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Review

Neuropsychiatric Manifestations in Systemic Autoimmune Diseases

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Abstract: Autoimmune diseases are heterogeneous, multifactorial disorders defined by a loss of immunological tolerance to self-antigens, resulting in chronic inflammation and tissue damage. Even though the immune system dysregulation most commonly elicits physical symptoms, neuropsychiatric manifestations are frequently observed in autoimmune diseases and are associated with increased morbidity, elevated mortality, and a marked decline in health-related quality of life. Although extensively characterized in systemic lupus erythematosus (SLE) due to its epidemiological relevance and diagnostic complexity, neuropsychiatric involvement holds clinical significance across a wider spectrum of rheumatologic disorders. The frequent co-occurrence of connective tissue disorders with mood and anxiety symptoms suggests shared etiological mechanisms. The early identification of neuropsychiatric manifestations in patients with chronic autoimmune diseases represents the cornerstone of clinical management, given the substantial impact these symptoms have on individuals already burdened by debilitating conditions. We reviewed the principal neuropsychiatric manifestations associated with selected systemic autoimmune diseases: the novelty of this research lies not only in its approach to autoimmune-related neuropsychiatric symptoms but also in the special emphasis placed on the immunopathogenic mechanisms potentially responsible for these manifestations and, more significantly, on therapeutic decision-making, including an evaluation of treatment strategies targeting immune dysregulation and their potential impact on the neuropsychiatric profile, to optimize clinical outcomes and ensure patients have a comprehensive cure.

Keywords: autoimmune disease; inflammatory myopathies; myositis; neuropsychiatric manifestations; rheumatoid arthritis; systemic lupus erythematosus

1. Introduction

Over the past few years, there has been increasing recognition of the complex, bidirectional relationship between the body and mind, especially in the context of autoimmune diseases. These conditions, marked by immune system dysregulation, frequently involve not only physical symptoms but also cognitive, emotional, and behavioural disturbances. The complex mutual interaction between psychological stress, neuroendocrine activity, and immune function highlights the deep connection between mental and physical health in the onset and progression of autoimmune diseases. Shedding light on these interactions is important to improve diagnostic

precision, simplify patient management, and adapt therapeutic regimens. Individuals with immune-mediated disorders often exhibit a wide spectrum of neuropsychiatric manifestations, prompting interest in the possibility of shared etiological processes. The high comorbidity between connective tissue diseases and psychiatric symptoms, mood and anxiety disorders being the most prominent, suggests the possibility of shared risk factors [1]. A recent study based on the Swedish population examined the association between primary humoral immunodeficiencies (PID), autoimmune disorders, and psychiatric illness [2]. The results showed that PID individuals were more likely to experience a wide range of psychiatric illnesses and suicidal behaviour compared to the general population. This association was particularly prominent among females and individuals with both PID and an autoimmune disorder [2]. It has been supposed that shared genetic susceptibilities or exposure to similar environmental stressors, including chronic stress or psychological trauma, may increase the risk of developing both autoimmune and psychiatric disease [3]. Evidence suggests that, in some cases, neuropsychiatric symptoms may be due to side effects of immunosuppressive treatment used to manage autoimmune diseases. This has created a renewed interest in steroid-sparing therapies, particularly the potential use of intravenous immunoglobulin (IVIg), which may help modulate immune dysregulation and address associated neuropsychiatric manifestations [4].

An important question in research and clinical practice is how to distinguish whether the neuropsychiatric symptoms observed in such patients stem from coexisting primary psychiatric disorders or are the consequence of systemic inflammation and immune-mediated mechanisms. We will then discuss the relevant neuropsychiatric manifestations in selected autoimmune diseases. Special focus will be given on therapeutic decision-making, including a discussion of treatment strategies aimed at targeting immune dysregulation and their potential impact on neuropsychiatric symptoms.

