Central Nervous System Manifestations of Systemic Lupus Erythematosus

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KEYWORDS

• Neuropsychiatric lupus • Anti-neuronal antibody • Blood–brain barrier dysfunction

KEY POINTS

- Neuropsychiatric systemic lupus erythematosus (NPSLE) is a severe manifestation of systemic lupus erythematosus (SLE) and can occur in about 40% of patients.
- Manifestations can be classified into diffuse manifestations (likely immune mediated) or focal manifestations (likely owing to vascular ischemia).
- Correct attribution of a neuropsychiatric event to active SLE is key and a challenging diagnostic dilemma.
- Important pathophysiologic aspects include the disruption of the blood–brain barrier, allowing passage of reactive antineuronal antibodies into the brain parenchyma.
- Sensitive biomarkers and imaging studies as well as high-quality evidence from clinical trials are needed to improve the diagnosis and management of NPSLE.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease characterized by autoantibody production and immune complex formation. It is the prototypic autoimmune disease, notable for its marked heterogeneity of disease manifestations. Internal organ involvement (such as the kidney and central nervous system) is characteristic of severe disease, and is what drives most of the disease morbidity and mortality.[1,2] Multiple mechanisms have been implicated in playing a role in the pathogenesis of neuropsychiatric SLE (NPSLE), including various arms of the immune system as well as nonimmune and environmental factors that could cause blood–brain barrier (BBB) dysfunction.[3] One of the most difficult aspects of central nervous system manifestations in clinical practice is their correct attribution to active

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SLE and this likely explains the wide range of reported prevalence of NPSLE (6.4%-93%).[4–6] Recent advances within the field include implementation of attribution models, which have been able to better define prevalence of NPSLE to 6% to 12% in the first year of diagnosis and a new calibrated overall prevalence of 19% to 38%.[7] In this review, we focus on central manifestations of NPSLE and summarize the latest understanding of disease pathogenesis, as well as specific clinical scenarios, treatment strategies, and outcomes.

DEFINITION AND CLASSIFICATION

In 1999, the American College of Rheumatology described 19 distinct phenomena, divided into central and peripheral manifestations, that are observed in NPSLE (**Box 1**). This schema was intended to establish a framework for research as well as clinical reporting[8]; however, it is nonspecific and not meant to be used as a diagnostic tool. Manifestations of NPSLE can be also classified into diffuse manifestations (such as psychosis and cognitive dysfunction) or focal manifestations (such as seizures and ischemic events), reflective of different disease mechanisms.

Box 1
Neuropsychiatric syndromes observed in systemic lupus erythematosus

Central nervous system

Aseptic meningitis

Cerebrovascular disease

Demyelinating syndrome

Headache (including migraine and benign intracranial hypertension)

Movement disorder (chorea)

Myelopathy

Seizure disorders

Acute confusional state

Anxiety disorder

Cognitive dysfunction

Mood disorder

Psychosis

Peripheral nervous system

Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome)

Autonomic disorder

Mononeuropathy, single or multiplex

Myasthenia gravis

Neuropathy, cranial

Plexopathy

Polyneuropathy

From The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42(4):599–608.