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Challenges and Approach Considerations of Neurological Manifestations of Systemic Lupus Erythematosus: A Review

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Abstract

Systemic lupus erythematosus is a chronic autoimmune disease with multisystem involvement and a wide range of neurological manifestations. This review aims to explore the variability in the presenting modes of neuropsychiatric lupus Erythematosus (NPSLE). A search strategy was done via various databases, including PubMed, EMBASE, Medline, and Cochrane, to retrieve relevant published articles. Each related article has been summarized and the main findings and conclusion of each manifestation and its main defining feature was made. Analysis was done for approximately twenty studies reveals that headache is the most frequently reported neurological symptom in SLE, followed by seizures, with significant clinical overlap observed with other diseases such as multiple sclerosis. The findings emphasize the diagnostic complexity and underscore the importance of differentiating NPSLE from other conditions with similar neurological presentations. Given the substantial impact on morbidity and the risk of irreversible damage, early recognition and appropriate clinical-radiological correlation are essential for effective diagnosis and management. In conclusion, the diagnosis and management of SLE are challenging for both the clinicians and radiologists. It is very important for specialist to be familiar with the clinical manifestations, imaging findings and complications of NPSLE; and to differentiate it from other causes that share the same clinical and radiological features; in order to have an appropriate scientific-based clinical workup and treatment plan.

Keywords: Key words: systemic lupus erythematosus, seizure, headache.

Introduction

Systemic lupus erythematosus (SLE) is a well-recognized connective tissue disease with multisystem involvement, affecting the musculoskeletal, mucocutaneous, cardiorespiratory, and nervous systems. Historically neurological involvement in SLE was referred to as “lupus cerebritis,” “CNS lupus,” or “neurolupus,” these terms failed to accurately describe the wide spectrum of neuropsychiatric syndromes associated with the disease. The current term, neuropsychiatric systemic lupus erythematosus (NPSLE), more comprehensively describes the complexity of its presentation (1).
NPSLE can affect both the central and peripheral nervous systems. Approximately 40% of NPSLE manifestations are present at the time of SLE diagnosis, and in some cases,

they may precede disease onset (2). Most commonly, it develops within the first year following diagnosis (3). Its clinical presentations range from higher cerebral function abnormalities to involvement of the spinal cord, cerebellum, basal ganglia, cranial and peripheral nerves, and the neuromuscular junction (4).
Symptoms of NPSLE can range from mild, diffuse complaints to acute, life-threatening manifestations. While most cases occur during active disease, it may also present in the absence of serologic or clinical disease activity. Pathologically, the underlying mechanisms are broadly classified as immune/inflammatory or thrombotic/ischemic events. A key pathological feature is the disruption of blood-brain barrier, which facilitates the diffusion of inflammatory cytokines into the cerebrospinal fluid (5). Numerous neuropsychiatric syndromes associated with lupus have been described in the literature; including headache, mood disorders, seizures, cerebrovascular disease, anxiety disorders, psychosis, acute confusional state, myelopathy, aseptic meningitis, movement disorders, while the peripheral nervous system includes: polyneuropathy, cranial neuropathy, plexopathy, mononeuropathy, and autonomic neuropathy(6). This review focus on the clinical approach to manage the neurological complications of SLE, including the diverse presentations and implications for patient outcomes.

Cerebral Vasculitis

Cerebral vasculitis refers to an inflammation of cerebral blood vessels, associated with a high risk of severe neurological complications and poor prognosis. The imaging modality of choice is magnetic resonance imaging (MRI) (6). Contrast enhancement on MRI is often detected in acutely inflamed vascular walls. However, due to the low specificity of MRI findings, brain biopsy remains the gold standard for confirming the diagnosis. Despite its low risk of complications, brain biopsy is not routinely performed (7).

Brain Atrophy

Brain atrophy is considered the hallmark of NPSLE and the most critical MRI marker for its diagnosis and prognosis. It typically progresses slowly over several years and may present as diffuse or focal atrophy with symmetrical involvement of both grey and white matter. The mean age of onset is approximately 42.5 years (8). Diffuse and regional brain atrophy is observed in up to 67% of patients. Brain atrophy correlates with several factors, including the extent of white matter lesions, lacunar infarcts, disease duration, cognitive dysfunction, the presence of antiphospholipid antibodies, and stroke (9).

Demyelinating Syndrome

The demyelinating lesions in NPSLE are primarily distributed in the periventricular white matter, corpus callosum, hypothalamus, medial thalamus, periaqueductal grey matter, dorsal pons, and medulla, including the area postrema. Up to 60% of NPSLE patients may have oligoclonal bands in their cerebrospinal fluid (CSF). Nonspecific demyelination on imaging is also common in SLE patients (10).

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a rare neurological disorder primarily affecting the posterior circulation of the brain. Clinical and radiographic resolution typically occurs within 1–4 weeks, but permanent brain damage can occur if diagnosis and treatment are delayed (11). PRES has been reported in 1.4% of systemic lupus erythematosus (SLE) patients, often in association with antiphospholipid antibodies, hypertension, immunosuppressive therapy, and renal failure. Clinical manifestations include headache, seizures, altered mental status, and visual disturbance (12).