2. Connective Tissue Diseases

2.1. Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease caused by an immune system dysfunction that leads to the production of autoantibodies directed against nuclear antigens. These autoantibodies, along with the immune complexes they form, trigger an inflammatory response that can affect skin, joints, kidneys, heart, lungs, and the nervous system. SLE presents with a wide range of clinical manifestations, from mild cutaneous symptoms to severe organ complications. Neuropsychiatric manifestations of SLE, commonly referred to as Neuropsychiatric Systemic Lupus Erythematosus (NPSLE), represent some of the most challenging complications to manage. This condition arises when the autoimmune response extends to the nervous system, resulting in a broad spectrum of neurological and psychiatric dysfunctions. Importantly, several psychiatric manifestations have been incorporated into the SLICC-2012 classification criteria and the more recent EULAR/ACR-2019 criteria, underlining the recognized importance of these clinical features in the definition of SLE. Furthermore, it should be noted that neuropsychiatric manifestations contribute to both SDI and SLEDAI-2K scores, emphasizing their influence on disease activity and long-term organ damage assessment [5,6]. NPSLE symptoms are highly heterogeneous in both type and severity: cognitive dysfunction is reported in SLE patients and includes attention deficits, learning disorders, and memory impairment [7]. Such alterations may range from mild cognitive impairment to significant dysfunctions affecting daily and occupational activities. Patients with NPSLE often exhibit slowed executive functioning. Anxiety and depression are among the most frequently observed psychiatric disorders, with depression being more prevalent in SLE patients than in the general population (8.5%) [8]. NPSLE may manifest with acute confusional states, characterized by altered consciousness, disorientation, and attention deficits. In some cases, psychotic symptoms such as hallucinations and delusions may occur. Seizures represent a severe neurological manifestation of NPSLE and may be focal or generalized. Frequent and intense headaches are common among SLE patients and may be associated with disease activity. Peripheral nervous system disorders include neuropathies such as polyneuropathy and mononeuropathy, which are characterized by pain, muscle weakness, and paraesthesia. Less common symptoms may include cerebellar ataxia, movement disorders such as chorea, myelopathy, and autonomic disturbances (Table 1) [9]. The mechanisms leading to neuropsychiatric manifestations in SLE are complex and still under investigation. Several factors may contribute, including autoantibodies. Antibodies to N-methyl-D-aspartate receptor (anti-NMDAR antibodies) target the NMDA glutamate receptor in the central nervous system. This ionotropic receptor is crucial for synaptic plasticity, learning, and memory. NMDA receptor activation increases calcium influx into neurons; excessive calcium influx may lead to excitotoxicity, a process where overstimulation of neurons causes cellular damage and death. These antibodies, when detected in the cerebrospinal fluid, have been associated with symptoms such as confusion, anxiety, cognitive impairment, mood alterations, and psychosis. Serum levels of anti-NMDAR

antibodies are generally higher in patients with NPSLE than in those without neuropsychiatric involvement [10]. Anti-ribosomal P antibodies (anti-RibP) have been linked to neuropsychiatric symptoms, including depression, and psychosis. They bind to the carboxy-terminal region of the 60S ribosomal subunit. Anti-RibP antibodies may cross the blood-brain barrier, penetrate neurons, and inhibit protein synthesis, thereby impairing neuronal function. These antibodies may also react with the P antigen on neuronal surfaces, particularly in the hippocampus, a brain region crucial for mood regulation and memory. Functional magnetic resonance imaging studies have shown that anti-RibP antibodies can alter brain networks and reduce neural efficiency, contributing to depressive symptoms [11]. Other autoantibodies, such as anti-double stranded DNA (anti-dsDNA) antibodies, anti-glyceraldehyde-3-phosphate dehydrogenase (anti-GAPDH) antibodies, and anti-ribonucleoprotein (U1RNP) antibodies, have also been implicated in NPSLE. Antibodies to glyceraldehyde-3-phosphate dehydrogenase (anti-GAPDH antibodies) have been associated with increased disease activity, inflammation, and intracranial pressure in patients with NPSLE. These antibodies have been detected in 50% of NPSLE patients presenting with schizophrenia and major depression. It is hypothesized that anti-GAPDH antibodies cross the blood-brain barrier due to meningeal inflammation, form immune complexes in the cerebrospinal fluid, and activate the classical complement pathway, contributing to NPSLE pathogenesis [10]. Antiphospholipid antibodies, when present, can promote thrombosis and strokes, contributing to neurological damage. Chronic inflammation, a hallmark of SLE, also plays a key role in neural injury. Damage to the central nervous system in NPSLE occurs through two complementary mechanisms. In the early stages, it can take place independently of overt blood–brain barrier disruption, likely driven by local microglial activation and the release of inflammatory cytokines within the brain parenchyma. As the disease progresses, compromise of the blood–brain barrier allows peripheral immune cells—particularly B cells—to infiltrate the central nervous system, amplifying local inflammation and neurological dysfunction. The infiltration of these immune cells further increases concentrations of pro-inflammatory cytokines, including IL-6, IL-12, IL-18, and IL-23, contributing to additional neuronal damage [12].

Table 1. Neuropsychiatric Systemic lupus erythematosus: Prevalence, Diagnostic Workup, and Treatment Recommendations [9].

