Demystifying Neuropsychiatric Lupus
Is It Possible?

John G. Hanly, M.D.

Abstract
The occurrence of nervous system events in patients with systemic lupus erythematosus (SLE) remains a diagnostic and therapeutic challenge due to the diversity of clinical manifestations, the correct attribution of events to SLE or other causes, and the lack of clinical trial data to facilitate the selection of treatment options. Over the past decade the classification and attribution of neuropsychiatric (NP) events has received more rigorous attention and new insights into the pathogenetic mechanisms have emerged through neuroimaging studies and elucidation of autoimmune and inflammatory mechanisms. Although much work remains to be done on this complex and fascinating aspect of lupus, there is an emerging consensus on the pathogenesis and treatment of NP-SLE.

Neuropsychiatric (NP) events in patients with systemic lupus erythematosus (SLE) include common entities, such as headache and depression, and rarer manifestations, such as psychosis and seizures. NP events are associated with a lower health-related quality of life (HRQOL) and, in some studies, with increased mortality. The lack of specificity for many of the NP manifestations described in SLE patients and the lack of diagnostic gold standards makes the correct attribution of such events difficult. Recent studies have provided insight into the immunopathogenic mechanisms that should eventually lead to improved treatment strategies. In this review, we will examine: 1. the clinical diversity and frequency of NP events in SLE, 2. the attribution of NP events and their impact on patients’ HRQOL, 3. the immunopathogenic mechanisms underlying those NP events directly attributable to SLE, and 4. the therapeutic options for the management of SLE patients with NP events.

Classification of NP-SLE
The 1987 revised classification criteria for SLE include seizures and psychosis, which is an under-representation of the totality of NP disease in SLE. In 1999, following a multidisciplinary consensus conference, the American College of Rheumatology (ACR) published a standard nomenclature and case definitions for 19 NP syndromes known to occur in lupus patients (Table 1) and which include 12 central nervous system and seven peripheral nervous system manifestations. For each of these syndromes, diagnostic guidelines were provided, and, significantly, a list of alternative diagnoses was included for consideration as an alternative explanation for the particular NP event. This aspect of the ACR case definitions, in conjunction with other variables, may be used to determine the attribution of NP events.

The ACR case definitions are the current standard for describing NP events in clinical studies of SLE. Despite their utilization, there is still a wide spectrum in the reported frequency of NP disease, ranging from 37% to 95% SLE. Differences in attribution rules for NP events are likely a major contributor to these discrepancies. In most of these studies, approximately half of the 19 NP syndromes occurred in less than 1% of patients, emphasizing the relatively low frequency of many of the individual NP syndromes.

NP-SLE SLICC Inception Cohort Study
In 2000, an international, multicenter disease inception cohort study was initiated to prospectively determine the frequency, attribution, and outcome of NP events in SLE.

John G. Hanly, M.D., is Professor of Medicine and Pathology, Division of Rheumatology, Department of Medicine and Department of Pathology, Capital Health and Dalhousie University, Halifax, Nova Scotia, Canada.

Correspondence: John G. Hanly, M.D., Department of Medicine, Capital Health and Dalhousie University, Halifax, Nova Scotia, Canada, B3H 4K4; john.hanly@cdha.nshealth.ca.
In this study, which is conducted by the Systemic Lupus International Collaborating Clinics (SLICC) research network, patients are enrolled within 15 months of their diagnosis of SLE and re-evaluated on an annual basis using a standardized protocol. In the first 572 patients enrolled with a mean disease duration of 5.2 ± 4.2 months, NP events occurred in 30% of patients, 48% of whom had more than one NP event. The most common events were headache, mood disorders, cognitive dysfunction, anxiety disorder, cerebrovascular disease, seizure disorders, acute confusional states, polyneuropathy, mononeuropathy, and psychosis. Each of the remaining eight NP syndromes occurred in less than 2% of patients. Decision rules were developed to determine the attribution of NP events. Two attribution models of different stringency were applied and indicated that NP events directly attributable to SLE accounted for 19% to 38% of all events and affected 6% to 12% of the study population. Of these events, the most frequent were seizure disorders, cerebrovascular disease, mononeuropathy, acute confusional states, cranial neuropathy, myelopathy, polyneuropathy, and psychosis, with each of the remaining syndromes affecting no more than 2% of patients. Regardless of attribution, the occurrence of NP events in this patient cohort was associated with a significant negative impact on patients’ self-reported HRQOL, as indicated by lower mental and physical component summary scores of the SF-36. In a separate study, the same association has been demonstrated over 8 years of follow-up. Thus, although NP events are common in SLE patients, it is likely that a minority are directly attributable to lupus. Regardless of attribution, the occurrence of NP events is associated with a significant negative impact on HRQOL.

