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Neuropsychiatric Symptoms in Lupus

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The neuropsychiatric aspects of systemic lupus erythematosus have been less studied than the peripheral aspects of the disease, and the importance of neuropsychiatric symptoms has been underestimated. Furthermore, until recently, the diagnostic criteria were not standardized and were not sufficiently based on systematic evidence from preclinical and clinical data.

Mental health professionals should be aware of the role of inflammation in neuropsychiatric symptoms and should more frequently assess the potential inflammatory basis of neuropsychiatric outcomes in patients who do not yet have a primary diagnosis of systemic lupus erythematosus.

DIAGNOSTIC CRITERIA

In 1999, The American College of Rheumatology (ACR) Ad Hoc Committee[1] on Neuropsychiatric Systemic Lupus Erythematosus released a consensus statement that reviewed the diagnostic criteria and nomenclature for neuropsychiatric systemic lupus erythematosus (NPSLE). It included 19 different forms of neuropsychiatric involvement (see Table, page 324) and was based on a growing recognition of the prevalence and importance of neuropsychiatric symptoms, an acknowledgment of the need to incorporate recent advances in clinical and preclinical data, and changes in prevailing opinions as to the underlying mechanisms of neuropsychiatric symptoms in SLE that would affect treatment recommendations.

The classification included a wider range of symptoms than had been regularly included in the past and distinguished between central and peripheral manifestations of NPSLE (see Table, page 324).[1]

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These criteria were not designed to aid in differential diagnosis but rather to "facilitate and enhance clinical research, particularly multicenter studies, and reporting"[1] and are thus subject to further modification and categorization from evidence-based clinical and preclinical sources.

The ACR consensus statement and the data emerging from the studies utilizing these criteria highlight the importance of identifying specific NPSLE syndromes and the importance of utilizing diagnostic tools that are sensitive to dysfunction in all of the neuropsychiatric domains identified.

The lack of standard, accurate, and sensitive diagnostic instruments has contributed to variability in the estimates of the prevalence of neuropsychiatric symptoms. It has also contributed to different estimations of treatment success, debate over mechanisms, and controversy about whether neuropsychiatric illness is due to the chronic disease state itself, other end-organ dysfunction, treatments for SLE, or if it is a primary outcome.[2]

Prevalence of NPSLE

Estimates of the prevalence of NPSLE vary greatly, as does the reported incidence of specific manifestations. Studies conducted before the inclusion of the broader range of symptoms tended to underestimate the incidence of NPSLE; there are still differences in the criteria used to define NPSLE. Even within those studies that adhere to the ACR guidelines there are great differences in reported prevalence.

When assessment is conducted using comprehensive and specific neurologic and psychological diagnostic tools sensitive to the detection of dysfunction in the relevant behavioral domains, the majority of SLE patients have some neuropsychiatric symptoms if mood disorders, headaches, and cognitive dysfunction are included in NPSLE criteria.[3–5]

Using such measures and including all categories of the ACR diagnostic guidelines, 80% to 90% of SLE patients have some neuropsychiatric manifestation, with the most common being depression (50% to 60%); headache (50% to 70%); and cognitive dysfunction (30% to 50%). Other less frequent manifestations include seizures, anxiety, acute confusional state, stroke, and psychosis.[6–8]

Symptoms of NPSLE

There is great variability in the reported rates of "soft" symptoms of NPSLE (eg, depression and cognitive function), in part due to wide differences in the diagnostic tools. Depression and cognitive dysfunction are among the most common and early signs of NPSLE. Cognitive dysfunction is reliably detectable before it reaches the level of the profound confusion and dementia. Although gross cognitive dysfunction is likely to be evident using a mini-mental state examination, less severe disabilities are often missed with this method.

Thus, it would be preferable to utilize comprehensive screening tools for mood, cognitive function, headaches, and autonomic function using standard and validated rating scales,[3,9–12] but this may not be logistically possible for routine screening.

