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Advances in the diagnosis, pathogenesis and treatment of neuropsychiatric systemic lupus erythematosus

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Abstract

Purpose of review—Diagnosing and treating neuropsychiatric systemic lupus erythematosus (NPSLE) remains challenging as the pathogenesis is still being debated. In this review, we discuss studies evaluating recent advances in diagnostic methods, pathogenic mediators and potential treatments.

Recent findings—Screening tools used for neurodegenerative diseases were found to be both sensitive and moderately specific for cognitive dysfunction in NPSLE. Neuroimaging can be used to distinguish systemic lupus erythematosus (SLE) patients from healthy controls, but further refinement is needed to differentiate between lupus patients with and without neuropsychiatric manifestations. Elevated levels of specific molecules in the cerebrospinal fluid and/or serum, as well as the presence of certain autoantibodies, have been identified as potential biomarkers in attempts to facilitate a more accurate and objective diagnosis. Among such autoantibodies, anti-NR2 and anti-ribosomal P autoantibodies also have a pathogenic role, although newer studies demonstrate that blood-brain barrier damage may not always be required as previously believed. These and other observations, together with new evidence for disease attenuation after microglial modulation, suggest direct involvement of the central nervous system in NPSLE pathogenesis.

Summary—Neuropsychiatric involvement of SLE includes a variety of symptoms that impact quality of life and patient prognosis. There have been recent advances in improving the diagnosis of NPSLE as well as in dissecting the underlying pathogenesis. The attenuation of neuropsychiatric disease in mouse models demonstrates the potential for targeted therapies, which are based on a clearer understanding of the pathogenesis of NPSLE. Further assessment of these treatments is required in NPSLE patients, as well as the potential use of neuroimaging to distinguish between SLE patients with or without neuropsychiatric manifestations.

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Conflicts of interest

There are no conflicts of interest.

Keywords

angiotensin-converting enzyme inhibitors; biomarkers; microglial activation; neuroimaging; neuropsychiatric lupus; systemic lupus erythematosus

INTRODUCTION

Neuropsychiatric systemic lupus erythematosus (NPSLE) can involve both the central and peripheral nervous systems, and is the second leading cause of mortality and morbidity in systemic lupus erythematosus (SLE) patients [1■]. Brain manifestations in NPSLE present as focal or nonfocal neurologic deficits, where the focal disease is caused by thromboembolic events predominantly because of anti-phospholipid antibodies. The pathogenesis of nonfocal NPSLE, or diffuse NPSLE (e.g. affective disorders and cognitive abnormalities) is, however, complex and not well understood. In this review, we will highlight recent findings in the diagnosis and assessment, management and pathogenesis of diffuse NPSLE disease.

DIAGNOSIS

The diagnosis of NPSLE is often challenging as clinicians must rule out alternative causes, such as infections and tumors, before they can finalize a diagnosis. The importance of attribution is still widely discussed as NPSLE has been primarily a diagnosis of exclusion, yet this diagnosis obviously carries critical implications for disease management and prognosis.

In clinical practice today, many clinicians use the widely accepted American College of Rheumatology (ACR) nomenclature for classifying NPSLE events. However, this nomenclature has been challenged lately with new attribution models. Bortoluzzi *et al.* [2] proposed an attribution algorithm that provides a probability score, ranging from 0 to 10. This algorithm considers four themes in the construction of the model, three of which were similar to those used in the ACR guidelines. The themes include the temporal relationship of neuropsychiatric events to the diagnosis of SLE, the recognition of confounding factors, the presence of minor or common neuropsychiatric events and the presence of SLE risk factors suggested by the European League Against Rheumatism (EULAR) (i.e. general SLE activity and anti-phospholipid antibodies). On the basis of generated probability score, the patients are considered to be experiencing nonneuropsychiatric events (<3), undefined events (3–6) or neuropsychiatric events attributable to SLE (>6). An alternative model was proposed by Magro-Checa *et al.* [3] involving a battery of neuropsychological, laboratory and radiological examinations performed by a multidisciplinary team of rheumatologists, neurologists, psychiatrists and vascular medicine specialists. In this model, the confirmation of SLE-attributed neuropsychiatric events was dependent upon a follow-up reassessment, as 13.8% of the neuropsychiatric events were initially misclassified. Both the Bortoluzzi *et al.* and Magro-Checa *et al.* studies concluded that SLE-attributed minor and diffuse neuropsychiatric events were challenging to ascertain in their models, and noted the persisting challenges in the development of attribution models for NPSLE.