### Pathogenesis of NP-SLE

When considering which lupus related immunopathogenic mechanisms contribute to NP events, it is helpful to consider whether the anatomical location of injury results in either a focal (e.g., stroke, seizure) or diffuse (e.g., acute confusion, psychosis) NP event. The factors that contribute to primary SLE include vasculopathy, autoantibodies, and inflammatory mediators (Fig. 1). Each plays a role in the pathogenesis of focal and diffuse NP events to a variable degree. For example, antiphospholipid antibodies are paramount in causing intravascular thrombosis leading to focal NP disease, while the production of intracranial inflammatory mediators is the major disease mechanism underlying diffuse NP events.

#### Antiphospholipid Antibodies and Vasculopathy

In addition to the thrombosis of large intracranial vessels mediated by antiphospholipid antibodies, neuropathological studies of SLE patients have indicated the presence of a microvasculopathy, characterized by endothelial proliferation and fibrinoid necrosis. Intraluminal plugging of small vessels due to leukoagglutination has also been identified. Both neuropathological abnormalities occur in close anatomical association with cerebral microinfarction, thereby implying a causal association.

#### Antineuronal Antibodies

Evidence from human studies implicating antineuronal antibodies in the pathogenesis of NP-SLE is largely circumstantial and includes the temporal relationship between the presence of circulating autoantibody and the NP event, the occurrence of autoantibodies in the cerebrospinal fluid (CSF), and, in a limited number of cases, the elution of autoantibody from brain tissue in SLE patients who have...
succeeded to their disease. More direct evidence is available from animal studies, in which the intracranial injection of antineuronal antibodies has induced memory deficits, seizures, and neuropathological changes. The source of these autoantibodies includes both the circulation, by virtue of passage through a permeabilized blood-brain barrier, and direct intrathecal production within the central nervous system. Efforts to characterize the fine specificity of antineuronal antibodies in order to further our understanding of their immunopathogenic role have met with mixed results. Studies in murine lupus models have revealed that a subset of anti-DNA antibodies reacts with the extracellular ligand binding domain of NR2 glutamate receptors, which are present throughout the forebrain, and, in particular, the hippocampus, a critical location for learning and memory. In contrast to other antineuronal antibodies, the binding of anti-NR2 antibodies has functional consequences, including apoptosis. In human SLE, anti-NR2 antibodies have been detected in both the circulation and in the CSF. Although the studies of circulating anti-NR2 and NP disease have yielded conflicting results, their detection in the CSF provides a closer association with NP events.

**Antiribosomal-P (Anti-P) Antibodies**

Anti-P antibodies occur in up to 20% of SLE patients and were initially reported in association with psychosis and depression. However, these findings have been replicated in only about half of the subsequent studies. A large meta-analysis of 1537 patients, 30% of whom had NP-SLE, found that the sensitivity of anti-P antibodies for the detection of any NP event varied between 24% to 29% and had a specificity of 80%. Although these findings emphasize the limited clinical utility of anti-P antibodies in the diagnosis of NP-SLE, recent work has provided a potential new link between anti-P and the brain. Koren and colleagues were the first to report an association between anti-P and antineuronal antibodies and further demonstrated that anti-P antibodies bound a 38-kDa surface protein on human neuroblastoma cells. More recently, Matus and coworkers have shown that anti-P antibodies from patients with and without lupus psychosis bind a novel neuronal surface protein that is not present on non-neuronal cells within the central nervous system. This antibody binding is due to the presence of amino acid sequences that are homologous to the P epitope on the surface neuronal protein, which the investigators named neuronal surface P antigen (NSPA). The binding of anti-P autoantibodies to NSPA induces neuronal apoptosis mediated by deleterious intracellular calcium influx.