Idiopathic Intracranial Hypertension (IIH)

IIH may present with features such as papillodema, scotomas, and sixth cranial nerve palsy. It has been reported in 0.7–1.5% of patients with SLE. The role of corticosteroids in the management of IIH in the context of SLE remains controversial (13).

Myelitis

Myelitis refers to inflammation of the spinal cord and is characterized by its extension over at least three vertebral segments, a condition known as longitudinally extensive transverse myelitis (LETM). Elevated levels of aquaporin-4 antibodies may indicate a concomitant diagnosis of neuromyelitis optica, which carries a high risk of relapse (14).

Seizures

Seizures occur in 2–8% of SLE patients and are more likely in those who are positive for antiphospholipid or anti-β2 glycoprotein antibodies (15). Stroke and lupus nephritis flares have been associated with seizure onset during disease progression. Recurrence of epileptic seizures, reported in 1.3% of patients and this has been linked to antiphospholipid syndrome (APS) (16).

Headache

One of the most common features of NPSLE is headache. Migraine, with or without aura, and tension-type headaches are the most frequently reported causes (17). Vascular causes of headache include stroke, cerebral venous sinus thrombosis, reversible cerebral vasoconstriction syndrome, and vasculitis has been described. Other possible causes include aseptic meningitis, intracranial neoplasms, intracranial hypertension, neuro-infections, or intracranial hypotension(18).

Stroke

Ischemic stroke develops in up to 20% of lupus patients. Careful evaluation for antiphospholipid syndrome is critical, as it may necessitate anticoagulation therapy rather than antiplatelet treatment (19). There is also a fourfold increased risk of subarachnoid hemorrhage in SLE patients, which is associated with high morbidity and mortality. Vasculitis accounts for stroke in approximately 7% of cases (20).

Myasthenia Gravis

Myasthenia gravis (MG) is rarely associated with SLE, typically presenting as generalized MG with symptoms such as ophthalmoplegia, ptosis, and proximal muscle weakness. In some cases, SLE has developed following thymectomy (21). Both conditions share overlapping features, such as a higher prevalence in females and positivity for antinuclear antibodies (ANA) (22). Most patients have MG preceding the diagnosis of SLE, with thymectomy potentially acting as a precipitating factor for SLE development (23,24). However, thymectomy does not influence the course of established SLE. Patients with both conditions tend to have less frequent cutaneous and renal manifestations (24).

Diagnosis

The diversity of clinical manifestations in NPSLE poses a significant diagnostic challenge. No laboratory or imaging study is sufficiently sensitive or specific enough to establish the diagnosis. The most important step is to exclude the secondary causes, such as infections, metabolic disturbances, adverse drug reactions, endocrine disorders, or malignancy-related manifestations.

A thorough physical and neurologic examination, detailed medical history, and medication review is essential (25). A lumbar puncture with CSF analysis should be performed in all patients presenting with neuropsychiatric symptoms or signs. CSF evaluation is critical for excluding central nervous system infections in suspected cases of NPSLE. The analysis should include cell count with differential, protein, glucose, Gram stain/culture, and tests for venereal diseases. Elevated CSF levels of interleukin-6 (IL-6) can help differentiate NPSLE from other psychiatric conditions (26). Additional studies, such as IgG levels, IgG index, oligoclonal bands, polymerase chain reaction (PCR), and specialized pathogen stains, may also provide valuable diagnostic information. Findings like mild lymphocytic pleocytosis and elevated CSF protein are sometimes observed (27).

Treatment

The management of NPSLE depends on its clinical presentation. Severe neurological manifestations, such as cerebral vasculitis, transverse myelitis, or mononeuritis multiplex, are treated with induction therapy using methylprednisolone (1 gram daily for 3–5 days), followed by disease-modifying therapies, commonly cyclophosphamide (28). Rituximab has also shown effectiveness, while azathioprine is often used for maintenance therapy (29). For refractory cases, plasma exchange may be employed as an adjunct to immunosuppressants(30).

Review of literature

Several published studies were done to identify the variation in the presentation, prognostic factors and predictors of NPSLE development as summarized in table 1 .Meier et al. (31) reported in a meta-analysis that the overall prevalence of NPSLE was 52.2%. The most common manifestation was headache, followed by cognitive dysfunction and mood disorders. In contrast, the prevalence of demyelinating syndrome, autonomic

disorders, Guillain-Barré syndrome, plexopathy, and myasthenia gravis was less than 0.5%. These findings agree with data previous described in literatures.

In regard to the average time from SLE diagnosis to NPSLE manifestations first develop; Fan et al. (32) found that 51% of patients developed neuropsychiatric manifestations within the first year of diagnosis, with seizures being the most common presentation (47%). This may be related to the nature of the disease and aggressiveness of presentation as well as poor compliance to treatment in some patients. Similarly, Rasheed et al. (33) concluded that the most common NPSLE manifestations were headache, depression, neuropathy, and psychosis. The study identified older age and longer disease duration as risk factors, this might be explained by delayed diagnosis in this age group; while predictors included the presence of antiphospholipid antibodies, lupus nephritis, and a high score on the six-item cognitive impairment test.