Manifestation	Prevalence/Characteristics	Recommended Investigations	Recommended Therapy
General NPSLE Events	May precede, coincide, or follow SLE diagnosis; commonly occur within the first year after SLE diagnosis (50–60%), often with generalized disease activity (40–50%).	Exclude non-SLE causes. CSF, EEG, neuropsychological assessment, NCS, MRI).	Glucocorticoids and immunosuppressive Therapy. Antiplatelet/anticoagulation therapy in thrombotic manifestations related to antiphospholipid antibodies. Symptomatic therapies (anticonvulsants, antidepressants)
Cerebrovascular Disease (CVD)	Common (5–15% cumulative incidence). Ischaemic stroke/TIA are over 80% of cases.	MRI/DWI, MRA, CT angiography, or conventional angiography.	Acute management similar to general population and secondary prevention.
Seizure Disorder	Common (5–15% cumulative incidence). Most are single isolated events. Can be generalised tonic–clonic or partial. Related to disease activity.	Diagnostic work-up aims to exclude structural brain disease, inflammatory, or metabolic conditions. MRI and EEG and CSF analysis mainly to exclude infection.	AED therapy for recurrent seizures or single seizures with high-risk features.
Severe Cognitive Dysfunction	Relatively uncommon (1–5% cumulative incidence). Most affected domains: attention, visual/verbal memory, executive function, psychomotor speed.	Neuropsychological tests in collaboration with a clinical neuropsychologist. Brain MRI (age <60, rapid decline, recent head trauma, new neurological symptoms)	Treatment of exacerbating causes (especially anxiety and depression) and control of cardiovascular risk factors. Psycho-educational group interventions have shown improvements.
Major Depression	Relatively uncommon (1–5% cumulative incidence). Steroid-induced depression more common than steroid psychosis.	There is no strong evidence to support the diagnostic utility of serological markers or brain imaging.	Management involves antidepressive agents. Biofeedback-assisted cognitive behavioural treatment has favourable impact on depressive symptoms.

Table 1. *Cont.*

Manifestation	Prevalence/Characteristics	Recommended Investigations	Recommended Therapy
Acute Confusional State (ACS)	Relatively uncommon (1–5% cumulative incidence).	Exclude infections, metabolic disturbances conditions. CSF, EEG and brain imaging are indicated if focal neurological signs, trauma history, malignancy, fever.	Correct underlying causes. Antipsychotics agents. Glucocorticoids with immunosuppressive agents. Plasma exchange, Rituximab used in refractory cases.
Peripheral Nervous System Disorders	Relatively uncommon (1–5% cumulative incidence) Includes polyneuropathy (2–3%), mononeuropathy, AIDP, myasthenia gravis, plexopathy.	Brain neuroimaging. NCS and needle electromyography. CSF analysis useful in AIDP. Nerve biopsy rarely needed.	Glucocorticoids alone or with immunosuppressive therapy. Intravenous immunoglobulin, plasma exchange, and rituximab used in severe cases.
Psychosis	Rare (<1% cumulative incidence). Steroid-induced psychosis is very rare.	Anti-ribosomal-P antibodies have limited diagnostic accuracy. Brain MRI has modest sensitivity/specificity; consider when additional neurological symptoms/signs present. Brain SPECT identifies perfusion deficits.	Antipsychotic agents. In generalised SLE activity: glucocorticoids and immunosuppressive therapy (usually cyclophosphamide, followed by azathioprine) Rituximab in refractory cases.
Myelopathy	Rare (<1% cumulative incidence). Presents as transverse myelitis (rapidly evolving) or ischaemic/thrombotic myelopathy.	MRI and CSF analysis (exclude infectious myelitis).	high-dose glucocorticoids followed by intravenous cyclophosphamide. Plasma exchange therapy used in severe cases.
Chorea (Movement Disorder)	Rare (<1% cumulative incidence). Associated with antiphospholipid antibodies and/or APS.	Brain imaging	Dopamine antagonists for persistent symptoms.
Cranial Neuropathy	Rare (<1% cumulative incidence). Includes inflammatory optic neuritis and ischaemic/thrombotic optic neuropathy.	Ophthalmological evaluation. Contrast-enhanced MRI, Brain MRI.	Pulse intravenous methylprednisolone in combination with intravenous cyclophosphamide.
Aseptic Meningitis	Rare (<1% cumulative incidence).	CSF analysis is crucial to exclude infectious meningitis. Brain imaging and EEG.	Glucocorticoids and immunosuppressive. Plasma exchange or rituximab for refractory cases.

Abbreviations: AED (Anti-Epileptic Drugs); AIDP (Acute Inflammatory Demyelinating Polyradiculoneuropathy); APS (Antiphospholipid Syndrome); CSF (Cerebrospinal Fluid); CT (Computed Tomography); DWI (Diffusion Weighted Imaging); MRA (Magnetic Resonance Angiography); EEG (Electroencephalogram); MRI (Magnetic Resonance Imaging); NCS (Nerve Conduction Studies); SPECT (Single Photon Emission Computed Tomography); TIA (Transient Ischemic Attack).

