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REVIEW

Central nervous system manifestations in rheumatic diseases

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Abstract
As the role of neurologists in managing patients with rheumatic diseases expands, collaboration between rheumatologists and neurologists becomes increasingly vital. This literature review provides an overview of the central nervous system (CNS) manifestations of major autoimmune rheumatic disorders, which may include parenchymal brain and meningeal disease (stroke, meningoencephalitis, meningitis), myelopathies, psychosis, chorea, seizure disorders, and various forms of cephalea. Novel findings linking specific autoimmune markers to CNS damage reveal a direct, previously underestimated link between systemic inflammation and neural injury. Besides, with the increasing use of biological therapies, it is crucial to recognize when neurological manifestations are related to adverse events of therapy, as this may significantly influence treatment decisions. Neurologists play a key role in this assessment, working closely with rheumatologists. Overall, addressing CNS involvement in rheumatic diseases is important for improving patient outcomes and advancing medical knowledge in this complex field. A thorough understanding of the neurologic aspects of rheumatic diseases is essential for optimal patient care, necessitating a multidisciplinary approach to management.

Keywords Central nervous system · Rheumatic diseases · Biological therapies · Adverse events · Lyme neuroborreliosis · Multidisciplinary approach

Introduction

The past decades have witnessed a notable rise in the attention given to rheumatic diseases (RDs) by healthcare professionals. This heightened focus can be attributed to the increasing prevalence of these diseases and the introduction of new and effective, albeit expensive, pharmaceutical treatments. Furthermore, RDs frequently result in prolonged disability and are associated with elevated mortality rates when compared to the general population [1, 2].

Rheumatologic disorders are distinguished by a diverse array of multiorgan symptoms and comorbid conditions. One of the greatest clinical challenges confronting rheumatologists is the timely diagnosis and appropriate treatment of neurological disorders linked to RDs [1, 3, 4].

Novel findings reveal a direct, previously underestimated link between specific autoimmune markers and central nervous system (CNS) damage, illustrating the connection between systemic inflammation and neural injury. Also, with the increasing use of biological therapies, recognizing when neurological symptoms may be related to adverse events of these treatments is crucial, as this significantly influences treatment decisions. As neurologists play a key role in this assessment, working closely with rheumatologists, their teamwork should incorporate the latest advances in the study of nervous and immune system interactions.

Search strategy and methods

Our literature review involved the comprehensive search in Medline/PubMed, Scopus and DOAJ from 1994 till June 2024. The keywords used in the search were “neurological manifestation of rheumatic diseases”, “rheumatic diseases and central nervous system involvement” “neurological complications of rheumatic diseases”.

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Prevalence

According to various reports (Table 1), the incidence CNS involvement in RDs varies widely, ranging from 1% in patients with rheumatoid arthritis (RA) [5] to as high as 96.4% in cases of systemic lupus erythematosus (SLE) [6]. Cerebrovascular pathology often plays a predominant role in the clinical presentation of diseases such as antiphospholipid syndrome, Takayasu's disease, Behçet's disease, nodular polyarteritis, and Sjögren's syndrome (SjS.) Furthermore, recent reports have emerged concerning manifestations of CNS involvement in individuals with RA [7, 8] and spondyloarthritis [9]. Table 2 presents the main neurological manifestations and the rheumatological diseases in which they occur.

The aforementioned pathologies frequently coincide with the development of both vascular and inflammatory brain lesions, particularly in younger individuals. This often results in the onset of both acute and chronic cerebral circulation disorders, highlighting the substantial importance of addressing this issue [10].

The wide range of neurological syndromes in autoimmune systemic diseases can be explained by the similarity in structure and functionality between the nervous and immune systems. This likeness allows for cross-reactivity, where immune responses directed at foreign antigens can inadvertently target neural tissues due to molecular mimicry [11].

