

Neuropsychiatric Lupus

Clinical and Imaging Aspects

Robin L. Brey, M.D.

Abstract

Neuropsychiatric lupus (NPSLE) manifestations are common in adults and children and are associated with an increase in both morbidity and mortality. Cognitive dysfunction, when standardly assessed using sensitive neurocognitive instruments, is the most common NPSLE manifestation. The pathogenic etiologies of NPSLE manifestations are likely to be multifactorial and may involve autoantibody production, microangiopathy, intrathecal production of proinflammatory cytokines and atherosclerosis. It is becoming more clear that the integrity of the blood-brain-barrier is very important in SLE-related neuropathology. Brain imaging is an important tool that allows us to evaluate the living brain. Thus far, anatomic brain imaging has revealed abnormalities such as subcortical white matter lesions and cerebral atrophy, but these findings are non-specific. Methods that evaluate metabolic processes and other functional imaging techniques have more promise as surrogates for central nervous system damage. This article reviews the current literature on clinical and imaging aspects of NPSLE.

Systemic lupus erythematosus (SLE) is an autoimmune, inflammatory disorder affecting multiple organ systems in females nine times more frequently than males.¹ The prevalence is approximately 130/100,000 in the United States, with African Americans, Hispanics, and Asians more frequently affected than nonHispanic Whites.² The nervous system is commonly affected in both children

and adults with SLE,³⁻¹¹ and its involvement is also associated with a worse prognosis and more cumulative damage.^{8,9,12} Neuropsychiatric lupus (NPSLE) manifestations can occur in the absence of either serologic activity or other systemic disease manifestations.¹³⁻¹⁵ The American College of Rheumatology (ACR) established case definitions for 19 central and peripheral nervous system syndromes listed in Table 1.¹⁶ The availability of these case definitions have been pivotal in studies of the incidence, prevalence, and risk factors for NPSLE and in allowing the comparison of results among studies.

NPSLE Neurobehavioral Syndromes

In adults, approximately 28% to 40% of NPSLE manifestations develop before or around the time of the diagnosis of SLE.^{9,13} A recent retrospective study of NPSLE in 185 Chinese children over a 20-year period found that 11% had NPSLE manifestations at the time of diagnosis and an additional 16% developed them within one year. In this study, the mortality rate was 45% in children with NPSLE and 17.4% in those without these manifestations.¹¹

Estimates of the prevalence of NPSLE have ranged from 14% to over 80% in adults^{3,4,6,7,9,10} and 22% to 95% in children.^{8,10,11} In the only prospective study of NPSLE in children, nervous system manifestations were more common over the six-year study period than glomerulonephritis (95% versus 55%, $p \leq 0.0001$).¹⁰ Headache occurred in 55%, mood disorder in 57%, cognitive dysfunction in 55% (sensitive tests of cognitive function were not routinely used), seizure disorder in 51%, acute confusional disorder in 35%, peripheral nervous system impairment in 15%, psychosis in 12%, and stroke in 12%. Another recent retrospective study of NPSLE in children in the San Francisco area also found NPSLE manifestations to be common and to occur early in the course of the disease; however, these manifestations were not necessarily associated with disease activity outside

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Table 1 Neuropsychiatric Manifestations of Systemic Lupus Erythematosus (NPSLE)

NPSLE associated with the central nervous system
Aseptic meningitis
Cerebrovascular disease
Stroke
Transient ischemic attack
Cerebral venous sinus thrombosis
Cognitive disorders
Delirium (acute confusional state)
Dementia
Mild cognitive disorders
Demyelinating syndrome
Headaches
Tension headaches
Migraine headaches
Movement disorders (chorea)
Psychiatric disorders
Psychosis
Mood disorders
Anxiety disorder
Seizure disorders
Transverse myelopathy
NPSLE associated with the peripheral nervous system
Autonomic neuropathy
Myasthenia gravis
Peripheral neuropathy
Sensorineural hearing Loss
Sudden onset
Progressive
Cranial neuropathy