Tools for assessing neuropsychiatric systemic lupus erythematosus

A combination of emerging screening tools, biomarkers and imaging techniques is being utilized to improve how NPSLE patients are evaluated.

Screening tools

There are several screening tools, developed for neurodegenerative conditions, that could be used to evaluate cognitive dysfunction, anxiety and depression in SLE patients. Chalhoub *et al.*[4] compared the Montreal Cognitive Assessment Questionnaire (MoCA), a one-page performance-based screening test, to the Automated Neuropsychological Assessment Metrics (ANAM), a computer-based tool, to assess cognitive impairment in SLE patients [5]. The MoCA was sensitive and moderately specific for cognitive disorders (0.83–0.94 and 0.27–0.46, respectively) in NPSLE patients when compared with normal controls or patients with rheumatoid arthritis. Additionally, the MoCA also evaluates cognitive domains included in the ANAM assessment, and six out of the 10 MoCA questions were significantly correlated with the ANAM total throughput score, the sum score generated from each ANAM subtest. In comparison, IQCODE (Informant Questionnaire on Cognitive Decline in the Elderly), a questionnaire filled out by a close family member (deemed 'informant'), did not perform as well as the MoCA questionnaire. The authors attributed this result to the inaccuracy of these 'informants' in reporting observed changes in the patient's neurocognitive function. Therefore, MoCA could be an effective screening tool for NPSLE patients and may be more practical to use compared to ANAM and IQCODE, because of its ease of use, accessibility in healthcare environments, high sensitivity and moderate specificity.

To evaluate anxiety and depression, Kwan *et al.* [5] utilized the Center for Epidemiological Studies - Depression Scale (CES-D), Hospital Anxiety and Depression Scale (HADS) and the Beck Anxiety Inventory (BAI) questionnaires. The goals were to evaluate the prevalence of anxiety and depression in SLE patients, assess these questionnaires' test-retest reliability, and study their diagnostic accuracy. The authors concluded that these questionnaires found 2–4 times higher rates of depression when compared to the Mini-International Neuropsychiatric Interview (MINI), the current gold standard. The CES-D questionnaire and the HADS Anxiety questionnaire were the best tools for depression and anxiety screening, respectively. Both questionnaires demonstrated potential to be used as screening tools for NPSLE.

Biomarkers

Serological tests in current use are not sufficiently accurate for the diagnosis of NPSLE and/or for assessing disease severity. Novel biomarkers might allow a more objective assessment and may be as simple as measuring levels of a particular biomarker in the serum. Autoantibodies, which are a hallmark of lupus, may also be useful in serving as biomarkers and will be discussed in the Pathogenesis section of this review.

Other than autoantibodies, there has been an interest in exploring molecules, circulating in the blood and/or cerebrospinal fluid (CSF), which could reflect neuroinflammation and indicate neuropsychiatric disease in lupus patients. Lipocalin 2 (LCN2), an iron transporter

important in innate immunity, and osteopontin (OPN), a secreted glycoprotein believed to inhibit B-cell apoptosis, were both elevated in the CSF of NPSLE patients compared to non-NPSLE. LCN2 elevation was shown across two different ethnicities [6], and OPN concentrations decreased after the treatment [7]. The specific role of these two proteins in NPSLE remains to be determined, but their correlation with disease may have promising applications.

As blood-brain barrier (BBB) disruption is commonly implicated in NPSLE, molecules whose levels may reflect an alteration in brain-barrier integrity may be important indicators of disease. In the CSF, albumin, haptoglobin and β−2 microglobulin levels, as well as the CSF/serum quotient of α−2 macroglobulin, were significantly elevated in NPSLE patients [8■,9]. CSF, which more likely reflects the central nervous system (CNS) milieu than serum, requires an invasive approach for collection. Serum, on the other hand, may be more feasible to monitor as sera can be readily collected as needed. S100B is a calcium-binding protein that is primarily produced by astrocytes and, therefore, when found in the serum, indicates BBB permeability. In the serum, S100B was significantly increased in SLE patients and even more so in NPSLE patients [10]. Moreover, serum S100B and peripheral neuropathy were strongly associated, suggesting S100B as a biomarker. Another candidate biomarker is brain-derived neurotrophic factor (BDNF), a molecule important in memory and learning, which is predominantly produced in the CNS. Therefore, serum BDNF may be an indicator of BBB disruption. BDNF levels were decreased in sera of active SLE patients compared to inactive SLE patients, but not when compared to healthy controls [10]. Interestingly, peripheral blood mononuclear cells of NPSLE patients also had decreased BDNF levels when compared to healthy controls, and these levels were associated with reduced thalamus, caudate and putamen volumes [11]. These results, whether in the serum or CSF, need to be confirmed in additional patient cohorts.