Neurological symptoms in patients with different rheumatologic profiles

Neurological pathology in rheumatologic diseases has the following characteristics [5, 12–16]:

1. The diversity of clinical manifestations, resulting from the combination of neurological and somatic disorders, especially in rheumatic lesions of the musculoskeletal system.
2. Multiple and multi-level involvement of the nervous system, with the development of mono- and polyneuropathies, myelopathies, and encephalopathies associated with multifocal brain lesions.
3. High frequency of neurological disorders in young age groups (in patients with systemic lupus erythematosus and antiphospholipid syndrome, the first occurrence of cerebral circulation disorders often occurs before 25 years of age).
4. Autoimmune pathology can increase the risk of infectious-inflammatory lesions of the nervous system through immunosuppression, disruption of the blood-brain barrier function, making the brain more vulnerable to infectious agents such as viruses or bacteria.
5. Rapid and significant regression of acute neurological symptoms under the influence of glucocorticosteroids and cytostatics, and the absence of such regression with traditional protocol-based neurological treatment.
6. Possibility of partial or complete regression of neurological and psychiatric disorders in patients with prolonged remission of rheumatic diseases.

According to reports by Sofat et al., one of the most severe neurological manifestations necessitating prompt diagnosis and treatment is CNS involvement, particularly encephalitis and meningoencephalitis [14]. Considering the statistics presented by Mitratza et al., inflammatory brain diseases have emerged as one of the primary contributors to premature mortality in instances of concurrent neurological and rheumatic pathology [17, 18].

One of the most prevalent types encountered in this patient cohort is Lyme neuroborreliosis (LNB), which manifests as a clinical presentation of Lyme borreliosis (LB), impacting both the central and peripheral nervous system (PNS) [19–22].

Neurological symptoms in patients of a rheumatologic profile can be categorized into three distinct groups:

First, symptoms that arise directly due to the rheumatic condition itself, influenced by its pathophysiological characteristics, such as neurological and neuropsychiatric symptoms associated with rheumatic conditions [13].

Second, symptoms that occur as complications resulting from the treatment applied, including those induced by immunosuppression from the use of specific rheumatologic medications like cytostatic and immunobiological therapy [23–25]. Table 3 focuses on the effects immunobiological therapies on CNS. The effects of other anti-rheumatic drugs on CNS have been well reviewed elsewhere [14].

And finally, symptoms related to antibody-associated autoimmune encephalitis which results from an immune response against neuronal autoantigens, leading to antibody production. This condition stands as one of the most prevalent causes of non-infectious encephalitis [26–28].

Such classification approach aids in better understanding and determining optimal treatment strategies for patients with rheumatic diseases accompanied by neurological symptoms.

Rheumatic conditions most frequently linked with concurrent neurological symptoms primarily encompass connective tissue diseases and vasculitides. These conditions can manifest in diverse ways, including unexplained delirium, cognitive decline, or depression. Autoimmune encephalitis can exhibit diffuse manifestations or localize to regions such as limbic, brainstem, or basal ganglia, resulting