the nervous system.⁸ In contrast, the overall prevalence of NPSLE manifestations was lower (25%), seizures were the most common manifestation, and the prevalence of headache was much lower (5%) than in the prospective study. The investigators explain this discrepancy in the prevalence of SLE-related headaches as possibly due to the strict adherence to the ACR (American College of Rheumatology) NPSLE case definitions for including headache as an NPSLE manifestation in their study. As with the prospective study, sensitive tests for cognitive function were not routinely performed. Importantly, this group was the first to systematically study the link between antiphospholipid antibodies and NPSLE manifestations in children. Antiphospholipid antibodies, more common in children than adults with SLE, have been linked with several NPSLE manifestations in adults.^{4,5} Although the presence of antiphospholipid antibodies was seen in 70% of children in this study (as compared to approximately 25% to 30% in adults SLE patients), the association of these antibodies with NPSLE was weak, with the exception of cerebrovascular disease. The investigators suggest that there may be a different underlying pathophysiologic mechanism for noncerebrovascular NPSLE manifestations in children as compared with adults with SLE; however, cognitive dysfunction, a manifestation that has been strongly linked to antiphospholipid antibodies in adults,

was not systematically studied in these pediatric patients. This may have led to an underestimation of the importance of antiphospholipid antibodies, overall, in relation to NPSLE manifestations in children. More work is certainly needed in both pediatric and adult SLE populations to better understand the underlying pathophysiology of NPSLE manifestations and the similarities and differences between children and adults that may be important in treatment considerations.

Studies in adults using the ACR case definitions collectively have detected the presence of 14 to 17 of the 19 syndromes and reported a limited range in the prevalence of the following syndromes: total spectrum of headache (39% to 61%), seizures (8% to 18%), cerebrovascular disease (2% to 8%), psychosis (3% to 5%), cranial neuropathy (1.5% to 2.1%), and movement disorder (1%). Interestingly, the range in the prevalence of mood disorders and cognitive dysfunction is much wider, with studies using systematic assessment of cognitive and psychiatric function finding a higher prevalence^{1,3,4,17} than studies that only evaluated patients using sensitive instruments if “clinically indicated.”⁹

The studies testing cognitive function in every patient using sensitive psychiatric and neuropsychological instruments found the prevalence of the total spectrum of mood disorders to be between 69% and 74% and the total range of cognitive disorders to be between 75% and 80%.^{1,3,4,17} This includes data from an inception cohort study in which SLE patients enrolled within nine months of an SLE diagnosis and were tested every four months using computerized neurocognitive testing and yearly using the more extensive battery recommended by the ACR.¹ This is in contrast to the results seen in another larger inception cohort study that was recently published in which 158 of 572 (28%) patients had at least one NPSLE manifestation at or around the time of SLE diagnosis. Of these, 12.4% had a mood disorder and 5.4% had evidence of cognitive dysfunction.⁹

The obvious methodological difference between the inception cohort study by Hanly and colleagues⁹ and the other studies is the lack of a standardized use of psychiatric interviews and neuropsychological testing in the inception cohort study. The investigators of this study argue that the use of sensitive neuropsychological testing routinely overestimates the degree of cognitive dysfunction in patients with SLE, by including those patients with mild cognitive dysfunction in prevalence estimates. There are problems with this argument on two counts. First, in these other studies, the number of patients with moderate to severe cognitive dysfunction was 25% to 40%, a number that is much higher than the 5.4% found in the study by Hanly and coworkers, suggesting that the failure to test all patients in that study underestimated clinically important cognitive dysfunction. Second, because we do not yet understand the cause or underlying pathophysiology of cognitive dysfunction in SLE, more work needs to be done to carefully track the evolution of this NPSLE manifestation. It is possible that the worsening of mild cognitive dysfunction in individual

patients will provide an important clue that suggests, in the context of yet to be identified biomarkers, a particular treatment option. Longitudinal study of cognitive functioning in SLE patient cohorts is required to obtain this information, which is difficult to impossible to fully characterize using "bedside" clinical testing alone.