Managing NPSLE is complex and requires a multidisciplinary approach involving rheumatologists, neurologists and psychiatrists. Treatment is primarily directed at controlling inflammation, relieving neuropsychiatric symptoms, and preventing further neural damage. Conventional treatment for severe SLE manifestations, including neuropsychiatric involvement, may include high-dose corticosteroids and cytotoxic agents such as conventional and biological disease-modifying antirheumatic drugs and biological disease-modifying antirheumatic drugs [8]. However, these medications carry risks of significant adverse effects, including secondary infections, ovarian toxicity, haemorrhagic cystitis, and carcinogenicity. While corticosteroids are effective in reducing systemic inflammation, they may cause psychiatric and cognitive side effects, such as mood swings, irritability, anxiety, and memory deficits. Their use should be carefully monitored and balanced against potential benefits. In certain cases, IVIg may be a suitable therapeutic alternative, even though the efficacy and

mechanisms of action are not fully understood. IVIg has been successfully used to treat patients with a broad range of SLE manifestations, including central nervous system involvement. Case reports have documented significant improvements in neuropsychiatric symptoms following IVIg treatment, in treating psychosis, mood disturbances, and encephalitis in SLE patients [13].

One study showed improvement in chronic cognitive impairment as a major neuropsychiatric manifestation following repeated high-dose IVIg cycles [14].

Another case reported complete resolution of acute depression, mania, and psychosis within 48 h of a 5-day IVIg treatment cycle in a woman with SLE [15]. In some cases, IVIg has been used successfully in combination with other agents, such as rituximab and corticosteroids, to treat severe SLE flares with neuropsychiatric involvement [16].

IVIg exerts immunomodulatory effects by blocking Fc receptors, modulating complement activity, and regulating T cells and idiotype–anti-idiotype networks. They may reduce serum titres of anti-dsDNA antibodies and lower corticosteroid requirements. IVIg is indicated in severe, treatment-resistant cases or when disease control is only possible with high-dose steroids, thereby acting as a steroid-sparing agent. Clinical response to IVIg is often swift, with significant improvement observed within a few days, although the duration of effect may be limited to several weeks. Sustained responses may be maintained through monthly infusions [13].

2.2. Idiopathic Inflammatory Myopathies

Idiopathic Inflammatory Myopathies (IIMs) are a heterogeneous group of autoimmune diseases mainly characterized by muscle inflammation. It can involve other organs such as skin, lungs, heart, and joints. In addition to common manifestations, neuropsychiatric symptoms, particularly depression and anxiety, may also arise [17]. Dermatomyositis (DM) is an idiopathic inflammatory myopathy that most commonly presents with progressive, symmetric, proximal muscle weakness and cutaneous manifestations; these patients have been reported to have poor quality of life. Interestingly, the patients with marked cutaneous features have a higher prevalence of mental illness, such as depression (10.1%) and anxiety (17.2%) [18]. In another study, 43.9% of the DM patients required treatment for depression or anxiety. Subsequent studies have established that severe muscle weakness is directly correlated with a detrimental impact on vitality and mental health in these patients [19].

The pathogenesis of myositis-associated neuropsychiatric manifestations is likely to be multifactorial, with chronic inflammation playing a key role. Systemic inflammation, which is typical in myositis, can attack the central nervous system directly along a variety of pathways, such as the secretion of pro-inflammatory cytokines. Association of interleukin-6 (IL-6) and C-reactive protein (CRP) with depression suggests a direct association, providing evidence for two-way modulation between the central nervous system and the immune system. In myositis, elevated inflammatory markers, such as erythrocyte sedimentation rate (ESR) and CRP, are correlated with worse long-term patient global assessment (PGA), and an increased risk of disease flare-related depressive symptoms [20,21]. Beyond the inflammatory components, additional pathophysiological mechanisms appear to be involved in the development of neuropsychiatric manifestations in patients with myositis. Chronic pain, disabling fatigue, and muscle strength loss, hallmark features of myositis, can significantly impact psychological well-being and quality of life, contributing to the development of depression and anxiety [20]. Inflammatory myopathies are traditionally managed using corticosteroids in addition to other immunosuppressive agents, such as methotrexate, mycophenolate mofetil, azathioprine, or rituximab. Although these drugs are central to the treatment of muscle inflammation, corticosteroids are known to be associated with neuropsychiatric adverse effects. IVIg and subcutaneous immunoglobulins (SCIg) represent new immunomodulatory therapies with expanding roles in the treatment of myositis [22]. Add-on therapy with IVIg has been safe and effective in DM patients, improving muscle strength, skin lesions, and dysphagia [23]; in addition, IVIg therapy facilitates corticosteroid tapering [4]. Physical improvement can have a positive impact on psychological well-being by reducing the frequency and severity of depression and anxiety. Due to the broad immunomodulatory mechanisms [24], IVIg may reduce chronic inflammation–the underlying substrate of myositis–by downregulating IL-6 and other pro-inflammatory cytokines involved in both myositis and the pathophysiology of depression [1]. Though less well understood, IVIg may also act directly on the central nervous system, potentially by modulating microglial activity, reducing neuroinflammation, or influencing blood-brain barrier integrity, which may help improve mental health outcomes [24].

