interferon-beta, positive regulation of macrophage activation and others [16].

Antibodies in NPSLE: types and their pathogenetic roles

One of the key features in the pathogenesis of SLE is the production of autoantibodies. According to the literature, approximately 116 antibodies have been reported, but none of them have been described fully from the pathogenetically point of view, their association remains controversial. As suggested by some researchers, from all this antibody pool, at least 11 brain-specific (anti-neuronal antibodies (Abs), brain-reactive Abs (BRAA), Anti-N-methyl-D-aspartate receptor Abs (NMDA), anti-microtubule-associated protein 2 Abs (MAP-2), anti-neurofilament Abs (ANFA), anti-synaptosomal Abs, anti-triosephosphate isomerase (TPI) Abs, anti-glial fibrillary acidic protein (GFAP) Abs, and anti-serum-lymphocytotoxic Abs (LCA)) and 9 systemic antibodies (anti-phospholipid (aPL)/cardiolipin (aCL) Abs, lupus anticoagulant (LAC), anti-beta 2- glycoprotein I (2GPI) Abs, anti-ribosomal P Abs (anti-P), anti-Ro Abs, anti-Sm Abs, anti-endothelial Abs (AECA), anti-serine proteinase (anti-PR3/C-ANCA) Abs, and anti-Nedd5 Abs) have been associated with NPSLE [2, 17]. Importantly, as highlighted by some researchers, the diversity and specificity of these antibodies suggest they play a multifaceted role in the pathogenesis of neuropsychiatric lupus, although their exact mechanisms remain to be fully elucidated.

Anti-N-methyl-D-aspartate Receptor (NMDAR) antibodies

The Anti-N-methyl-D-aspartate Receptor (NMDAR) is an ionotropic receptor, which modulates the function of a non-selective transmembrane ion channel (especially calcium entry into the cell). There are many subtypes of NMDA receptors, but all they share a similar structure – 2 N1 subunits with either 2 N2 or 2 N3 subunits. The subtype with the most physiological relevance being the N1/N2 NMDAR. These receptors are implicated in processes like long-term potentiation, synaptic plasticity, and memory formation. Besides that, because NMDA receptors are distributed in different areas of the brain such as the amygdala, hippocampus, and basal ganglia, and expressed and formed in CNS cells like pyramidal neurons, astrocytes, glial cells and ECs, they are thought to play a major role in the pathogenesis of some of the NPSLE manifestations. Studies suggest that antibodies against the N2 subunit are observed in 25%-40% of patients with SLE and represent a subset of anti-double-stranded DNA antibodies [1, 2, 18, 19]. The mechanisms through which the clinical symptoms form vary, but here are some possible explanations. Yoshio *et al.* showed that cerebrovascular endothelial inflammation that might cause cognitive dysfunction and psychiatric diseases in patients with SLE might be produced by the binding of these antibodies and activation of the ECs from the CNS. These ECs, through activation of the NF-κB signaling pathway, start to produce cytokines (mainly IL-6 and IL-8) which were shown experimentally that their mean production was higher in SLE patients' cells than in the control group. Also, the concentration of inflammatory adhesion molecules such as ELAM-1, ICAM-1, and VCAM-1 also were high, with an increased rate of production [20]. Also, an interesting mechanism of neuronal dysfunction can be through the hyperactivation of mitogen-activated protein kinase (MAP-kinase) and increased phosphorylation of MAP-2. This aberrant activation of the neurons can be another pathogenetic mechanism for the psychiatric manifestations [21]. Another important criterion for CNS function impairments is the status of the BBB. Studies show that in mice with healthy and undamaged BBB, there is no presence of brain pathology or any damage, and if there is an affection of the barrier, these antibodies bounded preferentially to hippocampal pyramidal neurons, leading to apoptotic death and deficit cognitive performances in those mice accompanied with MRI changes (decreased hippocampal N-acetyl aspartate/Creatinine (NAA/Cr) ratio) [17, 22-25].

