Rheumatology, 2024, **00**, 1–3
https://doi.org/10.1093/rheumatology/keae349
Advance access publication 2 July 2024
Editorial

British Society for Rheumatology RHEUMATOLOGY OXFORD

Editorial

Reflections on central nervous system lupus

Neuropsychiatric (NP) disorders are important in the morbidity (even mortality) in systemic lupus erythematosus (SLE). Aspects of central nervous system (CNS) lupus remain unsatisfactory, notably what constitutes this element of SLE. The American College of Rheumatology (ACR) (in 1971/1982) recognized 'seizures and psychosis' without other causes being identified, such as drugs or metabolic derangements [1]. An ACR working party (1999), however, proposed 19 different clinical features (12 central, seven peripheral) [2].

The European Alliance of Associations for Rheumatology (EULAR) and ACR taskforce produced revised criteria for SLE classification, proposing three NPSLE clinical features: delirium, psychosis and seizures [3]. Peripheral nervous system (PNS) features are not specified.

Challenges remain in the diagnosis of NPSLE. Precise diagnostic methods are lacking, and attributing NP manifestations to SLE is difficult. The ACR working party included depression and anxiety but who, told they have SLE, with warnings about uncertain outcome and the need for long-term steroids/immunosuppressives would not feel anxious and depressed?

Estimates of the frequency of CNS features vary widely. Knowledge of the pathogenesis, progression and management of this condition is incomplete. Limited access to cerebral tissue is evident. Brain biopsies are rarely requested, for diagnosis, pathogenesis or research, compared with renal and skin biopsies for lupus nephritis, or skin disease, respectively.

The pathogenesis of NPSLE is complex and variable (Fig. 1). The widely available and useful (for diagnostic, disease follow-up and subsetting purposes) serological biomarkers in non-CNS lupus are less common in CNS disease. Understanding the pathways leading to NP manifestations is important to facilitate optimized therapies.

The presence of an ongoing chronic inflammatory condition is frequently documented. However, no single pathogenic malfunction explains all NP symptoms. The development of NPSLE arises from diverse factors, including inflammatory cytokines, genetic elements, autoimmune antibodies, disruption of the blood–brain barrier, activation of the complement system and formation of immune complexes. Cerebral vascular ischaemia and thrombosis of small and large vessels and microhaemorrhagic lesions are relatively common in NPSLE patients, and may be linked to accelerated atherosclerosis, and enhanced by immunologic and inflammatory pathways.

Increased permeability of the blood–brain barrier (BBB), subsequent to endothelial lesions caused by vasculitis and vasculopathy, or from direct lesions induced by autoantibodies [e.g. anti-N-methyl-d-aspartate receptor antibodies (anti-NMDAR)] [4] probably contributes to the development of NPSLE, consequent upon the brain being exposed to neuropathic circulating autoantibodies.

Around 20 brain-specific and systemic antibodies are linked to NPSLE [5]. These may lead to neuronal and/or cerebrovascular injury, culminating in neuronal dysfunction and vasculopathy, intrathecal production of inflammatory cytokines and expedited atherosclerosis. Interpreting the pathogenic significance of these antibodies is difficult. The best studied are antiphospholipid antibodies (aPL), which correlate with focal and diffuse neurological manifestations. In the early development of NPSLE, aPL antibodies stimulate endothelial cells, platelets and monocytes, potentially resulting in prothrombotic factors. These autoantibodies may hasten atherosclerosis progression, independently increasing the risk of cerebrovascular ischaemia [6].

Anti-ribosomal P antibodies exhibit a high level of specificity for SLE. Some reports have linked them to mood disorders. They might contribute to persistent depression and, in elevated titers, to a broad spectrum of NPSLE manifestations, encompassing psychosis, seizures and coma [7]. However, these links are highly contentious and not universally accepted [8].

Other antibodies thought to associate with NPSLE include antibodies to anti-aquaporin 4 (anti-AQP4), anti-NMDAR, endothelial antigens (AECAs), ubiquitin carboxyl hydrolase L1 (anti-UCHL1) glyceraldehyde 3-phosphate dehydrogenase (anti-GAPDH) [5].