2.3 Sjögren's Syndrome

Sjögren's syndrome (SS) is one of the most common autoimmune diseases, characterized by chronic inflammation of the lacrimal and salivary glands, infiltration of mononuclear cells, and consequent damage and

hypophony of the lacrimal and salivary glands. While this disease is mainly known for causing problems with the glands, research has revealed a wide range of extra-glandular symptoms, showing a significant co-presence with various neurological and mental health issues that confirm a significant correlation between SS and several neuropsychiatric disorders [25]. The prevalence of central nervous system involvement in SS, known as central nervous system-SS, varies widely. Psychiatric manifestations are often variable and frequently underdiagnosed, making a comprehensive assessment of SS patients essential [26]. Sleep disturbances such as insomnia and frequent nighttime awakenings are extremely common in patients with SS and have a significant impact on the quality of their life, since the lack of restful sleep causes cognitive impairment, including reduced attention and slowed processing speed [27]. In addition, patients with SS can often have atypical mood disorders, characterized by a combination of depressive, somatic, and cognitive symptoms up to, in rare cases, psychotic manifestations such as hallucinations or catatonia and, in some cases, obsessive-compulsive traits up to real obsessive-compulsive disorders (OCD) [28]. Studies have even suggested a possible association between SS and bipolar disorder, although further research is needed to confirm this correlation [29]. The pathogenic mechanisms underlying neuropsychiatric disorders in SS are not completely clarified, but several explanations have been hypothesized to justify this correlation. Firstly, the immune system activity and, more specifically, inflammatory alterations in the central nervous system can play a key role in the development of psychiatric symptoms. Autoantibodies (as anti-NR2, anti-P, and aquaporin-4 antibodies), cytokines, and T cells may directly attack the central nervous system, causing a state of inflammation and neuronal dysfunction that results in the development of psychiatric disorders. Moreover, the mood and cognitive impairment described above may be due to a significant release of pro-inflammatory cytokines such as IL-1β and TNF-alpha, which can affect neurotransmission and neuronal function. Alterations in serotonin and glutamate levels have also been implicated in the pathogenesis of psychiatric disorders associated with SS [30]. Ischemic damage is also worth considering; vasculitis of the central nervous system, a rare but serious complication of SS, can cause ischemic damage to the brain, leading to neurological and psychiatric dysfunction [31]. Rituximab showed promising results in improving psychiatric symptoms in patients with SS [32,33]. Antidepressants, anxiolytics, and antipsychotics may be prescribed to manage specific psychiatric symptoms such as depression, anxiety, and psychosis. However, caution is important with drugs with anticholinergic effects, such as tricyclic antidepressants, because they can exacerbate dry mouth [34]. On one hand, improving knowledge about the pathogenic mechanisms involved would enable earlier diagnosis. On the other hand, the adoption of appropriate treatment strategies consisting of a comprehensive therapeutic approach, including immunosuppressants and psychotropic drugs along with non-pharmacological therapies, seems to be essential to optimise clinical outcomes and ensure patients have a comprehensive cure.

2.4. Systemic Sclerosis

Systemic sclerosis (SSc) is a chronic disease characterized by progressive fibrosis of the skin and internal organs, as well as vascular abnormalities. It is considered to result from both genetic predisposition and environmental exposures, which collectively disrupt the immune system, leading to excessive production of collagen and microvasculopathy [35]. In addition to the well-known organic manifestations, SSc is often associated with psychiatric symptoms, which can manifest as mood instability, irritability, psychosis, and depression. The prevalence of depressive symptoms in patients with SSc is significantly higher than in the general population and other rheumatic diseases. Cognitive impairment is also common, including waning in memory function, executive dysfunction (planning, organization, mental flexibility), and a general feeling of fatigue. These psychiatric manifestations have a significant impact on patients' quality of life, affecting their physical and mental well-being [36,37]. A recent study by Van Eeden et al. reported that approximately 50% of patients with SSc exhibited Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. These patients demonstrated significantly greater cognitive impairment compared to SSc patients without Myalgic Encephalomyelitis/Chronic Fatigue Syndrome [38].

It has been assumed that neuropsychiatric involvement in SSc is probably multifactorial. The primary proposed pathogenic mechanism indicates that vasculopathy involving both the central and peripheral nervous systems may be associated with extensive microvascular damage, which could potentially contribute to the development of mood disorders, anxiety, and cognitive impairment. Functional magnetic resonance imaging studies have shown alterations in the resting brain activity and functional connectivity in patients with SSc, partially associated with neuropsychiatric manifestations and tending to worsen with the duration of the disease. Another important aspect underlying neuropsychiatric manifestations is the psychological distress due to the physical manifestations of the disease: the fear of disease progression and body image concerns may exacerbate psychological distress. Changes in physical appearance secondary to skin fibrosis, chronic pain, debilitating fatigue, and functional disability can contribute significantly to the development of depression and anxiety. Consequently,