Anti-Microtubule Associated Protein 2 antibodies

Microtubule-associated protein 2 (MAP-2) is a highly specific cytoskeletal component predominantly expressed in neurons. Its primary function is to support the dynamic framework required for cellular migration and division, as well as to regulate and sustain cellular reshaping processes. MAP-2 plays a crucial role in intracellular trafficking, leveraging its scaffolding properties to recruit cytoskeleton-modifying proteins and signaling pathway components to specific subcellular sites. This function underscores its importance in maintaining neuronal structure and function. MAP-2 is considered a microtubule stabilizer, minimizing the frequency of depolymerization events during microtubule formation and assembling, promoting their growth. This protein is also responsible for process formation and for maintaining mature dendritic structure; errors in the MAP-2 expression lead to decreased dendritic length and microtubule density in hippocampal neurons [26]. Yamada *et al.* in their study measured CSF concentration of anti-MAP-2 antibodies in a group of NPSLE patients and a non-NPSLE control group [21]. They found that anti-MAP-2 antibodies were present in 33.3% of patients with NPSLE and absent in the control group. The most prevailed symptom in antibody-positive was an acute confusional state as an NPSLE manifestation. This data leads to the conclusion that these antibodies are specific for NPSLE patients and could be used as a useful future biomarker in the diagnosis of NPSLE. Also, they measured the concentrations of CSF markers such as IL-6 and anti-ribosomal P protein antibodies and correlated them with the anti-MAP-2 antibody results. The results were that high concentrations of both IL-6 and anti-ribosomal P protein were found in patients with CSF anti-MAP-2 antibodies. Again, they point out the importance of the permeability and state of the BBB, stating that in anti-MAP-2 positive patients, the BBB damage was more severe, and respectively the IL-6 and anti-ribosomal P protein antibody concentration titters were elevated in CSF. Other studies associate the presence of anti-MAP-2 antibodies with neurological manifestations such as seizures, chorea, psychosis, headache, sensory neuropathy, and schizophrenia with an association value of 77% [2, 17, 27].

Anti-Glyceraldehyde-3-Phospate Dehydrogenase antibodies

Anti-Glyceraldehyde-3-Phospate Dehydrogenase (GAPDH) is an NAD^+ and inorganic phosphorus-dependent enzyme that catalyzes the conversion of glyceraldehyde-3-phosphate to 1,3-biphosphoglycerate within the glycolytic pathway. Besides glycolytic function, scientists identified its function in such fundamental cellular processes such as interaction with mRNAs and influencing their stability and gene expression, prevents rapid telomere shortening, interacts with p22 protein to aid in the microtubule organization process, and has an important role in DNA replication and its repair process [28, 29]. According to the opinions of some researchers, a potential mechanism by which GAPDH may contribute to neuronal dysfunction and the manifestations of NPSLE involves the production of toxic byproducts, particularly methylglyoxal (MG) [14, 17, 22]. MG is a highly reactive α-ketoaldehyde capable of oxidizing proteins, lipids, and other cellular components, resulting in cytotoxic effects and cellular damage [30]. Anti-GAPDH antibodies have been found in 50% of NPSLE patients with schizophrenia and major depression. Studies show that serum levels of anti-GAPDH antibodies were positively correlated with intracranial pressure and increased incidence of cerebrovascular lesions. These patients also showed high SLICC-ACR scores, suggesting that NPSLE patients with high

concentration titers of anti-GAPDH autoantibodies were in a more active disease status. Further investigations are needed to find out more correlations and exact mechanisms of how these antibodies are affecting CNS, but for now, anti-GAPDH autoantibodies have a future potential to become a biomarker in the NPSLE diagnostic process [31, 32].

Anti-Ribosomal P Protein (Rib-P) antibodies

Anti-Rib-P antibodies are considered a relative specific markers for SLE, found also in high titters in CSF of NPSLE patients, with a very high specificity and a sensitivity value between those of the anti-Sm (18.7%) and anti-DNA (74.0%) antibodies [33, 34]. These antibodies considered to have a higher affinity for neurons located in the hippocampus, cingulate cortex, primary olfactory piriform cortex, and all parts of the limbic system. The primary target of these antibodies is the epitopes located in the C-terminal end of 3 highly conserved phosphoproteins P_0, P_1, and P_2, which are components of the 60S subunit of the ribosomes. Besides this target, in the CNS, anti-Rib-P antibodies cross-react with another high-mass plasma membrane protein called neuronal surface P antigen (NSPA). One of the roles of the NSPA is to enhance glutamatergic postsynaptic transmission in the hippocampal neurons, involving both AMPAR and NMDAR activation, playing a major role in long-term potentiation and memory tasks. Because of its relation to NMDAR, anti-Rib-P antibodies can reproduce or even enhance the neuronal effects of anti-NMDAR in SLE patients [35]. According to some researchers, a potential mechanism for how these antibodies induce neuropsychiatric manifestations can be due to their effect on calcium homeostasis [22, 25, 28]. Rats exposed to anti-Rib-P antibodies showed a very rapid and sustained increase in cytosolic calcium in neurons. This resulted in neuronal stress, which was characterized by reduced denditric, decreased viability, nuclear alterations, and activation of the apoptotic marker caspase-3 [36, 37]. High titers of these antibodies are associated with an active phase of the SLE, with the most characteristic neuropsychiatric manifestations being mood disorders, long-term depression-like symptoms, psychosis, seizure, coma, and deficits in attention and planning [35, 38].