Occurrence of NPSLE with regard to disease activity has been studied as well. Zhang Y et al. (34) noted that NPSLE frequently occurs when SLE is serologically and clinically active, often associated with higher SLE disease activity index scores (SLEDAI). Useful diagnostic tests include antiphospholipid antibodies (APL), anti-ribosomal-P, anti-neuronal, and anti-ganglioside antibodies. Khare et al. (35) reported that neurological involvement in SLE typically occurs early in the disease course and correlates with disease activity. Neurological improvement was observed in 86% of his study population and most recovered upon optimal and early treatment, while 11% of patients died, and 4% remained unchanged.

Ragab et al. (36) stated that SLE patients with neuropsychiatric symptoms (50.7% of their cohort) often have lower complement levels and elevated lupus anticoagulant antibodies. Associated antiphospholipid syndrome requires baseline monitoring regardless of disease activity as it may affect the treatment plan. Joseph et al. (37) studied 41 SLE patients and identified movement disorders such as parkinsonism and myoclonus early in the disease course. Surprisingly; these conditions responded well to immunosuppressants rather than dopaminergic drugs.

Sharma (38) described MRI findings in cerebral vasculitis (lupus angiitis) as non-specific white matter hyperintensities on T2-weighted sequences, which may or may not enhance with gadolinium. Angiography can reveal focal segmental vascular narrowing and beading.

Huang et al. (39) analyzed 276 patients and had a nine years long follow-up of these patients, and identified prior cyclophosphamide use and high disease activity as risk factors for developing neuropsychiatric manifestations. Poor prognostic predictors included hematologic disorders, frontal-parietal lobe MRI lesions, and psychosis.

Ota et al. (9) highlighted distinguishing features between SLE and MS-associated myelitis. MS lesions are typically T2-hyperintense, enhancing, and span less than three vertebral segments, whereas neuromyelitis optica (NMO) lesions often involve the central spinal cord. Medullary and periaqueductal brainstem lesions are more specific to NMO than MS. Demyelinating lesions in SLE can resemble MS, but the distribution and associated findings may aid differentiation.

Table.1: Summary of SLE studies

Authors	Number of patients/ number of studies metanalysis	Recommendations and conclusion
Meier et al. (31)	Metanalysis of 25 studies	The frequency of variable neuropsychiatric manifestations is different than in individual studies. They concluded that the mean lag time from SLE diagnosis and the first neuropsychiatric SLE manifestation was 4.5 years. Accelerated atherosclerosis and its long-term sequelae are most probably also responsible for NP events among patients with SLE. 193 of 688 patients (28.1%) had neurological manifestations. CNS isolated involvement was present in 70.5% and peripheral nervous system isolated involvement was present in 17.6%, 11.9% had both systems involved. Autoantibodies percentage did not differ in those with and without NPSLE.
Fan et al. (32)	1772 patients	median age of developing NPSLE was 28 years, it developed within one year of SLE diagnosis. Of the 76 NPSLE patients, 51% of cases developed NPSLE within 1 year of the diagnosis. Only 17.1% of patients developed NPSLE at time of diagnosis
Zhang Y et al. (34)	308	This study concluded that the NPSLE mortality was 11.2%. giving this relatively high mortality rate, it was recommended that early diagnosis and appropriate treatment are needed to improve the prognosis
Khare et al. (35)	35 patients	Of those patients who presented with NPSLE, the most common age group was 20–29 years. 66% had seizures, and the least common manifestation was cognitive decline, myelopathy and depression (each was 3%).
Ragab et al. (36)	134 patients	50.7% of the study population had NPSLE. The most frequent manifestations were Headache, seizures and psychosis. Those with NPSLE had lower complement levels and high levels of lupus anticoagulant antibodies.
Joseph et al. (37)	41	Ten patients developed movement disorders as parkinson and myoclonus, four patients developed it early in the disease course., which responded well to immunosuppressantsrather than dopaminergic drugs.
Huang et al. (39)	267	Of this large number and nine years prospective study, the most common neuropsychiatric manifestation was mood disorders and that psychosis was associated with final outcomes. Possible risk factors for mood disorders included focal lesions and presence of >5 MRI lesions. Fronto–parietal and inflammatory lesions were risk factors of psychosis.

Conclusions

The wide variety of the mode of neurological presentation make the diagnosis and management are of real challenge for both the clinicians and radiologists. It's of importance to be familiar with the clinical manifestations, imaging findings and complications of NPSLE; and to differentiate it from other causes that share the clinical and radiological features; in order to have an appropriate scientific-based clinical workup and treatment plan.

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Competing interest statement

None, the authors declare that they have no conflicts of interest.

Ethics statement

The authors declare that the author approved that this research follows the journal's Attach Ethic Approval guidelines as appeared on the journal's author guidelines page.

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