these neuropsychiatric manifestations can lead to social challenges, such as difficulties in interpersonal relationships and maintaining employment, which in turn negatively affect the mood [39–41]. Eventually, some medications used by patients may also cause psychiatric side effects. Among the main causes of neuropsychiatric manifestations, there are corticosteroids [42]. Regarding the treatment of psychiatric manifestations, standard pharmacological therapies, such as antidepressants, anxiolytics, or antipsychotics, depending on the specific symptoms, should be administered as appropriate. Considering cerebral vasculopathy, calcium-antagonist drugs appear to have a beneficial effect on hypoperfusion. Additionally, psychological interventions such as cognitive behavioural therapy, mindfulness-based stress reduction, self-management programs, and multidisciplinary approaches can help reduce anxiety, increase self-esteem, and significantly improve the overall outlook of patients with SSc. Although IVIg may appear less effective in improving respiratory function and radiological findings, it has demonstrated beneficial effects in reducing skin thickening, muscle and joint pain, gastrointestinal symptoms, as well as lowering steroid doses, and improving patient-reported quality of life [43].

3. Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) is a chronic disease characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies responsible for joint pain, swelling, stiffness, and fatigue. Although RA mainly affects the joints, several neuropsychiatric manifestations can be observed [44]. One study found that about half of patients with RA had a major depressive disorder (21.7%) or anxiety (16.9%) during the psychiatric evaluation [45]. The most common disorders range from peripheral neuropathy–pain, numbness, paresthesia, muscle hypofunction typically due to nerve compression–to more complex neuropsychiatric manifestations including mood disorders (depression, anxiety, irritability, and emotional lability), and cognitive impairment–concentration difficulties, memory problems, and reduced executive function [46]. Among the causes that may contribute to anxiety and depression in patients with RA, psychosocial factors emerge first: chronic pain, disability, and fatigue, the unpredictable course of the pathology, lead to psycho-social stress in the patient, whose depressive state negatively affects physical function, the view of the disease, and satisfaction with treatment [47,48]. Cognitive function in patients with rheumatoid arthritis has been found to correlate with pain intensity (assessed by VAS), levels of inflammatory markers, frequency of disease flare, and history of surgical interventions. These findings suggest that both systemic inflammation and overall disease burden may contribute to neuropsychological outcomes [49]. A study showed that the extent of pain and fatigue is a valid predictor of depression in patients with RA. Psychiatric symptoms have been found mainly in patients at an advanced stage of the disease, which greatly limits daily activities [50]. Elevated disease activity is independently associated with increased rates of anxiety and depression. Another factor involved in the pathogenesis of neuropsychiatric symptoms in patients with RA is the ability that pro-inflammatory cytokines, such as TNF-α, have to influence the turnover of central monoamines. Some studies have shown that patients with major depression have significantly higher serum TNF-α levels than controls. In summary, TNF-α appears to be a key mediator between the inflammation associated with RA and psychiatric disorders such as depression and anxiety, and modulation of TNF-α through specific drugs may have positive effects on the mental state of patients with RA [51]. Compared to the therapeutic strategies considered so far, it appears essential to manage both RA symptoms and neuropsychiatric disorders. Therapeutic strategies should include the use of antidepressants, anxiolytics, and neuropathic pain medications. Although the main treatment remains focused on managing joint inflammation with drugs such as DMARDs, biological, and corticosteroids, the IVIg may be considered in situations where there is a neurological or immunological component that justifies the use. The decision, taken by the attending physician, would depend on the specific clinical condition of the patient. In addition to the pharmacological approach, other interventions may be introduced to improve physical function, reduce pain, and improve quality of life. These strategies include cognitive-behavioural therapy and other psychotherapeutic approaches that may help patients cope with chronic pain, stress, and emotional problems. Finally, regular exercise, a healthy diet, and stress management techniques can improve both physical and mental health.

4. Vasculitis

Vasculitis refers to a group of autoimmune disorders characterized by inflammation of blood vessel walls. It can affect vessels of any size, from large vessels, as seen in Takayasu arteritis and giant cell (temporal) arteritis, to medium-sized vessels, such as in polyarteritis nodosa and Kawasaki disease, to small vessels. One of the small-vessel vasculitides subgroups is anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV), including microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). ANCA autoantibodies directed against myeloperoxidase (MPO) and