Anti-Phospholipid (aPL) antibodies (anti-cardiolipin, lupus coagulant, anti-β2-glycoprotein)

Besides the autoimmunity impact on the nervous system and the interaction of the antibodies with specific neuronal targets, another important trigger that leads to NPSLE manifestations is the ischemic processes. A key component of ischemic injury is the antiphospholipid antibody syndrome (APS) and the presence of the aPL antibodies. These antibodies are directed against the plasma proteins, especially β_2-glycoprotein (β_2-GPL), though their name states otherwise. Following antibody binding, the affinity of β_2-GPL to anionic phospholipids is greatly increased, starting to compete for its interaction with clotting factors for these phospholipids. Another binding target of this aPL- β_2-GPL complexes are platelets, specifically the LRP-8 (an LDL receptor-related protein) which in consequence activates them and increases their adhesion to collagen and their aggregation, raising the risk of thrombosis, due to the hypercoagulable state. Another implication of these antibodies in the coagulation processes is the inhibition of the nitric oxide formation by the endothelial nitric oxide synthetase resulting in a diminished bioavailability [39-42]. One of the most common neuropsychiatric symptoms found in aPL-positive SLE patients were cerebral ischemia, placing these patients in the high-risk group. These recurrent ischemic events are one of the main causes of other neuropsychiatric manifestations such as dementia, cognitive dysfunction, depression, psychosis, and seizures [43, 44]. Also, studies suggest that there is a higher prevalence of aPL in NPSLE compared with SLE patients lacking neuropsychiatric manifestations [45].

Other antibodies

In SLE patients, including those with neuropsychiatric symptoms, among brain-specific antibodies also are identified antinuclear antibodies (ANA). These antibodies can interact with cellular self-antigens like their nucleus, ribonucleoproteins, histone proteins, double-stranded DNA (dsDNA), DNA-histone complexes, various nuclear enzymes, and other antigens. Even though they are found in about 90% of patients with SLE and NPSLE, their titers are considered nonspecific for diagnosis due to frequent false positives, and they show a low statistical association with NPSLE. In contrast, the situation is different for the extractable nuclear antigen (ENA) antibodies. These are a subset of ANAs, named for their extraction from the acid-soluble, non-histone fraction of the cell nuclei and are regarded as more sensitive markers. Besides those mentioned in the above paragraphs, antibodies such as anti-Ro anti-LA, anti-Sm, anti-dsDNA, and others are also associated with NPSLE, with patients being positive for these antibodies in 50-60% of cases. Some studies suggest that anti-Sm antibodies are associated with NPSLE pathogenesis and BBB disruption, leading to neuropsychiatric manifestations such as organic brain syndrome and acute confusional state. Another interesting marker that can help in NPSLE diagnosis are anti-ds-DNA antibodies. Their serum concentration is variable in time depending on the activity of the disease and are associated with poor performance of visuospatial skills, attention, and executive function. Even though there are studies that conclude that systemic autoantibodies can be used as a predictive and diagnostic tool, true for some, further investigations should be performed to discover their true role and explain the importance of all these antibodies in the SLE and NPSLE pathogenesis and symptom formation [1, 17, 46]. Summarizing the data from the specialized literature that we have analyzed, we propose a comprehensive integrative synthesis that provides a broad perspective on the clinical utility of autoantibodies in NPSLE, facilitating the optimization of diagnostic and therapeutic strategies (Table 2).

Table2. Clinical utility of autoantibodies in NPSLE.