Several diagnostic instruments have been proposed that implement shortened versions of standard neurologic and psychiatric exams to indicate the presence of neuropsychiatric symptoms in SLE patients,[3–5,12] but many of the proposed diagnostic scales have yet to be validated, and some are more sensitive to dysfunction in specific behavioral domains (such as depression).[13]

The majority of neuropsychiatric events are considered to be central[14] (although it is presently unclear why the peripheral nervous system should be less frequently affected). Furthermore, several lines of evidence indicate that NPSLE symptoms can be primary manifestations of central inflammatory disease rather than simply outcomes of end-organ dysfunction and/or treatment.[2,15]

First, neuropsychiatric manifestations can precede the onset of active SLE or be either initial or early symptoms.[16–18] Second, neuropsychiatric symptoms can occur or flare when other disease symptoms are relatively absent or stable. Adverse neuropsychiatric effects of steroids can be differentiated from primary central disease manifestations in properly designed studies.[15] The “soft” signs of NPSLE, such as cognitive impairment, have been extensively evaluated in relation to systemic disease activity and progression, but it is not clear if they are a function of general SLE.[19]

This suggests that autoimmune manifestations in different behavioral domains may have different pathologic mechanisms,[20] which has led to the proposal that symptoms be classified into subsets or clusters based on the proposed similarities of pathologic correlates, underlying mechanism(s), and other criteria.[21]

Motor Dysfunction

Motor dysfunction is not included in most criteria until debilitating and obvious symptoms (eg, chorea, Parkinson’s-like symptoms) are evident. Few studies include even perfunctory assessments of subtle motor signs, but the prevalence of damage to motor areas of the brain[22,23] suggests that the investigation of more subtle motor deficits may reveal a different prevalence of measurable motor dysfunction similar to the high incidence of other “soft” neurologic signs.

Sleep and Circadian Dysfunction

Sleep and circadian dysfunction have been examined systematically in only a few studies.[24] Although sleep and circadian dysfunction are often comorbid with depression and fatigue, these are distinguishable from fatigue and depression, and including the formal assessment of these symptoms should be encouraged.

Fatigue and Behavior

Fatigue is a symptom that has also been examined systemically in only a small number of studies.[25] It is not included in the ACR criteria but it can significantly affect behavior and function,[26] is extremely common in SLE, and often does not respond to traditional SLE treatments.[27] In this respect, quality-of-life questionnaires usually include fatigue, so

although they should not replace more comprehensive neurologic and psychological instruments, they are useful to include in the diagnostic repertoire.[28]

EVIDENTIARY BASIS OF TREATMENT

The treatment of NPSLE is empirical due to the lack of controlled studies.[29] European League Against Rheumatism (EULAR) recommendations[17] indicate that therapeutic choices should reflect the nature of the underlying process (ie, inflammatory or thrombotic). It is necessary, therefore, to consider the current hypotheses regarding the underlying mechanisms of NPSLE.

POTENTIAL MECHANISMS OF NPSLE Vascular Events

Cerebrovascular events can lead to central nervous system (CNS) dysfunction. Interruption of blood supply to brain tissues can induce a range of intermittent and permanent neuropsychiatric symptoms, and can result from clotting, hemorrhage, and vasculopathy.[30] Negative neuropsychiatric outcomes from cerebrovascular events are a function of the anatomic site, extent, and duration of injury. These are comparatively rare manifestations of SLE unless headaches are considered within this symptom cluster.

Autoantibodies and NPSLE

Studies investigating the relationship between autoantibodies and NPSLE focus on several classes of autoantibodies, including antiphosphospholipid antibodies (especially in thrombosis-related manifestations), antibodies to nuclear and cytosolic antigens (such as DNA, RNA, and ribosomal P), antibodies to lymphocyte cell surface antigens and lymphotoxic antibodies, and brain-reactive antibodies.