proteinase 3 (PR3) play a direct pathogenic role in these disorders by neutrophil activation and triggering the inflammatory cascade. Amidst the broad spectrum of systemic manifestations, neuropsychiatric involvement is a prominent feature in many forms of vasculitis, affecting both the central and peripheral nervous system [52]. Neuropsychiatric symptoms, including headache, impairment of cognition, mood change, and dysphasia may be presented by the patients [53]. Autoimmune mechanisms of neuropsychiatric manifestations in vasculitis are multifactorial. In ANCA-associated vasculitis, ANCAs are themselves pathogenic through neutrophil activation and vascular endothelial injury. The blood vessels inflammation may cause ischemia, necrosis, tissue damage to the central and peripheral nervous system. Although the pathogenesis of neuropsychiatric manifestations is unclear, systemic autoimmune activity and ongoing inflammation are key players. Additionally, physical disabilities that moderately impair daily activities lead to a decline in quality of life, which in turn increases the risk of developing anxiety and depression. In primary angiitis of the central nervous system, a rare idiopathic vasculitis of exclusively small and medium-sized vessels of the central nervous system, patients develop common cognitive and affective symptoms as well as headache. They are typically associated with multifocal brain lesions at magnetic resonance imaging and cerebrospinal fluid inflammatory changes [54]. Notably, even when vasculitis is in remission, the presence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome is associated with a substantial cognitive burden, suggesting that chronic fatigue may contribute to persistent neurocognitive deficits in patients with AAV [55]. Systemic treatment with immunosuppressive drugs is a key element of vasculitis therapy. Significant doses of glucocorticoids are often required, but they can cause a broad spectrum of side effects, including the aggravation of neuropsychiatric symptoms. IVIg therapy has also been shown to be effective for a variety of autoimmune and inflammatory disorders, as previously mentioned. In ANCA-associated vasculitis, IVIg can be particularly helpful in refractory disease, in the presence of concomitant infection, or in patients with severe acute conditions [56]. Observational evidence has demonstrated that IVIg therapy is linked to an improvement in disease activity scores such as the Birmingham Vasculitis Activity Score (BVAS), and to a reduction in glucocorticoid dose in relapsing or refractory AAV patients [57]. The precise mechanism of action of IVIg in vasculitis remains unknown, but it is believed to occur through modulation of the immune system, inhibition of neutrophil extracellular trap (NET) generation, and anti-idiotypic action against ANCAs [58]. Efficacy of IVIg for treatment of peripheral neuropathy in ANCA vasculitis has also been shown in certain trials [59]. Reduction of systemic inflammation, improvement of peripheral neuropathy, decreased reliance on corticosteroids, and overall clinical improvement might indirectly bear a positive impact on mood and anxiety and lead to the alleviation of neuropsychiatric manifestations usually encountered with vasculitis.

5. Conclusions

The deep interplay between mind and body is well recognized, making the early identification of neuropsychiatric symptoms in patients with chronic autoimmune diseases increasingly important, given the added burden these symptoms place on individuals already coping with debilitating conditions (Table 2). In diseases like SLE, neuropsychiatric symptoms represent a significant manifestation that often arises early in the disease course, making timely diagnosis essential. This requires targeted assessment using neuroimaging and neuropsychological testing [9]. Moreover, the association of NPSLE phenotype with distinct patterns of structural brain abnormalities that can be reliably detected through magnetic resonance imaging (MRI), highlights the central role of MRI not only in delineating disease-specific brain alterations, but also in enhancing diagnostic precision, supporting longitudinal monitoring, and informing therapeutic strategies. Moreover, MRI-derived biomarkers hold promise for advancing research into the underlying pathophysiological mechanisms and for guiding the development of targeted interventions in patients with SLE presenting with neuropsychiatric manifestations. emphasize the pivotal role of MRI not only in identifying disease-specific brain alterations, but also in refining diagnostic accuracy, facilitating disease monitoring, and potentially guiding therapeutic decision-making. Furthermore, MRI-based biomarkers may provide valuable insights for future research aimed at elucidating pathophysiological mechanisms and developing targeted interventions for patients with systemic lupus erythematosus presenting with neuropsychiatric involvement. In addition, the identification of specific autoantibodies associated with neuropsychiatric disorders may help the development of targeted therapies. For example, some studies suggest that anti-P ribosomal antibodies are associated with depression and altered brain connectivity and may serve as biomarkers for monitoring disease progression and treatment response in patients with NPSLE [11]. Since it has become increasingly evident that the integrity of the blood-brain barrier plays a critical role in the pathophysiology of neuropsychiatric disorders, studying the involvement of cytokines in the development of neuropsychiatric manifestations in major autoimmune diseases, and further investigating how these cytokines infiltrate the central nervous system, amplifying inflammation, could pave the way for the development of new therapeutic strategies.