Autoantibody	Pathogenetic mechanism	Clinical correlations	Diagnostic utility	Prognostic utility	Therapeutic implications
Anti-NMDAR	Neuronal damage through excessive NMDA receptor activation and neuronal apoptosis	Psychosis, cognitive impairment, seizures	Present in 25-40% of NPSLE patients, associated with severe neuropsychiatric involvement	Correlated with brain lesion severity and cognitive decline	High titers may indicate the need for aggressive immunosuppressive therapy (rituximab, corticosteroids)
Anti-MAP-2	Synaptic dysfunction and neuronal structural damage	Acute confusional state, seizures, schizophrenia	Highly specific for NPSLE, absent in SLE patients without neuropsychiatric involvement	High titers correlate with severe cognitive impairment and executive dysfunction	May indicate the need for biologic therapy and close monitoring of disease progression
Anti-Rib-P	Neuronal dysfunction through impaired ribosomal protein metabolism	Psychosis, severe depression, acute confusional state	Moderate sensitivity but high specificity for NPSLE	Associated with severe episodes of psychosis and depression, requiring close monitoring	High titers may indicate the need for intensified immunosuppressive therapy
Anti-GAPDH	Metabolic and oxidative neuronal damage via accumulation of toxic byproducts (methylglyoxal)	Major depression, schizophrenia, cerebrovascular lesions	Correlated with neurovascular damage, more common in severe NPSLE cases	Associated with rapid and progressive neurocognitive decline	Potential therapeutic target in combination with neuroprotective agents
aPL	Prothrombotic state induction via endothelial and coagulation pathway dysfunction	Stroke, vascular dementia, cerebral thrombosis	Essential for assessing thrombotic risk in NPSLE patients	Correlated with recurrent ischemic cerebral events	Requires chronic anticoagulation therapy (warfarin, heparin)
Anti-dsDNA	Immune complex formation and complement activation leading to endothelial damage	Cognitive impairment, neurovascular involvement, lupus encephalopathy	Correlates with overall disease activity but has low specificity for NPSLE	High titers indicate a risk of cerebral involvement and rapid disease progression	May guide the need for intensified immunosuppressive therapy (cyclophosphamide, belimumab)
Anti-ENA (Ro, La, Sm, U1-RNP)	Generalized immune dysfunction and autoimmune neuronal damage	Cognitive impairment, psychosis, peripheral sensory dysfunction	Useful for stratifying patients with NPSLE and severe SLE forms	Correlated with progressive neurological deterioration	May guide therapeutic decisions regarding the use of biologic agents

Note: *NPSLE - neuropsychiatric systemic lupus erythematosus, SLE - neuropsychiatric systemic lupus erythematosus, aPL – anti-phospholipid antibodies, anti-NMDAR – anti-N-methyl-D-aspartate receptor antibodies, anti-MAP-2 – anti-Microtubule-Associated Protein 2 antibodies, anti-Rib-P – anti-Ribosomal P protein antibodies, anti-GAPDH – anti-Glyceraldehyde-3-Phosphate Dehydrogenase antibodies, anti-phospholipid (aPL) – anti-phospholipid antibodies, including anti-cardiolipin (aCL), lupus anticoagulant (LAC), and anti-β2-glycoprotein I (β2-GPI) antibodies, anti-dsDNA – anti-double-stranded DNA antibodies, anti-ENA (Ro, La, Sm, U1-RNP) – anti-Extractable Nuclear Antigen antibodies, including anti-Ro (SSA), anti-La (SSB), anti-Smith (Sm), and anti-U1-ribonucleoprotein (U1-RNP) antibodies. The most diagnostically relevant autoantibodies are anti-NMDAR, anti-MAP-2, and anti-Rib-P, as they are strongly correlated with severe neuropsychiatric manifestations. aPL and anti-dsDNA are crucial for assessing vascular and ischemic risk in NPSLE patients. High autoantibody titers are correlated with disease severity, allowing patient stratification and personalized treatment approaches. The presence of specific autoantibodies can guide therapeutic decisions, including the use of corticosteroids, biologic agents (rituximab, belimumab), or anticoagulants, depending on the patient's risk profile.*

Discussions

This study critically examines the current understanding of NPSLE, focusing on its pathogenesis and the role of autoantibodies in clinical manifestations. Despite considerable progress, NPSLE remains a complex condition with significant diagnostic and therapeutic challenges. Numerous autoantibodies have been identified in association with NPSLE, providing insights into its pathogenesis. However, an ideal diagnostic tool has yet to be identified, negatively affecting the management of such patients and NPSLE remaining "a disease complex much in search of pathogenetic autoantibodies, whereas most of the antibodies thus far described in NPSLE are still in search of a disease" [47]. This limitation has led to the characterization of NPSLE as a condition where the identified antibodies often lack clear and consistent associations with the disease, complicating clinical decision-making and patient management.