Brain-reactive antibodies cross-react with a number of neuronal and glial moieties, including neurotransmitter receptors and other cell surface receptors, gangliosides, microtubule and microfilaments, as well as many other as yet-unidentified antigens. Generally, a subset of SLE patients has autoantibodies in the cerebrospinal fluid (CSF);[31–35] most of these have some neuropsychiatric manifestations.[31–36]

There is a need for critical interpretation of the data from these studies. First, there are special aspects of the brain circulation, such as the blood–brain barrier and the CSF barrier, that limit the direct application of pathologic principles from peripheral organs directly to mechanisms of brain dysfunction.

Second, the correlations between autoantibodies and NPSLE can be weak and are generally limited to a few subclasses of autoantibodies and some comparatively uncommon NPSLE outcomes.

Lastly, although there are a large number of studies reporting relationships of some NPSLE symptoms to specific autoantibodies, these have not been consistently reproduced.

There has also been little systematic attempt to differentiate between significant general progression of SLE and specific NPSLE symptoms or nonspecific effects of treatments. In

fact, SLE disease activity index (SLEDAI) scores and other disease indicators are consistently higher in patients with higher autoantibody titers.[37]

There are also few studies that address the variable nature of autoantibody profiles and titers, and their inconsistent correlation with patient signs and symptoms, the presence of autoantibodies in non-patient controls.[38–40] This and the changing nature of the autoantibody profile in individual patients,[41,42] limit support for autoantibodies as the (sole) proximate primary cause of NPSLE.

Antiphospholipid Autoantibodies

Antiphospholipid autoantibodies (as well as antiribosomal autoantibodies) are among the most widely studied classes of autoantibodies in relation to NPSLE. They are considered exemplars of the nature of the data (more detailed reviews about them can be found elsewhere[43,44]).

The most consistent finding is that antibodies against phospholipid-binding plasma proteins (such as beta2-glycoprotein I, lupus anticoagulant, and prothrombin) are associated with thromboembolic/vascular events.

However, several studies have failed to find an association between cerebrovascular disease (stroke, transient ischemic attack, chronic multifocal disease, subarachnoid or intracranial hemorrhage, and sinus thrombosis) and the presence of anti-beta2 glycoprotein I, anticardiolipin antibody, or lupus anticoagulant.[7,14,45]

Antiribosomal Autoantibodies

There have also been numerous reports of correlations between antiribosomal autoantibodies and some NPSLE symptoms, particularly psychosis.[6] However, patients with high autoantibody titers tend to have an earlier disease onset and a higher SLEDAI score,[6,37,46] and more than 25% of patients with neuropsychiatric symptoms do not have antiribosomal autoantibodies.[42]

The relationship of serum and CSF levels of autoantibodies to the disease process is complex, and some subsets of negative behavioral outcomes may be initiated by different mechanisms than those that regulate pathology in peripheral organs and the later-onset, more clinically severe symptoms of NPSLE.

Although there is no definitive evidence to date that autoantibody pathology initiates the earliest manifestations of the negative behavioral outcomes, there is some evidence that brain levels of autoantibodies may play a role in NPSLE at some point in the disease process.

Concentrations of intrathecal autoantibodies are more likely to be more critically related to NPSLE than are serum autoantibody titers. Increases in brain autoantibody titers would require either an influx of antibodies or lymphocytes from the peripheral circulation and a disintegration of the blood–brain barrier (BBB).

Alternatively, it has been suggested that there may be an intrathecal source of autoantibodies,[47,48] but this would presumably also require a permeablized BBB to permit entry of activated B cells.

Thus, it is plausible that serum autoantibodies are not the primary pathologic agents for the CNS in the presence of functional BBB and CSF barriers, but they do become important in the pathologic process once other inflammatory processes affect the integrity of the BBB.