A very important finding in the study by Hanly and associates that deserves emphasis was that the occurrence of neuropsychiatric events in these newly diagnosed patients is associated with reduced quality of life and increased organ damage, irrespective of whether the particular event is judged to be SLE related or non-SLE related. Whether or not this association strengthens or becomes more specific with time is currently investigated in this study. This finding, along with the data presented earlier on the relationship between NPSLE manifestations and mortality in children with SLE, strengthens the need for additional longitudinal studies evaluating the relationship between NPSLE manifestations and SLE-related morbidity and mortality.

Psychological distress is common in patients with SLE, contributes to a lower quality of life, and may also contribute to a worsening of other neuropsychiatric symptoms.¹⁸ Haupt and colleagues demonstrated the ability to improve coping using a novel psychological group intervention.¹⁹ Patients receiving this intervention showed a significant and sustained improvement on a number of symptoms, such as depression, anxiety, and overall mental burden. The control group, consisting of individuals placed on a waiting list, showed no such improvement. Kozora and coworkers underscored the importance of the relationship between self-reported and objectively measured cognitive dysfunction and depression, fatigue, and pain symptoms in patients with SLE.¹⁸ The investigators suggest that multiple behavioral problems in patients with NPSLE manifestations may be related and that this may represent a reflection of global nervous system dysfunction. This also suggests that treatment aimed at improving any of these symptoms, such as the intervention described by Haupt and associates above, may have a beneficial effect overall. The complex relationship between these symptoms, quality of life assessments, and long-term outcomes are clearly in need of further study.

Neuropathology/Pathophysiology

The pathogenic etiologies of NPSLE manifestations are likely to be multifactorial and may involve autoantibody production, microangiopathy, intrathecal production of proinflammatory cytokines and atherosclerosis.²⁰ Histopathologic studies reveal a wide range of brain abnormalities caused by multifocal microinfarcts, cortical atrophy, gross infarcts, hemorrhage, ischemic demyelination, and patchy multiple-sclerosis-like demyelination in people with SLE.²¹ A microvasculopathy is seen that was formerly attributed to deposition of immune complexes but now is suspected to arise from activation of complement, and appears to be the most common microscopic brain findings in SLE.²²

Consistent with these small vessel changes, SPECT (single photon emission computed tomography) and MR (magnetic resonance) spectroscopy studies suggest that both cerebral atrophy and cognitive dysfunction in SLE patients may be related to chronic diffuse cerebral ischemia.^{14,23,24} However, all of these are nonspecific findings, as patients without overt NPSLE manifestations also show these changes²⁰ and the brain can be pathologically normal in a patient with NPSLE manifestations.²¹

It is becoming more clear that the integrity of the blood-brain-barrier is very important in SLE-related neuropathology.²⁵ Processes leading to brain dysfunction in SLE probably involve abnormal endothelial-white blood cell interactions that allow proteins or cells access to the central nervous system (CNS). As will be discussed further below, this may be a mechanism whereby autoantibody-mediated CNS effects can occur. This can be stimulated by proinflammatory cytokines or autoantibodies that up-regulate the expression of adhesion proteins on endothelial cells, facilitating lymphocyte entry into the central nervous system.²⁶ Soluble serum levels of ICAM-1 increase with systemic disease activity in patients with SLE²⁶⁻²⁸ and normalize with remission,²⁹ strengthening the hypothesis that activated endothelial cells and a lack of integrity of the blood-brain barrier might be an important requisite for disease activity in the brain.