Table 1 Selected studies featuring CNS involvement in rheumatologic disorders

References	Type of study	Study population	Comments
Meier et al. [6]	A systematic review and cohort study	688 patients of Swiss SLE cohort and meta-analysis of 22 studies	Frequency of NPSLE ranged from 10.6–96.4%. Severe events including cerebrovascular accidents, seizures and psychosis appeared in 7.1%, 5.3% and 6.5% of patients, respectively.
Fan et al. [7]	Retrospective case series study	933 patients with RA	The symptoms of meningitis occurred after onset of arthritis in five patients and before onset in one patient. Headache, hyperacute focal neurological deficits and seizures were the most prevalent clinical neurologic features.
Yang et al. [9]	Case report	1 patient	A 54-year-old male with untreated SpA and a 17-day history of headache, malaise, fever and hyperintense signals in the frontoparietal lobe and corpus callosum on MRI. The patient improved with corticosteroid therapy.
Budhram et al. [10]	Case report	2 patients	Two patients developed striatal (basal ganglia) encephalitis, a rare variant of NPSLE.
Bradshaw et al. [23]	Review and cases report series	2 patients	Patients on immunosuppressive therapy for RD and CNS infections
Warnatz et al. [25]	Review and cases report	3 patients	Three patients with either longstanding or suspected systemic rheumatic diseases (SLE, vascultitis with polyangiitis, and cerebral vasculitis) who presented with various neuropsychiatric symptoms are discussed.
Kitamura et al. [27]	Case report	1 patient	A report of 57-year-old man who presented with subacute headache, depression, and anorexia before the onset of RA. Brain MRI revealed medial temporal lobe lesions. Immunotherapy improved symptoms.
Angst et al. [28]	Case report	1 patient	A report of a 44-year-old female with a history of SLE with asthenia and myalgia 7–10 days before admission, followed by anterograde amnesia and temporal disorientation.
Kalaszi et al. [42]	Case report	1 patient	A report of a 55-year-old man with presented with chest pain, right lower limb weakness, urinary and bowel dysfunction and spinal cord infarction on MRI. Lyme immunoblot confirmed intrathecal IgG to borrelia.
Ogrinc et al. [45]	Retrospective, cohort study	77 patients attending LB outpatient clinic between November 2005 and October 2013	Common symptoms/signs included radicular pain (100%), sleep disturbances (75%), erythema migrans (60%), headache (47%), fatigue (44%), malaise (39%), paresthesias (33%), peripheral facial palsy (36%), meningeal signs (20%), and pareses (7.8%).
Hieber et al. [52]	A case-report	1 patient	A case of acute neuroborreliosis that manifested as extended isolated cervical myelitis.
Knudtzen et al. [53]	A retrospective cohort study	431 patients with LNB	Common symptoms included painful radiculitis (6%), cranial nerve palsy (43%), and headache (28%). Post-treatment residual symptoms affected 28% of patients, with delayed treatment initiation significantly associated with higher risk.
Akkurt et al. [56]	A case-report	1 patient	Neuroradiological interventions, such as spasmolysis, PTA, and, if necessary, stenting, can and should be considered in cases of LNB-induced vasculitis and stroke that do not respond to optimal medical treatment alone
Smíšková et al. [63]	Retrospective observational study	241 patients with LNB	In LNB patients, facial nerve palsy was the most frequent neurological deficit (117patients; 79.6%), followed by lower limb paresis in 23 patients (15.6%). Of 134 LNB paretic patients who completed follow-up. Paresis resolved within 3 weeks in 53 LNB patients (39.5%).

AIRD autoimmune rheumatic disease(s), *CNS* central nervous system, *CSF* cerebrospinal fluid, *LB* Lyme borreliosis, *LNB* Lyme neuroborreliosis, *NPSLE* neuropsychiatric systemic lupus erythematosus, *MRI* magnetic resonance imaging, *RA* rheumatoid arthritis, *RD* rheumatological disease(s), *SSc* systemic sclerosis, *SLE* systemic lupus erythematosus, *TIA* transient ischemic attack, *TNF* tumour necrosis factor, *SpA* spondyloarthritis

Table 2 Central nervous system manifestations in rheumatic diseases

Neurologic symptoms and syndromes	Rheumatologic entitites
Meningoencephalitis	SLE, SjS, Behcet's disease, SpA, RA, Lyme disease, Vasculitis
Aseptic meningitis	SLE, SjS
Stroke	SLE, Vasculitis, Antiphospholipid syndrome, Takayasu's arteritis
Psychosis	SLE
Encephalopathy	SLE, SjS, Vasculitis
Seizure	SLE, SjS, Behcet's disease
Headaches	SLE, SjS, Behcet's disease, Vasculitis, Lyme disease, Antiphospholipid syndrome
Myelopathy	SLE, SjS, RA, Lyme disease, Antiphospholipid syndrome
Chorea	SLE, Antiphospholipid syndrome,

RA rheumatoid arthritis, *SjS* Sjögren syndrome, *SLE* systemic lupus erythemetosus, *SpA* spondyloarthritis

Table 3 Reported adverse effects of immunobiological therapy for rheumatic diseases on the central nervous system

