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Neuropsychiatric systemic lupus erythematosus reconsidered

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With the improved longevity of patients, it is increasingly appreciated that neuropsychiatric systemic lupus erythematosus (NPSLE) is a major cause of chronic disability, and that there are few specific therapies for many of the disease manifestations. In the 1999 consensus conference, the most recent of several consensus conferences on NPSLE, 19 specific syndromes affecting the neuromuscular junction, nerves, nerve roots, spinal cord, meninges or brain were designated to be potentially disease-related.[1] This categorization considers stroke, seizure, movement disorders, transverse myelitis, insidiously progressive cognitive impairments, thought and mood disorders, headaches and neuropathy as a single disease entity, implying that there might be shared pathoetiologic features among these symptoms. Although the 1999 guidelines have been useful in the clinical setting, they have been less useful for dissecting pathological mechanisms of NPSLE or identifying appropriate thera pies. Some impediments to the progression of our understanding of NPSLE seem to relate to the current classification of symptoms; therefore, it is timely to consider a reclassification of symptoms based on a pathoanatomic localization of the disease: vascular, central nervous system (CNS) and peripheral nervous system (PNS).

Vascular disease begins within vessels and does not involve a neuron-specific mechanism; injury depends on the location, duration and degree of vascular compromise. Vascular compromise of the brain or spinal cord from an embolus or thrombosis has been associated with antibodies that bind cardiolipin, phospholipids and other (as yet unidentified) molecules, activate a clotting cascade, and promote a hyper-coagulable state.[2] There is also evidence that these antibodies directly or indirectly activate endothelial cells. The etiology and treatment of thrombosis in the brain vasculature in NPSLE does not differ significantly from the etiology and treatment of thrombosis occurring elsewhere in patients with SLE. Although increases in intracranial pressure can be responsible, headaches in NPSLE are most often a result of vascular pathology: changes in vascular tone that result in headache are likely to relate to effects on endothelial and smooth muscle cells that are mediated by antibodies, cytokines or vasoactive molecules. A therapeutic approach to vascular NPSLE manifestations could involve deletion or inactivation of autoantibodies, interference with the clotting cascade, or inhibition of endothelial cell activation. Although rare, it should be noted that inflammation of small-to-medium-sized blood vessels in the CNS or PNS can also cause vascular disruption.

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In the proposed pathoanatomic scheme, CNS disease would include disorders related to disturbances in the brain parenchyma, such as cognitive dysfunction (assuming it is not related to microinfarcts), mood disorders, psychosis, movement disorders and acute confusional states. Headache might also result from parenchymal disease of the CNS; however, this probably occurs far less frequently than headache resulting from vascular events. For CNS disease to occur, the pathological agent, whether it be antibody, cytokine, chemokine or cells capable of producing these molecules, must cross the blood-brain barrier to affect neurons or other cells within the CNS. These agents might directly cause injury, or recruit CNS-resident cells to mediate an inflammatory process. While some neurotoxic antibodies have been identified,[3–5] it is likely that many more—as yet unidentified—antibodies affect neuronal viability, function, or both, either directly or through their effects on astrocytes and glial cells. CNS symptoms are likely to arise independently of systemic disease activity; the insults that breach the blood-brain barrier might result from infection, hypertension or behaviors such as smoking, and could lead to surges of antibody penetration of the CNS or to chronic small leaks in barrier protection.[6] As the blood-brain barrier regulates access to the CNS, it is not expected that serum levels of potentially neurotoxic proteins will correlate directly with symptoms; however, levels of neurotoxic agents in the cerebrospinal fluid should do so. Protection of the integrity of the blood-brain barrier is a crucial therapeutic consideration. Successful use of neuroprotective agents would rely on their ability to penetrate the blood-brain barrier. Another potential therapeutic approach might be to inactivate antibodies or cytokines before they penetrate the CNS, although this might not alter an ongoing process within the brain. More research is needed to determine if delayed degenerative and regenerative processes develop in the CNS, after the initial immune-mediated damage.

Peripheral neuropathies remain the most problematic manifestations of NPSLE to classify, even with this suggested reclassification. These neuropathies might reflect local vasculitis and represent vascular disease. Alternatively, although the acetylcholine receptor is the only specific antigen that has been identified as a target in the PNS manifestations of NPSLE, it is highly likely that many antigens exist and that they will differ from antigenic targets in CNS disease. For example, anti-N-methyl D-aspartate receptor antibodies can bind to CNS neurons and affect viability and function,[5] but there is little evidence that N-methyl D-aspartate receptors are expressed on peripheral neurons. Antibodies to peripheral nerves have no anatomic barrier to impede interaction with the target antigen; therefore, there should be a direct relationship between the serum antibody titer and clinical symptoms. Because complement components are not limited in the circulation, antibody-mediated damage in the PNS might be more likely to involve complement activation than antibody-mediated damage in the CNS.

This proposed reclassification scheme represents a first draft of a new mechanistic framework for understanding NPSLE. It does not eliminate all problems; there will still be some disease manifestations (such as headache or peripheral neuropathy) that do not clearly fit into a single category. In some cases, imaging techniques or other diagnostic tests might assist in assigning a disease manifestation to a particular neuron-anatomic category. It will also remain critical to eliminate all non-SLE insults as potential etiologic factors before attributing a clinical symptom to NPSLE. Nonetheless, since the location of injury and target antigens is paramount in understanding the mechanisms involved, this reclassification of symptoms should facilitate clinical studies. By distinguishing three distinct subsets of NPSLE, it should be easier to identify causative factors as well as predictors of disease outcomes. Moreover, it will facilitate appropriate patient selection for clinical trials of new therapies and, therefore, enhance the potential of these clinical trials to yield definitive results.

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