A variety of autoantibodies have been implicated in NPSLE manifestations, but the evidence for most is not consistent across studies. As has already been mentioned, antiphospholipid (aPL) antibodies are associated with both cerebrovascular disease and cognitive dysfunction in people with SLE. A variety of effects on platelets, coagulation proteins, and endothelial cells, including tissue factor up-regulation, have been ascribed to aPL antibodies, making them not only serological markers but also potentially direct contributors to the development of thrombosis and other NPSLE manifestations. The majority of evidence favors a prothrombotic mechanism that amplifies thrombosis in certain settings. Pierangeli and Harris demonstrated larger clot size, with a longer time to dissolution in mice treated with human aPL antibody, compared to control IgG using a pinch clamp injury model.³⁰ Taken together, these studies provide converging evidence that antibodies to phospholipids and phospholipid-binding proteins like β_2 GP-1 can cause thrombosis and other antibody-mediated clinical manifestations, such as stroke. The mechanism for the association of aPL antibodies with cognitive dysfunction in SLE in the absence of thrombosis, however, is less clear.

Much attention is currently directed at the potential role of anti-glutamate receptor antibodies in cognitive dysfunction and psychiatric disease in patients with SLE. Diamond and colleagues first demonstrated that a subset of lupus anti-DNA antibodies cross-reacts with the NR2 glutamate receptor in patients with SLE.³¹ This group showed that the NR2 receptor is recognized by both murine and human anti-DNA antibodies, and that these antibodies mediate

apoptotic cell death of neurons *in vitro* and *in vivo*. The relationship between anti-glutamate receptor antibodies and NPSLE manifestations in humans with SLE has been conflicting. Most studies report that these antibodies are seen in 25% to 30% of patients with SLE.³²⁻³⁴ Some studies find no cross-sectional relationship between anti-glutamate receptor antibodies and any clinical manifestations¹ or cognitive dysfunction specifically.^{34,35} Others have reported an association between anti-glutamate receptor antibodies and both cognitive dysfunction and depression³³ or depression but not cognitive dysfunction.³⁵ A recent study by Kowal and coworkers using an animal model suggests that anti-glutamate receptor antibodies are associated with cognitive dysfunction and hippocampal apoptosis only in the presence of blood-brain barrier disruption.³⁶ It is possible that the magnitude and degree of blood-brain barrier dysfunction, in concert with the type and level of autoantibodies in human patients with SLE, may be the determining factor regarding their "pathogenicity" in the brain.

Supporting Laboratory Studies

There is no single diagnostic test that is sensitive and specific for SLE-related neuropsychiatric manifestations. The assessment of individual patients is based on clinical neurologic and rheumatologic evaluation, immunoserologic testing, brain imaging, and psychiatric and neuropsychological assessment. These examinations are used to support or refute the clinical diagnostic impression, rule out alternative explanations, and form the basis for prospective monitoring of clinical evolution and response to treatment interventions.

An important consideration in the diagnostic approach to a patient with possible NPSLE manifestations is whether the particular clinical syndrome is due to SLE-mediated organ dysfunction, a secondary phenomenon related to infection, medication side-effects, or metabolic abnormalities (e.g., uremia), or is due to an unrelated condition. It cannot be stressed strongly enough that infection is a major cause of central nervous system syndromes in hospitalized SLE patients.³⁷ Thus, it is always important to suspect infection in patients with SLE and central nervous system manifestations.

Brain Imaging

Brain magnetic resonance imaging (MRI) studies in patients with antiphospholipid antibodies, with or without SLE, have revealed small foci of high signal in subcortical white matter scattered throughout the brain.³⁸⁻⁴⁰ This type of pattern is seen in many other disease processes and is therefore nonspecific. The correlation between MRI lesions in patients with aPL and clinical nervous system symptoms is reported to be high by some investigators³⁸⁻⁴⁰ and not by others.^{42,43} Appenzeller and associates⁴⁴ have demonstrated a reduction in cerebral and corpus callosum volumes in SLE patients that are associated with disease duration and cognitive impairment and other central nervous system manifestations, but not total

corticosteroid dose or the presence of aPL.