Complement activation is linked to the underlying mechanisms of CNS inflammation. This activation may be involved in the development of NPSLE [5]. A key element influencing the generation of circulating autoantibodies in NPSLE and their interaction with subsequent thrombotic injuries might connect to complement deposition.

Inflammatory mediators can cause neurological diseases by disrupting the BBB. Neuronal and glial cells produce cytokines and chemokines intrathecally. The BBB disruption permits the entry of circulating autoantibodies. Inflammatory cytokines such as tumor necrosis factor-α (TNF- α), TNF-like weak inducer of apoptosis (TWEAK), interferon-γ (IFN-γ), interleukin-6 (IL-6) and B-cell activating factor (BAFF) are present in the cerebrospinal fluid of patients with NPSLE(5), implying that the inflammatory response is central to NPSLE progression.

IL-6 is the cytokine most strongly associated with NPSLE and holds potential as a diagnostic marker for the disease,

Accepted: 27 June 2024.

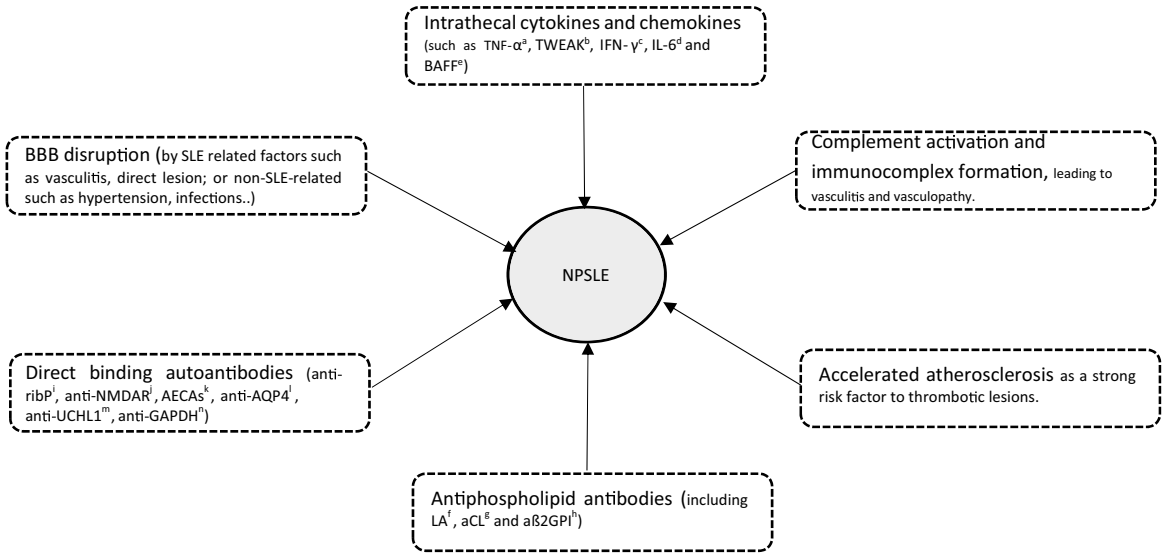

Figure 1. Pathogenesis pathways of NPSLE. [a]tumor necrosis factor-α; [b]TNF-like weak inducer of apoptosis; [c]Interferon-γ; [d]Interleukin-6; [e]B-cell activating factor; [f]Lupus anticoagulant; [g]Anticardiolipin antibodies; [h]Anti–b2-glycoprotein I antibodies; [i]Anti-ribosomal P antibodies; [j]Anti-N-methyl-d-aspartate receptor antibodies; [k]Anti-endothelial antibodies; [l]Anti-aquaporin 4 antibodies; [m]Anti-ubiquitin carboxyl hydrolase L1 antibodies; [n]Anti-glyceraldehyde 3-phosphate dehydrogenase antibodies

with significant specificity and sensitivity, particularly in acute confusional states. Numerous additional autoantibodies and proteins, including anti-microtubule-associated protein 2 antibodies in cerebrospinal fluid and osteopontin, may be biomarkers to identify NPSLE.

The biggest frustration in CNS lupus is the difficulty in designing studies for these patients. It maybe the lack of standardized diagnostic tools or because of an undue concern about morbidity/mortality. Knowledge of the use of biologic drugs in CNS lupus is based upon individual case histories or small case collections. This is unsatisfactory. Current management objectives encompass a dual approach, both symptomatic and causal. Thus, anxiolytics, mood stabilizers, antipsychotics and antidepressants are administered for psychiatric disorders or antiepileptic treatment for seizures; metabolic derangements, increased clotting predisposition and hypertension must also be corrected if present. Corticosteroids and immunosuppressives are invariably co-prescribed.