	Neurologic Reactions	
	EMA [70]	FDA [71]
Adalymumab	No reported effects in animal studies. Demyelinating disorders (including multiple sclerosis.	Rare cases of new onset or exacerbation of CNS demyelinating disease, including multiple sclerosis and optic neuritis.
Certolizumab	Rare cases of new onset or exacerbation of demyelinating disease, including multiple sclerosis and seizure disorder.	Demyelinating disease, exacerbation or new onset, may occur.
Etanercept	Rare reports of CNS demyelinating disorders.	Rare cases of new onset or exacerbation of central nervous system demyelinating disorders; optic neuritis, multiple sclerosis, and new onset or exacerbation of seizure disorders.
Golimumab	Dizziness, headache, paraesthesia Balance disorders Demyelinating disorders, dysgeusia	CNS demyelination
Infliximab	New onset or exacerbation of clinical symptoms and/or radiographic evidence of CNS demyelinating disorders, including multiple sclerosis.	Rare cases of seizures and/or radiographic evidence of central nervous system demyelinating disorders, including multiple sclerosis and optic neuritis.
	Interleukin-6-receptor inhibitor	
Sarilumab	No information	No information
Tocilizumab	No information	Multiple sclerosis
	T-cell co-stimulation modulator	
Abatacept	No information	Headache, dizziness
	anti-B-cell (CD20)	
Rituximab	No information	Progressive multifocal leukoencephalopathy Dizziness Anxiety
	Interleukin-17 A inhibitors	
Secukinumab	Headache	No information
Ustekinumab	Common: Dizziness, headache Uncommon: Facial palsy	Headache Dizziness Depression
Guselkumab	Headache	Headache
	Janus kinase inhibitors	
Tofacitinib	Headache Paraesthesia	Increased risk of serious heart-related events such as heart attack, stroke or blood clots.
Baricitinib	Headache	No information

CNS central nervous system, *FDA* U.S. Food and Drug Administration, *EMA* European Medicines Agency

in various symptoms. Common presenting symptoms may encompass unexplained delirium, psychosis, catatonia, strokes, and seizures [26, 29].

As of today, the most extensive research available in scientific databases pertains to the manifestation of CNS involvement in SLE [29, 30].

The most extensive research to date was conducted by Meier et al. [6], who analysed 530 studies spanning from January 1999 to January 2020. Additionally, a retrospective study was undertaken, covering data collected between April 2007 and August 2019 from 688 patients sequentially enrolled in the Swiss SLE Cohort Study. It was found that

neuropsychiatric systemic lupus erythematosus (NPSLE) ranged from 10.6 to 96.4%. Severe events, including cerebrovascular insults, seizures, and psychosis, occurred in 7.1% of cases. The authors stress the importance of regular neuropsychological testing and imaging for all SLE patients, given that the prevalence of neuropsychiatric disorders in this cohort significantly exceeded that of similar population-based studies. Moreover, NPSLE has been linked to increased morbidity and mortality.

According to the report by Ozgocmen et al. [30], the course of SjS has demonstrated similarly serious implications. CNS involvement was observed in nearly 48% of cases, characterized by both focal (such as sensorial and motor deficits, brain stem and cerebellar lesions, seizures, migraines, etc.) and non-focal (including encephalomyelitis, aseptic meningitis, neuropsychiatric dysfunctions) findings, as well as multiple sclerosis-like illness and optic neuritis.

Despite the gravity of neurological symptoms linked to conditions such as SLE, Sjögren's syndrome, or vasculitides, their potential neurological manifestations are well-recognized and extensively documented. Guidelines for their diagnosis have been established and integrated into the latest recommendations for patient management. However, despite considerable interest from scientists across various specialties (including infectiologists, rheumatologists, and dermatologists), neurological manifestations of Lyme disease have garnered remarkably little attention. Given the high prevalence, frequent disability, and occurrence of fatal cases, serious attention to the issue of tick-borne borreliosis is warranted.

Exploring the triad: Lyme disease, rheumatology, and the CNS

Autoimmune and infectious diseases trigger inflammation that can affect the CNS. While CNS infections typically affect cognition, other non-CNS infections can indirectly influence cognition. Many patients with autoimmune and/or infectious diseases undergoing neuropsychological evaluation already have a preliminary diagnosis [31–33].

In the scientific literature pertaining to research conducted in North American and European countries, there has been a troubling increase in the prevalence of Lyme disease (LD) in recent decades. As early as 1990, an article published in the New York Times cited statistical data indicating that LB in the USA is the second fastest-growing infectious disease after HIV infection [34].

According to the Centers for Disease Control and Prevention (CDC) in the USA, the incidence of LD in endemic areas of Europe and America reaches 200 cases per 100,000 population [35, 36].