The discovery of brain-specific autoantibodies such as anti-NMDAR, anti-MAP2, and anti-Rib-P has offered important insights into NPSLE pathogenesis. These antibodies have been associated with distinct neuropsychiatric manifestations, such as depression and cognitive dysfunction linked to anti-NMDAR, and seizures and psychosis associated with anti-MAP2 [21, 27, 29, 35]. Anti-Rib-P antibodies show strong correlations with severe depression and psychosis [17, 21, 34]. Despite these associations, inconsistencies in their specificity and sensitivity reduce their reliability as standalone diagnostic markers [11, 22, 41]. Future research should aim to identify combinations of these biomarkers to improve diagnostic accuracy and their correlation with specific clinical manifestations.

The integrity of the BBB emerges as a critical factor in the development of NPSLE. Disruption of the BBB facilitates the entry of inflammatory and neurotoxic mediators into the CNS, exacerbating neuronal damage. Understand-

ing how autoantibodies, cytokines, and other pathological mechanisms interact with the BBB remains a key research priority. Current studies emphasize the importance of developing assays to detect early BBB dysfunction, which could serve as predictive markers for disease progression and improve early intervention strategies [17, 25, 32].

A major challenge in advancing NPSLE research is the lack of standardized diagnostic criteria. Variations in patient selection, antibody testing methodologies, and result interpretation have led to inconsistent findings across studies [7, 9, 16, 28]. This lack of standardization hampers the ability to draw definitive conclusions about the role of autoantibodies in NPSLE. Efforts to establish unified criteria for patient inclusion, standardized assays for antibody detection, and consistent protocols for measuring antibody dynamics over time are essential. Integrating modern diagnostic tools such as advanced neuroimaging and CSF analysis will further enhance the understanding of NPSLE and refine diagnostic approaches [34, 37, 40].

Contradictory findings in the literature regarding the utility of autoantibodies as biomarkers highlight the need for more robust research. While some studies suggest strong correlations between specific autoantibodies and neuropsychiatric symptoms, others fail to confirm these relationships [25, 41, 43]. We tried to rank the most relevant biomarkers in NPSLE according to their specificity for the disease and clinical applicability (Table 3), considering their role in diagnosis, prognosis, and treatment guidance [22-27, 35, 39, 41, 43]. But a lot of inconsistencies may arise from differences in study design, population heterogeneity, or methodological limitations. Future investigations should prioritize multicenter studies with larger, diverse cohorts and longitudinal designs to validate these associations and establish clearer connections between antibody titers, disease activity, and clinical outcomes.

Table 3. Ranking of biomarkers in NPSLE based on specificity and clinical utility.

Biomarker	Specificity for NPSLE	Diagnostic utility	Prognostic utility	Clinical applicability
Anti-NMDAR	⋆ ⋆ ⋆ ⋆	Highly specific for NPSLE; associated with psychosis, seizures, cognitive dysfunction	Correlates with cognitive impairment severity and brain lesion extent	Guides aggressive immunosuppressive therapy (rituximab, corticosteroids)
Anti-MAP-2	⋆ ⋆ ⋆ ⋆	Found almost exclusively in NPSLE patients; linked to acute confusional states	High titers correlate with severe cognitive dysfunction and executive impairment	Helps identify high-risk patients who need close neurological monitoring
Anti-Rib-P	⋆ ⋆ ⋆ ⋆	Moderate sensitivity, high specificity for NPSLE; strongly linked to psychosis and depression	Associated with worsening neuropsychiatric symptoms	Can predict need for early immunosuppressive therapy intensification
aPL	⋆ ⋆ ⋆	Important for identifying vascular complications (stroke, dementia)	High titers predict recurrent ischemic cerebral events	Guides long-term anticoagulation (warfarin, heparin) and risk stratification
Anti-GAPDH	⋆ ⋆ ⋆	Correlates with major depression and schizophrenia in NPSLE	Predicts neurovascular damage and progressive cognitive decline	Potential therapeutic target for neuroprotective agents
Anti-dsDNA	⋆ ⋆	Indicates general SLE disease activity but has low specificity for NPSLE	Correlated with CNS involvement and disease progression	Supports broader SLE management rather than NPSLE-specific treatment
Anti-ENA (Ro, La, Sm, U1-RNP)	⋆ ⋆	Useful for identifying severe SLE patients with neuropsychiatric involvement	Associated with progressive neurological deterioration	May inform decisions on biologic therapy (belimumab, rituximab)