Imaging

MRI is the current radiological gold standard used in assessing patients with SLE, but approximately 50% of NPSLE patients do not have detectable abnormalities with the resolution of current scanners. Newer advanced MRI techniques and software may have increased sensitivity to identify changes in the brains of NPSLE patients. Sarbu *et al.* [12] explored the use of advanced MRI techniques including voxel-based morphometry (VBM), FreeSurfer, diffusion-tensor imaging (DTI) and white matter hypersensitivity volumetry. These techniques could map the microstructure of the brain by fractional anisotropy and mean diffusivity (DTI), indicate differences in brain anatomy (atrophy/tissue expansion (VBM) or cortical thickness (FreeSurfer)) and identify any white matter hypersensitivity lesions. In a cohort of 28 primary central NPSLE patients, 22 SLE patients without NPSLE and 20 healthy controls, NPSLE patients had increased brain atrophy, decreased left frontal sublobar white matter, increased water diffusion in both temporal lobes and decreased fractional anisotropy in the right frontal lobe. The DTI findings (increased mean diffusivity and decreased fractional anisotropy) and decreased brain volume loss correlated with disease activity and severity.

Not all lupus patients with neuropsychiatric symptoms may need to undergo radiologic evaluation; judicious use of MRIs is important, especially when considering the cost and the specialized expertise required in image acquisition and interpretation. Roldan *et al.* [13] evaluated whether formal neurocognitive assessment correlates with quantitative brain lesion loads (the number of fluid-attenuated inversion recovery hyperintensities) and if so, would identify NPSLE patients who require additional workup. Neurocognitive testing across all domains (e.g. attention, motor, executive function and memory) and erythrocyte sedimentation rate were independently associated with whole brain lesion load. Therefore, these diagnostic tools could be used to identify patients with functionally significant brain lesions who may benefit from further imaging evaluation.

PATHOGENESIS

Efforts are continuing in dissecting the pathogenesis of NPSLE, as a better understanding of disease-relevant pathways will help in the development of more targeted therapies.

Autoantibodies

Many autoantibodies have been linked to NPSLE but have yet to be confirmed to participate in mechanisms of pathogenesis. Anti-NR2 antibodies (which recognize a subunit of the N-methyl D-aspartate receptor (NMDAR) that is necessary for synaptic plasticity and memory in the brain) and anti-ribosomal P antibodies (which recognize ribosomal proteins) have been commonly studied in recent years, as these autoantibodies are neurotoxic in preclinical studies once the BBB is bypassed. Lauvsnes *et al.* [14■] reported that anti-NR2 antibodies in the CSF were associated with motor functioning and visuospatial processing impairment in SLE, whereas Nestor *et al.* [15■■] found that anti-NR2, with other anti-NMDAR antibodies, were linked with spatial memory impairment in both mice and lupus patients. Another study by Wang *et al.* [16] used primary brain microvessel endothelial cells to generate evidence indicating that anti-NR2 antibodies in NPSLE can damage the BBB and enter the brain. However, serum levels of anti-NR2 in SLE patients show no significant association with the ANAM total throughput score, even with elevated levels of S100B or anti-S100B (which indicate BBB disruption). Furthermore, excluding the association of anti-phospholipid antibodies with ischemic brain changes, SLE-related serum autoantibodies were unrelated to inflammatory-like lesions on MRI in a recent study by Magro-Checa *et al.* [17]. Therefore, as the correlation with neurologic deficits is stronger in CSF than serum, intrathecally produced anti-NR2 antibodies may be those most likely involved in the pathogenesis of NPSLE.

Serum anti-ribosomal P antibodies are significantly correlated with a worse prognosis for patients with diffuse NPSLE [18■]. Gaburo *et al.* [19] demonstrated that injecting these antibodies, isolated from patient sera, into the ventricle of rats was enough to induce electro-oscillogram changes and prolonged immobility compared to those injected with control IgG. Moreover, structural analysis suggests that anti-ribosomal P and anti-Sm antibodies have shared clonotypic determinants and thus a common B-cell clonal origin that may play a pathogenic role [20]. In lupus patients with an acute confusional state, serum anti-Sm levels were significantly elevated with an increasing CSF/serum albumin quotient, even when anti-

NR2 and anti-ribosomal P were not, which may indicate a role of anti-Sm in BBB disruption [21].