The European Centre for Disease Prevention and Control reports that LD is now the most common natural focal disease in Europe. The number of cases in Europe has been steadily increasing, with more than 360,000 cases reported during the year 2014. Central Europe, including the Czech Republic, Estonia, Lithuania, and Slovenia, has the highest incidence of Lyme borreliosis, with over 100 cases per 100,000 population [37, 38].

According to WHO experts, the number of registered cases is at least 5 times lower than the actual number. In the United States, in 2022, the Centers for Disease Control and Prevention reported 63,000 cases of LB. However, recent estimates using other methods suggest that approximately 476,000 people may be diagnosed with LD each year [39, 40]. A similar indicator for Ukraine approaches around 4,500 cases per year [41].

Unfortunately, a considerable proportion of those affected often do not come under the care of neurologists and rheumatologists. Instead, they seek help from other specialists. The diagnoses presented by patients in medical facilities, such as rheumatoid arthritis, meningitis, encephalitis, arthritis, SLE-like syndrome, scleroderma, fibromyalgia, myocarditis, pericarditis, and arrhythmias, offer little chance of a favorable prognosis. This unfortunate outcome stems from an unwitting encounter with an infected tick. Although neurological manifestations are a relatively rare complication of LD, they constitute the most common cause of severe illness and fatalities [42–44].

Early LNB (Fig. 1) constitutes over 95% of neurological presentations, with symptoms emerging within six months of infection [45]. Acute meningitis caused by Borrelia is frequently the initial manifestation of early LNB. It typically manifests during the secondary phase of the illness, affecting approximately 20% of untreated patients, with a higher prevalence observed among children and teenagers. This form of meningitis accounts for 16% of all cases characterized by lymphocytic meningitis. Moreover, acute borrelia meningitis often accompanies cranial neuritis, with the facial nerve being the most commonly affected, alongside radiculoneuritis. These collective symptoms frequently culminate in the development of Bannwarth syndrome or meningoradiculitis, which are hallmark indicators of LNB [45–47]. These conditions can mask central nervous system involvement and be considered as a cause of rheumatic disease activity [48].

Late-stage LNB (Fig. 2) affects fewer than 5% of patients, persisting for a duration ranging from 6 months to several years. The onset of late neurological manifestations following infection can vary significantly over time. Rauer reported that this period ranges from 6 months to 17 years, with an average of 5 years. Changes associated with late LNB may be preceded by peripheral or central nervous

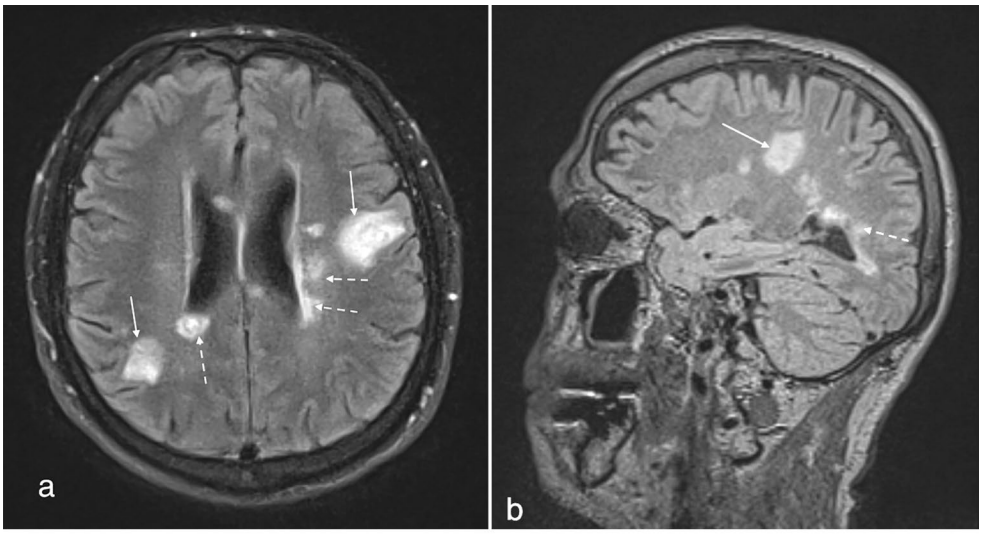

Fig. 1 Axial (**a**) and sagittal (**b**) brain T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence MRI scans of a 56-year-old male with early neuroborreliosis demonstrate foci of high-signal intensity (*solid arrows*) appearing as "bright" lesions affecting the white matter of the parietotemporooccipital regions, with a predilection for the periventricular area (*dashed arrows*). Clinically, the patient presented with fever, headaches, elements of Wernicke's aphasia and vestibular ataxia. He was diagnosed with Lyme encephalitis