Note: *NPSLE – neuropsychiatric systemic lupus erythematosus, SLE – neuropsychiatric systemic lupus erythematosus, CNS – central nervous system, aPL – anti-phospholipid antibodies, anti-NMDAR – anti-N-methyl-D-aspartate receptor antibodies, anti-MAP-2 – anti-Microtubule-Associated Protein 2 antibodies, anti-Rib-P – anti-Ribosomal P protein antibodies, anti-GAPDH – anti-Glyceraldehyde-3-Phosphate Dehydrogenase antibodies, anti-phospholipid (aPL) – anti-phospholipid antibodies, including anti-cardiolipin (aCL), lupus anticoagulant (LAC), and anti-β2-glycoprotein I (β2-GPI) antibodies, anti-dsDNA – anti-double-stranded DNA antibodies, anti-ENA (Ro, La, Sm, U1-RNP) – anti-Extractable Nuclear Antigen antibodies, including anti-Ro (SSA), anti-La (SSB), anti-Smith (Sm), and anti-U1-ribonucleoprotein (U1-RNP) antibodies. Anti-NMDAR, Anti-MAP-2, and Anti-Rib-P are the most specific biomarkers for diagnosing NPSLE and correlating with severe neuropsychiatric manifestations. aPL and anti-GAPDH are important for predicting vascular and metabolic complications that contribute to neurological decline. Anti-dsDNA and Anti-ENA are less specific but still useful in broader disease stratification for SLE patients. Biomarker-based stratification can guide personalized treatment decisions, optimizing immunosuppressive and anticoagulation therapy to prevent complications.*

Given the complexity of NPSLE, a personalized approach to patient management is crucial [32, 39, 45, 47]. Advances in biomarker research, imaging techniques, and CSF analysis hold promise for tailoring diagnostic and therapeutic strategies to individual patients. Collaborative efforts among rheumatologists, neurologists, and immunologists are necessary to develop comprehensive care protocols [15, 21, 39, 47]. The ultimate goal is to establish precise, biomarker-driven approaches that address the systemic and neuropsychiatric manifestations of lupus, improving patient outcomes and quality of life.

While significant progress has been made in understanding NPSLE, many questions remain unanswered. The interplay between autoantibodies, BBB dysfunction, and neuroinflammation is a critical area of ongoing research. Addressing these gaps through interdisciplinary collabora-

tion and innovative methodologies will be essential for advancing the diagnosis, prognosis, and management of this multifaceted condition.

Conclusions

NPSLE represents a complex and multifaceted condition that challenges clinicians and researchers alike due to its diverse clinical manifestations, intricate pathogenesis, and diagnostic uncertainties. Despite significant advances in understanding the role of autoantibodies and the critical influence of blood-brain barrier (BBB) integrity, an ideal diagnostic tool remains elusive. Autoantibodies, such as anti-NMDAR, anti-MAP2, and anti-Rib-P, offer valuable insights into disease mechanisms, correlating with specific neuropsychiatric symptoms. However, inconsistencies in sensitivity, specificity, and clinical utility highlight the need for more precise biomarkers.

The disruption of neuroimmune interfaces, particularly the BBB and the blood-cerebrospinal fluid barrier (BCB), is central to the pathogenesis of NPSLE. These disruptions allow pathogenic autoantibodies and inflammatory mediators to penetrate the central nervous system (CNS), amplifying neuroinflammatory processes. Understanding the molecular interplay between these barriers, cytokines, and autoantibodies is crucial for identifying early markers of disease progression and tailoring interventions.

Standardization in diagnostic criteria, antibody detection assays, and patient selection are urgently required to resolve discrepancies in current literature and improve research outcomes. Modern neuroimaging techniques and cerebrospinal fluid analysis offer promising avenues for enhancing diagnostic accuracy and understanding disease mechanisms.

A personalized approach to patient management, integrating biomarker-driven diagnostics and therapeutic strategies, holds promise for improving outcomes in NPSLE. Collaborative efforts between rheumatologists, neurologists, and immunologists are essential to develop comprehensive care protocols and advance precision medicine in this field.

Despite substantial progress, significant gaps remain in our understanding of NPSLE. Addressing these challenges through interdisciplinary research, innovative methodologies, and standardized protocols will pave the way for more effective diagnosis and management of this enigmatic condition, ultimately improving patient care and quality of life.

Competing interests

None declared.

Contribution of authors

ER and CN conceived the research idea; CN, ER, LG developed the aim and objectives of the literature review; CN, AP, MS, IL drafted the manuscript and realized the literature search; ER, LG and LC designed the study and revised the manuscript critically. All authors have read and approved the final version of the manuscript.

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