For this reason, although invasive and labor-intensive, cerebrospinal fluid analysis remains, to date, a critical diagnostic tool for the timely detection of cytokines and antibodies, thereby providing evidence of the inflammatory state that may be linked to and potentially explain the neuropsychiatric manifestations in patients with systemic autoimmune diseases. Since traditional treatments include corticosteroids and immunosuppressants, it is important to be aware that, in some cases, their potential neuropsychiatric side effects may serve as a trigger for these patients. For this reason, steroid-sparing options such as IVIg are emerging as valid treatments that can target both immune dysregulation and related neuropsychiatric manifestations. Among non-pharmacological therapies, psychotherapy and exercise are key, showing a positive impact on mood and anxiety. Studies have shown that exercise, through the release of myokines from skeletal muscle, plays a significant role in reducing inflammation, which is itself an important trigger for the development of neuropsychiatric symptoms. Reducing inflammation not only prevents the development of neuropsychiatric symptoms but also contributes to regulating the activity of the underlying autoimmune disease. In diseases as myositis, high-intensity physical activity has been shown to improve not only the quality of life but also muscle resistance and strength [60]. In addition to physical exercise, psychological support and self-help groups can improve the quality of life of patients and provide correct information about the disease, thus mitigating anxiety and improving the coping skills of patients, as reported in SSc [35,39]. Despite the lack of standardized diagnostic criteria and reliable biomarkers to monitor neuropsychiatric manifestations over time–along with other significant unmet needs in the treatment of autoimmune neuropsychiatric disorders–continue to represent a significant hurdle for clinicians, the growing importance of integrative medicine and a multidisciplinary approach to symptom management is clear. Effective care increasingly requires collaboration among rheumatologists, neurologists, and psychiatrists. Treatment strategies must address both the control of the underlying autoimmune disease activity and the management of concomitant psychiatric symptoms. Effective prevention and management of neuropsychiatric symptoms rely on early screening to identify at-risk patients, enabling timely implementation of preventive measures, informed therapeutic decisions, and appropriate non-pharmacological interventions.

Table 2. Overview of Neuropsychiatric Involvement in Autoimmune Diseases.

Autoimmune Disease	Neuropsychiatric Manifestations	Proposed Pathogenic Mechanisms
Systemic Lupus Erythematosus	Cognitive dysfunction (memory, attention, executive slowing), depression, anxiety, acute confusional states, psychosis (hallucinations, delusions), seizures (focal/generalized), headache, peripheral neuropathy (poly-/mononeuropathy), cerebellar ataxia, chorea, myelopathy, autonomic disturbances	Autoantibodies (anti-NMDAR, anti-RibP, anti-dsDNA, anti-GAPDH antibodies); chronic inflammation, cytokines (IL-6, TNF-α).
Idiopathic Inflammatory Myopathies	Depression, anxiety, emotional distress, sleep disturbances, fatigue, mood disorders due to disease flares	Chronic systemic inflammation (IL-6, CRP, ESR).
Sjögren's Syndrome	Depression, insomnia, fatigue-related cognitive impairment (attention, processing speed), psychosis (hallucinations, catatonia), obsessive-compulsive traits/OCD, possible bipolar features	Autoantibodies (anti-NR2, anti-P, aquaporin-4); cytokines (IL-1β, TNF-α); neurotransmitter imbalance (serotonin, glutamate); CNS vasculitis
Systemic Sclerosis	Depression, anxiety, psychosis, irritability, cognitive dysfunction (memory, executive function), fatigue, mood instability	Cerebral microvasculopathy, chronic pain, psychological distress, CNS hypoperfusion
Rheumatoid Arthritis	Depression, anxiety, emotional lability, cognitive symptoms (concentration, memory, executive dysfunction), peripheral neuropathy (paresthesia, pain, hypofunction)	TNF-α-related neurotransmitter changes; chronic pain and fatigue; inflammatory cytokine burden; psychosocial stress
Vasculitis (ANCA-associated)	Cognitive impairment, mood changes, headache, dysphasia, peripheral neuropathy, multifocal CNS symptoms	ANCA-mediated neutrophil activation, endothelial injury, CNS ischemia, chronic inflammation.

Abbreviations: ANCA, antineutrophil cytoplasmic antibodies; anti-dsDNA, antibodies to double-stranded DNA; anti-GAPDH, antibodies to glyceraldehyde-3-phosphate dehydrogenase; anti-NMDAR, antibodies to N-methyl-D-aspartate receptor; anti-NR2, antibodies to NR2 subunit of the NMDA receptor (N-methyl-D-aspartate receptor); anti-RibP, antibodies to ribosomal P; CNS, central nervous system; OCD, obsessive-compulsive disorders.

Author Contributions

M.G.D. and Y.S. were responsible for the study's conception and design. M.B. and S.C. reviewed the studies and wrote the first draft. E.B., M.S., E.L. contributed to analyses of the references. All Authors contributed to analyses of the references. M.G.D. and Y.S. revised the manuscript critically for intellectual content. All authors gave their final approval of the version of the manuscript to be published. The authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. The authors confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. The authors further confirm that the order of authors listed in the manuscript has been approved by all of us. The authors understand that the Corresponding Author is the sole contact for the Editorial process. The Corresponding author is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships for themselves and their immediate family/significant others that could be construed as a potential conflict of interest. Given the role as Editor-in-Chief, Yehuda Shoenfeld had no involvement in the peer review of this paper and had no access to information regarding its peer-review process. Full responsibility for the editorial process of this paper was delegated to another editor of the journal.

Use of AI and AI-Assisted Technologies

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