Several recent studies have revealed novel auto-specificities that may be associated with NPSLE. Autoantibodies against neuronal regulatory brain cytoplasmic RNAs impede the localization of endogenous BC1 RNA to synapto-dendritic domains, thus causing phenotypic abnormalities, including epileptogenic responses and cognitive dysfunction upon entry into the CNS [22]. Anti-GAPDH was significantly elevated in lupus serum, especially in patients with NPSLE, and associated with disease severity [23]. Anti-UCH-L1 (which identifies ubiquitin carboxy-terminal hydrolase L1, a deubiquitinating enzyme) in the CSF was found to be highly specific for severe NPSLE and positively correlated with organ involvement and serum antibody levels [24]. Anti-suprabasin antibodies, directed against a molecule known to be present in differentiating keratinocytes, may also be important as immune complexes of suprabasin were found in the CSF of NPSLE patients, and astrocytes exposed to antisuprabasin antibodies had significantly altered senescence and autophagy pathways [25].

Structural integrity

In several recent studies, MRI and DTI showed association of white matter lesions with SLE activity and differentiated between healthy controls and SLE patients [26–30]. These imaging modalities, however, could not reliably distinguish between lupus patients with or without NPSLE. Liu *et al.* [29] specifically looked at lupus patients without known NPSLE and discovered an association between white matter volume and cognitive impairment. This result suggests that structural brain atrophy could preface and subsequently contribute to neurological manifestations, a finding that would be useful for early detection. Cannerfelt *et al.* [30] similarly found that white matter volume does correlate with verbal memory but could not distinguish NPSLE patients from SLE patients without NPSLE. The latter study suggests alternatively that white matter lesions may not specifically contribute to NPSLE presentation, but rather reflect more general SLE disease activity.

The BBB has often been proposed as the entry point of systemic effectors that cause inflammation and injury leading to neuropsychiatric symptoms. MacKay *et al.* [31] examined lupus patients for signs of barrier disruption and cognitive dysfunction, using DTI and fluorodeoxyglucose-PET [(FDG-PET), a resting-state functional imaging test], respectively. In this study, regional hypermetabolism was associated with reduced microstructural integrity and decreased cognitive performance and was consistent over 15 months, suggesting another method of early detection. In a study by Ploran *et al.* [32■■], resting hypermetabolism in the anterior putamen/caudate and frontal cortex, assessed by FDG-PET, was associated with successful spatial navigation task (SNT) completion in SLE patients, whereas high serum anti-NMDAR antibody titers were associated with the inability to complete the SNT. Although needing further validation, the authors suggested that the resting hypermetabolism may be a compensatory neural recruitment mechanism facilitating the completion of the SNT. Another study measuring BBB integrity indicators, however, did not find any associations between levels of TWEAK (TNF-like weak inducer of apoptosis; a TNF-family member that can stimulate the production of proinflammatory cytokines and

induce cell death) with neuropsychiatric manifestations. TWEAK levels were higher in the CSF than serum, which implies intrathecal production and thus BBB disruption as a result rather than a cause [14■]. More in-depth discussion on the BBB's role in NPSLE can be found in a recent review [33].

Two separate studies also evaluated neuronal networks in SLE patients compared to healthy controls. Alterations in white matter microstructure correlated with disease duration and fatigue in SLE patients [34], and network metrics also correlated with disease duration, SLE-induced damage and white matter hypersensitivity volume [35]. Both studies support the need for further investigation to determine if alterations in brain networks may contribute to disease.

Cell mediators

Aside from autoantibodies and structural changes, alterations in brain-resident cells in the CNS may be instrumental in the development of neuropsychiatric symptoms.

Microglia, the brain-resident macrophages, are commonly studied in neurological disorders and play a role in synaptic pruning. BV2 cells, a mouse microglial cell line, showed increased activation after TNF treatment, with elevation in IL-6 [36]. Treating lupus-prone MRL/lpr mice with a sphingosine-1-phophate (S1P) receptor modulator, which decreases proinflammatory cytokine secretion by microglia, significantly improved spatial memory and depression-like behavior as well as decreased macrophage infiltration [37]. Similarly, microglial depletion by a CSF1R inhibitor resulted in preserved neuronal integrity in an inducible mouse model (NMDAR peptide immunized BALB/c mice), comparable to nonimmunized controls [15■■]. Another model of lupus, 564Igi mice, showed complementary results as microglia became activated and engulfed neuronal material after being stimulated with type I IFNs [38■■]. The latter study also demonstrated evidence for increased type I IFN signaling in postmortem brain sections of SLE patients. Direct injection of SLE patient serum into the ventricle of mice stimulated activation of microglia in the cortex and the hippocampus, with increased levels of proinflammatory cytokines and adhesion molecules [39■]. These results suggest the importance of microglial activation in the brains of lupus mouse models and potentially of NPSLE patients that may lead to neuropsychiatric manifestations.