It is therefore likely that both cytokines and chemokines are initiators of CNS pathology and give rise to some subtypes of NPSLE symptoms.[36,49–52]

Cytokines and Chemokines

Cytokines and chemokines do not need to pass the BBB to regulate neural function. They are reliably related to affective and cognitive dysfunction in humans in preclinical models in general and in NPSLE-specific models.[53–57] Detection by the brain of increased secretion of peripheral inflammatory cytokines can occur across an intact BBB, in part via the vagus nerve.

This induces glia and microglia to produce cytokines and other inflammatory and cytotoxic agents (including prostaglandins, leukotrienes and nitric oxide). These are documented to elicit the physiologic and behavioral symptoms of depression and mood disorders.

Clinically, cytokine-mediated depression occurs during cytokine administration (eg, when used as treatments in cancer and viral infections).[58,59] Proinflammatory cytokines and chemokines have been linked to depression and cognitive dysfunction in humans in general and to neuropsychiatric symptoms in NPSLE patients in particular, notably in conjunction with altered expression of proteins that are important in regulating BBB integrity.[19,50–57,60–65]

These include CXCL8, CXCL9, CXCL10, CXCL16, CCL2 (MCP-1), CCL5 (RANTES), CX3CL1 (fractalkine) in the chemokine family and interleukin (IL)-6, IL-1, IL-8, IL-10, tumor necrosis factor, and interferon-gamma in the cytokine family.[52,65] Anti-inflammatory cytokines can also reduce disease severity, whereas proinflammatory cytokines are positively correlated with disease severity.

Blood–Brain Barrier

The normal CNS is protected by blood–tissue barriers at three sites: 1) the brain endothelium; 2) the choroid plexus epithelium (blood–CSF barrier); and 3) the arachnoid epithelium, all of which serve to regulate and limit passage of molecules and cells between blood and CSF and brain.

The integrity of the blood–CSF barrier primarily determines the protein content of the CSF and, thus, concentration of various measures of specific proteins can be used to estimate loss of barrier integrity. Similarly, the tight junctions of the BBB prohibit passive entry of cells, proteins, and other molecules, including some contrast agents used in brain imaging. However, BBB damage may be local and/or transient, and hence may be underestimated.

The two main candidate mechanisms for BBB damage are microthrombi in cerebral vessels leading to ischemia, and immune-mediated attack and activation of the endothelium leading to local cytokine production, entry of serum autoantibodies, and CNS localization of activated B and T cells. Steroid therapy can also induce changes in BBB permeability.[15] Damage to the BBB is likely to allow for neuropsychiatric syndromes from a variety of underlying causes.[66]

Several lines of evidence show that the BBB of NPSLE patients is compromised.[66] High brain levels of MRI contrast agents following intravenous administration in a proportion of NPSLE patients indicate a more permeable BBB.[67] An alternative measure to investigate CSF barrier integrity is the albumin quotient, which is a ratio of the albumin concentration in serum and CSF[68–70] that is altered in several neurologic diseases,[69] including NPSLE.[15,66]

However, there is also evidence that the BBB is intact in lupus patients with NPSLE, in whom serum and CSF levels of soluble inflammatory mediators, (such as APRIL and BAFF) differ, indicating an intact barrier.[69]

TREATMENT OF NPSLE

The current strategy of management, essentially unchanged for several decades, includes administration of corticosteroids and immunosuppressive drugs such as cyclophosphamide and azathioprine. There are several alternative and off-label therapies in use, including mycophenolate, plasma exchange, and rituximab (an anti-CD20 monoclonal antibody directed against a B-cell surface protein).[17,71]

These primarily target cell-mediated mechanisms, and thus do not directly address the large increases in chemokines, cytokines, and early mediators of inflammation. Recent studies suggest that manipulation of inflammation “stop” signals, such as lipoxins, resolvins, protectins, and nitrolipids,[71,72] may be promising novel candidates for putative therapeutic agents.