**Inflammatory Mediators**

Studies of CSF from SLE patients have implicated a number of proinflammatory cytokines in the pathogenesis of NP-SLE. These include interferon-alpha (IFN-α), IL-2, IL-6, IL-8, and IL-10. Intracranial cytokines are produced by both neuronal and glial cells and may be regulated by autoantibodies within the intrathecal space. Santer and associates have demonstrated recently that CSF from SLE patients is a potent inducer of IFN-α production. In fact, studies of matched CSF and serum samples from the same SLE patients indicated that CSF was over 800-fold more potent than serum at inducing this response. The effect was also significantly greater than that seen with CSF from patients with other autoimmune inflammatory disorders and patients with multiple sclerosis. The induction of IFN-α and, indeed, of other proinflammatory cytokines and chemokines is mediated by the binding of immune complexes to FcγRII on plasmacytoid dendritic cells, followed by endocytosis and activation of endosomal TLR7. The immune complexes are formed by autoantibodies and RNA-protein antigens. The plausibility of this mechanism is supported by: 1. neuronal and glial degradation products in the CSF of SLE patients, which provides a potential source of antigen; and 2. elevated levels of CSF matrix metalloproteinase-9 (MMP-9), which increases the permeability of the blood-brain barrier and, thereby, provides access of circulating autoantibodies to the intrathecal space.

**Proposed Pathogenic Model for Primary NP-SLE**

The combined evidence from both animal and human studies suggests two separate and potentially complimentary autoimmune pathogenic mechanisms for NP-SLE: 1. vascular injury involving both large and small caliber vessels mediated by antiphospholipid antibodies, immune complexes, and leukoagglutination, which results in focal NP events, such as stroke, and in diffuse NP events, such as cognitive dysfunction; and 2. inflammatory mediated injury, in which increased permeability of the blood-brain barrier, formation of immune complexes, and production of IFN-α and other inflammatory mediators leads to diffuse NP manifestations, such as psychosis and acute confusional states. Some human studies indicate that these separate autoimmune pathogenic pathways correlate with clinically distinct NP events. Additional research involving large numbers of patients with well characterized NP disease, in association with neuroimaging to identify structural and functional abnormalities, are required to provide further validation to this proposed pathogenic model.

**Diagnostic Evaluation of Patients with NP Events**

Given the wide range of potential NP manifestations, the diagnostic work up of individual patients must be tailored to their specific NP event and circumstances. The correct attribution is determined on a case by case basis using all of the available clinical, laboratory, and neuroimaging data. Of the autoantibodies, antiphospholipid antibodies have the greatest clinical utility, particularly for focal NP disease. Examination of the CSF is performed primarily to exclude infection but can also be used to determine permeability of the blood-brain barrier, the presence of autoantibodies, and
inflammatory mediators. Electrophysiological assessment confirms the presence of peripheral nervous system disease, and neuropsychological assessment should be considered in patients in whom there is suspicion of significant cognitive dysfunction. The selection of specific neuroimaging modalities will be dependent upon local availability and access but an assessment of brain structure and brain function should be considered.

Management of NP-SLE (Table 2)

Following the diagnosis of NP-SLE, all potential non-SLE contributing factors should be identified and treated, including hypertension, infection, and metabolic abnormalities. Symptomatic therapies should be introduced if applicable, for example, in the treatment of convulsions, anxiety, and depression. The role of anticoagulation with either anti-platelet agents or full anticoagulation with heparin or warfarin is generally accepted when antiphospholipid antibodies are implicated.

A number of clinical studies, most of which are uncontrolled, support the use of corticosteroids and immunosuppressive therapies. In an open study of 13 patients with lupus psychosis, Mok and colleagues reported a favorable response to a combination of high dose oral corticosteroids and oral cyclophosphamide for 6 months, followed by azathioprine as maintenance immunosuppressive therapy. In a study of 32 patients with predominantly neurological disease, Barile-Fabris and coworkers compared intensive intravenous cyclophosphamide and methylprednisone therapy over 2 years, with significantly better efficacy in the cyclophosphamide group but comparable toxicity in both groups. Finally, in a study of 10 female SLE patients who had a wide variety of NP manifestations and were followed for up to 35 months, B-cell depletion therapy with rituximab was associated with a favorable response in the majority of patients.

Summary

Nervous system disease in SLE patients consists of a variety of both common and rare NP disorders, which are best characterized using the ACR case definitions for NP syndromes. Although the correct attribution of NP events remains a challenge, it is likely that the majority are not attributable to SLE. Regardless of attribution, their occurrence is associated with a lower HRQOL. The etiology of primary NP-SLE is multifactorial, but current evidence implicates a limited number of autoantibodies and inflammatory mediators that work through distinct pathogenic pathways, culminating in nervous tissue injury. Evidence of clinical efficacy for different therapeutic strategies is largely derived from uncontrolled studies. However, treatment options include symptom control, anticoagulation, and immunosuppression. Further work is required to characterize pathogenic mechanisms and to determine the long-term outcome and optimal therapies for all NP events in SLE patients.

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References