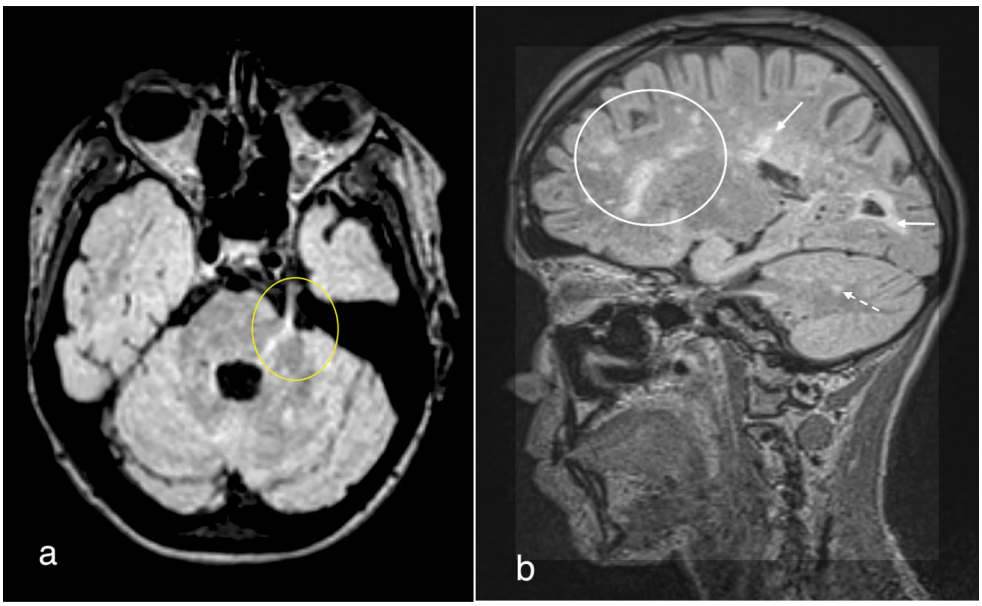

Fig. 2 Axial (**a**) and sagittal (**b**) brain T2-weighted FLAIR sequence MRI scans of a 29-year-old female with late neuroborreliosis show increased signal intensity in the pons at the site of the origin of the left trigeminal nerve and in the left trigeminal nerve itself (*yellow circle*). Additionally, multiple confluent subcortical and white matter hyperintense lesions are seen in the frontoparietal (*white circle*) and periventricular areas (*solid arrows*), as well as in the cerebellum (*dashed arrow*). Clinical manifestations in this patient included trigeminal neuropathy, right-sided hemihypesthesia, and lower-limb peripheral polyneuropathy. She was diagnosed with Lyme encephalomyelitis

system manifestations in the early phase, or conversely, they may be the initial neurological complications of the disease [49–51]. M. Hieber suggested that a late form of LNB typically presents as encephalomyelitis, characterized by a spastic-atactic gait and bladder dysfunction [52]. According to a recent Swedish study, the prevalence of encephalitis among LNB patients is 3.3%, and the yearly LNB encephalitis incidence is 0.93–1.35 cases per million inhabitants [53].

In rare cases, LNB can be associated with cerebral vasculitis, which may lead to cerebrovascular events such as transient ischemic attacks, intracranial hemorrhage, or ischemic stroke [54–56]. In patients with rheumatic diseases, there arises a need for careful differential diagnosis in antiphospholipid syndrome, which can be secondary to central nervous system vasculitis and systemic vasculitides [57].