Although an evidence-based approach to therapy is optimal, the actual evidence from controlled trials testing the effectiveness of immunosuppressive therapies in NPSLE is still quite limited.[27] Thus, although it is generally thought that NPSLE responds well to traditional immunosuppressive treatments, the evidence for this is actually sparse and inconsistent. Reports that steroids, cyclophosphamide, or the combination of the two are effective in NPSLE should be interpreted with caution as these studies may refer to a small and uncommon symptom subset, are based on very small sample sizes or case studies, are not placebo controlled (particularly important in a fluctuating disease), and have small effect sizes.

The majority of studies finding benefits of these immunosuppressive agents examine such symptoms as seizures, psychosis, acute confusional state, abnormal consciousness, transverse myelitis, peripheral neuropathy, cerebral infarction, aseptic meningitis, optic neuritis, peripheral or cranial neuropathy, coma, brain stem disease, or transverse myelitis.[73,74]

Although these may be the most severe and life-threatening symptoms, they are also arguably less common NPSLE symptoms and the most related to general disease state. These studies also tend to lack diagnostic power, as the instruments used to assess NPSLE tend to be crude (ie, mini-mental state exams vs. comprehensive cognitive and mood assessments).

Furthermore, a substantial minority of patients is refractive to standard immunosuppression by the criteria used.[75] In the few studies that have specifically examined nonfatal NPSLE symptoms (eg, cognitive function) with suitable diagnostic instruments, most patients developing or continuing to manifest cognitive dysfunction were treated with steroidal and/or immunosuppressive therapies.[76]

More problematic is that less severe but more common symptoms, such as negative mood, are positively correlated with steroid administration,[15,77] and standard steroid therapy can induce NPSLE symptoms in patients who did not previously exhibit them.[15] Thus, the existing literature does not currently support standard SLE treatments as widely beneficial for important subsets of NPSLE symptoms.

Belimumab is the first new drug approved to treat lupus in more than 50 years.[78–82] It is a monoclonal antibody that inhibits B-cell activating factor and appears to be well tolerated. However, in clinical trials for SLE belimumab was only modestly effective and had a relatively high number-to-treat index.

It also may not be effective in some ethnic groups, must be administered intravenously, and is costly. Its real-world efficacy may even be lower than indicated in the trials, as patients with lupus nephritis and CNS symptoms were excluded in the clinical trials. Its effects in NPSLE have, therefore, not been assessed; however, given its mechanism of action, it is only likely to target B-cell–mediated mechanisms, so it is not yet clear whether it will provide much direct benefit in NPSLE.

CONCLUSIONS

The revision and standardization of the diagnostic criteria of NPSLE have done much to inform the progress of research regarding several aspects of NPSLE. However, much still needs to be addressed. This includes the potential categorization of NPSLE into symptom clusters based on similar pathology, response to therapy, onset, behavioral domain, and other criteria.

In particular, identifying the time course of symptom onset would be helpful to characterizing the mechanisms initiating NPSLE and differentiating the primary causative agents from the complex cascade of secondary mechanisms that can further the decline. Currently, there are no highly reliable pathologic or serologic diagnostic markers for NPSLE. Thus, the importance of implementing well-validated and comprehensive psychological and neurologic exams and questionnaires cannot be overstated.

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EDUCATIONAL OBJECTIVES

1. Learn the symptoms, diagnostic procedures, and prevalence of neuropsychiatric lupus (NPSLE).
2. Understand the current hypotheses regarding the putative mechanisms underlying NPSLE.
3. Become familiar with some of the current strategies for treatment of NPSLE and understand their limitations.

TABLE

Diagnostic Criteria and Nomenclature for Neuropsychiatric Systemic Lupus Erythematosus

Central Nervous System	Peripheral Nervous System
Aseptic meningitis	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré)
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy, single/multiplex
Headache	Myasthenia gravis
Movement disorder	Plexopathy
Myelopathy	
Seizure disorders	
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Neuropathy, cranial	
Mood disorder	
Psychosis	

Source: Adapted from American College of Rheumatology[1]