Axonal injury in the CNS may also contribute to neuropsychiatric disease, as both lupus-prone mice and CSF of NPSLE patients showed increased levels of neurite outgrowth inhibitor (Nogo)-a, which is mainly expressed in the CNS and known to stunt recovery of the CNS after injury. After treatment with a Nogo-a antagonist, mice had improved cognitive dysfunction, and proinflammatory cytokines, including IL-1B, TNF-a and IL-6, were diminished [40].

The responsible cells in the development of NPSLE manifestations may not only be resident cells but rather infiltrating cells that also contribute to the CNS insult. MRL/lpr mice have large clusters of leukocytes infiltrating the choroid plexus. Immunofluorescence staining and transcriptomic analysis of the choroid plexus suggested tertiary lymphoid structure formation, with evidence for antigen-presenting cell-lymphocyte interactions, cytokine

production and in situ somatic hypermutation [41]. Brains of NPSLE patients have shown similar localization of leukocytes to the choroid plexus; this, coupled with the study proving that SLE sera is enough to upregulate adhesion molecules to attract leukocytes to the brain [39■], raises the question whether functional tertiary lymphoid structures are present in NPSLE patients as well. Finally, for an expanded discussion on the pathogenesis of NPSLE, see recent articles by Nikolopoulos *et al.* and Hanly *et al.* [42,43].

TREATMENT

The diverse neuropsychiatric manifestations experienced by NPSLE patients and the limited understanding of its complex pathogenesis have so far restricted the development of targeted therapies. Current therapies include the use of anti-psychotics and anti-depressants to treat the manifesting symptoms or nonspecific immunosuppressants to inhibit the systemic disease. Moreover, a potential confounder in the treatment of NPSLE is the common use of corticosteroids, which have known CNS side-effects [44].

Recent studies have identified promising therapies that may specifically modulate key cell types, particularly microglia. Shi *et al.* [45] and Mike *et al.* [37] evaluated the effects of fingolimod, an S1P receptor modulator in B6.MRL-lpr and MRL/lpr mice, respectively. Both studies concluded that fingolimod administration attenuated neuropsychiatric manifestations, reversed the entry of immune components, and decreased BBB leakage. Fingolimod-treated mice showed significant improvements in depressive-like behaviors (tail suspension test and Porsolt swim test) and in spatial and recognition memory deficits (object placement and object recognition tests). In conjunction with the approved use of fingolimod in relapsing-remitting multiple sclerosis, these studies may support the potential use of fingolimod as a therapeutic for NPSLE patients. Additionally, angiotensin-converting enzyme (ACE) inhibitors, captopril and perindopril, improve cognitive deficits in mice immunized to produce anti-DNA antibodies that are cross-reactive with NMDAR [15■■]. Nestor *et al.* demonstrated that immunized mice had increased ACE expression, similar to that seen in an Alzheimer's mouse model. ACE inhibitor treatment in the lupus model suppressed microglial activation, which in turn preserved dendritic complexity in hippocampal CA1 neurons. Further analysis is needed to understand how ACE inhibition prevents or reverses microglial activation, but this class of therapeutics may also be considered in the future to treat cognitive impairment in NPSLE patients.

CONCLUSION

NPSLE is a disease with a complex pathogenesis, involving diverse central and peripheral nervous system manifestations. Recent studies have identified potential assessment modalities, including screening tools and biomarkers, and new therapeutic approaches, which may improve diagnosis and management. Advanced imaging techniques have also emerged as powerful tools that show structural differences in the brains of patients, but may still need to be further adjusted to enable differentiation between SLE patients with or without NPSLE and in that way be useful as a disease monitoring tool. Further studies evaluating lupus patients not yet meriting a formal diagnosis of NPSLE should be performed to ascertain whether the presence of structural changes may indicate early detection of

NPSLE or general SLE activity. Although several aspects of NPSLE remain enigmatic, many of the recent findings bring us closer to an improved understanding and ultimately a clearer picture of this key lupus manifestation.

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KEY POINTS

- Appropriate attribution of neuropsychiatric manifestations remains a challenge in the diagnosis of NPSLE.
- Advanced imaging techniques are being developed to evaluate SLE patients with neuropsychiatric disease, but these are not sufficiently sensitive or specific enough at this time.
- Preclinical studies (animal models) have indicated that microglial-targeted therapies show potential in NPSLE.