Papachristos *et al.* [9] reviewed the treatment of inflammatory NPSLE in 90 studies. Only two were randomized controlled trials and one pilot study. High-dose glucocorticoids and intravenous cyclophosphamide remain the cornerstone treatments presenting with severe symptoms caused by neuroinflammation. Azathioprine and mycophenolate are used for maintenance despite the paucity of evidence. Where these drugs are ineffective or when severe symptoms are present, alternatives such as rituximab, intravenous immunoglobulin or plasma exchange are considered.

Among biological therapies, of 14 studies including 166 patients, 12 focused on rituximab and two on belimumab. Rituximab (plus corticosteroids) given to patients refractory to previous therapies showed positive results, with overall clinical response ranging from 73% to 100%. Data about belimumab are scarce and based on small populations, lacking statistical significance.

For ischemic thromboembolic manifestations, especially in the presence of the antiphospholipid syndrome, anticoagulation, with antiplatelet therapy, statins and antimalarials are used to help prevent recurrent thrombosis [5].

Thus, despite the significant morbidity and mortality associated with NPSLE, current understanding of these manifestations remains seriously limited. Investigations into the underlying pathogenesis of NPSLE are urgently needed, aiming to identify more precise targeted, potentially life-saving therapies.

Data availability

Not applicable.

Funding

No financial support was provided for the writing of this article.

Disclosure statement: The authors have declared no conflicts of interest.

Joana Moutinho[1] and David A. Isenberg[2,*]

[1]Department of Internal Medicine, Centro Hospitalar Universitário do Algarve—Hospital de Portimão, Portimão, Portugal
[2]Department of Ageing, Rheumatology and Regenerative Medicine, Division of Medicine, University College London, London, UK

*Correspondence to: David A. Isenberg, Department of Ageing, Rheumatology and Regenerative Medicine, Division of Medicine, University College London, 4th Floor, 5 University Street, London WC1E 6JF, UK. E-mail: d.isenberg@ucl.ac.uk

References

1. Tan EM, Cohen AS, Fries JF *et al.* The 1982 revised criteria for the classification of Systemic Lupus Erythematosus. Arthritis Rheum 1982;25:1271–7.
2. Gordon C, Alarcón GS, Straaton KV *et al.*; ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes ACR ad hoc committee on neuropsychiatric lupus nomenclature. Arthritis Rheum 1999; 42:599–608.
3. Aringer M, Costenbader K, Daikh D *et al.* 2019 European League Against Rheumatism/American College of Rheumatology

classification criteria for systemic lupus erythematosus. Ann Rheum Dis 2019;78:1151–9.
4. Ota Y, Srinivasan A, Capizzano AA *et al.* Central nervous system systemic lupus erythematosus: pathophysiologic, clinical, and imaging features. Radiographics 2022;42:212–32.
5. Liu Y, Tu Z, Zhang X *et al.* Pathogenesis and treatment of neuropsychiatric systemic lupus erythematosus: a review. Front Cell Dev Biol 2022;10:998328.
6. Schwartz N, Stock AD, Putterman C. Neuropsychiatric lupus: new mechanistic insights and future treatment directions. Nat Rev Rheumatol 2019;15:137–52.
7. Jeltsch-David H, Muller S. Neuropsychiatric systemic lupus erythematosus: pathogenesis and biomarkers. Nat Rev Neurol 2014; 10:579–96.
8. Shi ZR, Cao CX, Tan GZ, Wang L. The association of serum antiribosomal P antibody with clinical and serological disorders in systemic lupus erythematosus: a systematic review and meta-analysis. Lupus 2015;24:588–96.
9. Papachristos DA, Oon S, Hanly JG, Nikpour M. Management of inflammatory neurologic and psychiatric manifestations of systemic lupus erythematosus: a systematic review. Semin Arthritis Rheum 2021;51:49–71.

Rheumatology, 2024, 00, 1–3
https://doi.org/10.1093/rheumatology/keae349
Editorial