Focal neurological and neuropsychological symptoms of SLE-related stroke correlate with structural MRI abnormalities. Using structural MRI, the majority (40% to 80%) of abnormalities in NPSLE are small focal lesions concentrating in periventricular and subcortical white matter.^{14,45} Cortical atrophy, ventricular dilation, diffuse white matter, and gross infarctions are also common.¹⁴ MRI reveals multiple discrete white matter lesions in periventricular, cortical/subcortical junction, and frontal lobe tissues that are more commonly found in patients with past NPSLE manifestations than in SLE patients without history of NPSLE.^{14,24,45}

Visually analyzed FDG-PET (fluoro-2-deoxy-D-glucose and positron emission tomography) scans consistently reveal abnormalities in prefrontal, parietal (inferior and superior), parieto-occipital, posterior temporal, and occipital gray and white matter regions in active and quiescent NPSLE.^{46,47} Prefrontal, anterior cingulate, and inferior parietal white matter abnormalities have been seen during acute NPSLE but not during quiescent NPSLE.¹ The metabolic disturbances in parieto-occipital (peritrigonal) white matter remain an intriguing finding. Approximately 60% to 80% of active minor and major NPSLE patients consistently show bilateral parieto-occipital white matter FDG-PET hypometabolism in the context of normal conventional MRI and no other PET abnormalities.^{46,47}

More recently, magnetic resonance spectroscopy (MRS) has revealed neurometabolic abnormalities, even in white and gray matter that appears normal on conventional MRI. Such abnormalities are thought to reflect neuronal injury or loss and demyelination; they have been found during active as well as quiescent periods of NPSLE manifestations.⁴⁸ Kozora and colleagues¹⁸ recently found a correlation between changes in cerebral white matter by MRS and cognitive impairment in SLE patients, even in the absence of overt NPSLE symptoms. This suggests that some of these newer imaging techniques may have promise as surrogates for CNS damage and could be used as biomarkers in treatment trials.¹⁸

Treatment

The general management of patients with NPSLE includes symptomatic and immunosuppressive therapies, but evidence for the efficacy of the treatment modalities commonly used is largely limited to uncontrolled clinical trials and anecdotal experience.⁸ The key to treatment is to first establish the correct diagnosis by carefully considering all possible etiologies, both SLE-related and those that are not.

Conclusion

Estimates of the prevalence of NPSLE have ranged from 14% to over 80% in adults and 22% to 95% in children. The presence of any NPSLE manifestation in children has been associated with an increased risk for SLE-related mortality. In adults, any NPSLE manifestation has been associated with

reduced quality of life and increased non-central nervous system organ damage. Studies testing cognitive function in every patient using sensitive psychiatric and neuropsychological instruments found the prevalence of the total spectrum of mood disorders to be between 75% and 80% and the total range of cognitive disorders to be between 75% and 80%. Psychological distress is common in patients with SLE and contributes to a lower quality of life and may also contribute to a worsening of other NPSLE symptoms. The pathogenic etiologies of NPSLE manifestations are likely to be multifactorial and may involve autoantibody production, microangiopathy, intrathecal production of proinflammatory cytokines and atherosclerosis. It is becoming more clear that the integrity of the blood-brain-barrier is very important in SLE-related neuropathology. Thus far, anatomic brain imaging has revealed abnormalities such as subcortical white matter lesions and cerebral atrophy, but these findings are non-specific. Methods that evaluate metabolic processes and other functional imaging techniques have more promise as surrogates for central nervous system damage and may be particularly helpful as outcome measures in treatment trials.

Disclosure Statement

None of the authors have a financial or proprietary interest in the subject matter or materials discussed in the manuscript, including, but not limited to, employment, consultancies, stock ownership, honoraria, and paid expert testimony.

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