The mechanism of neural tissue damage in LNB remains incompletely understood. There is ongoing inquiry into how *Borrelia burgdorferi* (Bb) manages to breach the CNS, given the protective barriers of the blood-nerve, blood-cerebrospinal fluid, and blood-brain barriers. It is generally believed that Bb disseminates within the human host through either the bloodstream or along peripheral nerves. The argument favoring the bloodstream route is supported by the ability to culture Bb from blood samples of LD patients. Moreover, many other bacteria utilize the bloodstream pathway [58, 59]. Also, the substantial prevalence of peripheral nerve impairment suggests consideration of the pathway along these nerves [58, 60–62]. The impairment of neural cells in LNB might result from borreliae adhering to nerve or glial cells, inducing direct cytotoxicity and cross-reactity against neural tissue antigens [58, 63, 64].

Immunological markers of CNS lesions

Research on the link between immunological markers and CNS lesions often focuses on SLE and antiphospholipid syndrome (APS). Brain-reactive antibodies penetrate the CNS through compromised barriers, attacking CNS components and causing damage. Antibodies to phospholipids (aPL) are found in 10–44% of SLE patients, leading to thrombus formation and atherosclerosis, and disrupting the BBB. In lupus chorea patients, aPL prevalence can reach up to 92%. Non-thrombotic neurological issues, like seizures, headaches, transverse myelitis, sensorineural hearing loss, and multiple sclerosis, affect up to 40% of patients with high aPL levels. Seizures occur in about 10% of APS patients, either due to vascular lesions or without stroke evidence. In vitro studies suggest aPL interact with neuronal membranes, linking APS to epilepsy. Strongly positive aPL, IIF-ANA, anti-SS-A/Ro, and anti-RNP antibodies are found in APS patients Transverse myelitis (TM), though rare in APS (< 1% prevalence), causes acute thoracic spinal cord inflammation, resulting in sensory loss, motor, and sphincter disturbances. SLE shows a strong link between aPL positivity and TM [65–67].

Antibodies against N-methyl-D-aspartate receptors (NMDAR) are present in 30–40% of SLE patients, causing neuronal death via increased calcium influx, leading to glutamate excitotoxicity, mood disorders, acute confusion, and cognitive dysfunction. Anti-Rib-P antibodies, found in 46% of SLE patients, target neurons in the hippocampus and limbic system, associated with psychosis and NPSLE-related conditions like seizures, coma, and aseptic meningitis. Antibodies against aquaporin 4 (anti-AQP4) in SLE patients indicate brain involvement, transverse myelitis, and recurrent optic neuritis, causing selective astrocyte destruction and suggesting neuromyelitis optica (NMO). Other autoantibodies, such as anti-MAP2, anti-SBSN, anti-U1-RNP, and anti-GABAR(B), are linked to autoimmune processes but need more research. Anti-MAP2 antibodies associate with diffuse NPSLE conditions like psychosis and seizures. Anti-U1-RNP antibodies are linked to aseptic meningitis and can induce pro-inflammatory cytokines [68, 69].

Conclusions

The presence of inflammation in the meninges or brain parenchyma may indicate the activity of autoimmune rheumatic diseases (RA, SpA, SLE, SjS and vasculitides), highlighting the complex interplay between immune dysregulation and CNS pathology. Conversely, CNS lesions in this patient cohort are associated with infectious processes, underlining the importance of considering multiple etiologies in the differential diagnosis of inflammatory CNS disorders. Autoimmune and infectious disorders should be meticulously evaluated in patients with rheumatic diseases who present with inflammatory CNS involvement, such as meningitis or encephalitis, as prompt recognition and treatment are crucial for optimal outcomes. Early assessment of suspected autoimmune encephalitis should include evaluating the activity of specific rheumatic diseases, which can guide therapeutic decisions and improve patient management strategies. Furthermore, in cases of autoimmune processes without specific associated autoantibodies, a thorough search for infectious disorders is warranted, particularly targeting pathogens such as Lyme disease, given its potential to mimic autoimmune CNS pathology. Collaboration between rheumatologists, neurologists, and infectious disease specialists is essential for comprehensive evaluation and management of these complex cases. Additionally, ongoing research into the mechanisms underlying autoimmune and infectious CNS disorders is imperative to enhance diagnostic accuracy and develop targeted therapies. By integrating clinical, laboratory, and imaging findings, clinicians can optimize patient care and minimize the risk of long-term neurological sequelae. Overall, a multidisciplinary approach is paramount in navigating the diagnostic and therapeutic challenges posed by inflammatory CNS disorders in patients with rheumatic diseases.

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