Review
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# Neurological Manifestations in Primary Sjögren's Syndrome: A Comparative Review of Inflammatory Mechanisms

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**Abstract**
Primary Sjögren's syndrome (pSS) is a systemic autoimmune disorder marked by chronic inflammation, with neurological involvement often overlooked. This review highlights the inflammation-driven mechanisms underlying both peripheral and central nervous system (PNS, CNS) manifestations of pSS. PNS complications, particularly axonal sensorimotor and pure sensory neuropathies, are more common than CNS involvement. CNS abnormalities include diffuse white matter lesions and hippocampal atrophy. Immune dysregulation plays a central role, with emerging evidence implicating NLRP3 inflammasome activation and vasculitic processes. Aberrant B-cell activity may lead to pathogenic autoantibody production and direct neural injury. Infiltration of T- and B-cells into neural tissues, facilitated by astrocyte-mediated disruption of the blood-brain barrier, promotes cytokine-driven neuroinflammation. These processes contribute to cognitive, sensory, and motor dysfunction in pSS. Although conventional and biological therapies show promise, robust clinical trials are lacking. Understanding the immunopathogenesis of pSS may pave the way for targeted interventions. This review synthesizes current findings on neuroinflammatory mechanisms in pSS and their clinical implications.
**Keywords:** Primary Sjögren's syndrome, central nervous system, neuroinflammatory diseases, pathology

## Introduction

Sjögren's Syndrome (SS) is a persistent autoimmune condition marked by inflammation affecting the exocrine glands, particularly the salivary and lacrimal glands, resulting in symptoms such as xerostomia (dry mouth) and xerophthalmia (dry eyes).[1,2] The occurrence of primary Sjögren's syndrome (pSS) ranges widely from 0.01% to 4.8%, influenced by variations in diagnostic standards, definitions, geographical regions, and the age of those affected.[3] Women are disproportionately impacted by pSS, exhibiting a prevalence up to 10 times greater than men, with the disease typically manifesting around age 50.[4]

The manifestations of pSS extend beyond the exocrine glands, with impaired extraglandular function, musculoskeletal pain, and fatigue being the primary symptoms.[5] These manifestations can lead to long-term severe complications, cause psychological stress, result in significant physical disabilities, and impose substantial financial burdens on pSS patients.[6] Notably, neurological complications are reported in a significant proportion of pSS patients, affecting between 8.5% and 70% of cases, with a diagnosis often made within the first two years of disease onset in 25% to 60% of patients.[7] In some cases, severe neuropsychiatric manifestations of pSS may be observed even in seronegative patients, highlighting the importance of clinicians being familiar with the neurological manifestations of pSS.[8] The neurological complications of pSS can be categorized into peripheral nervous system (PNS) and central nervous system (CNS) involvement. Among these, peripheral neuropathy, particularly sensory polyneuropathy, is the most frequently reported complication.[9] While cases of concurrent PNS and CNS involvement have been reported, pSS-related CNS complications are relatively less common,[10,11] occurring in only 2% to 25% of cases compared to PNS complications.[12,13] Involvement of the autonomic nervous system and cranial nerves is relatively uncommon.[14,15]

Despite extensive research, the pathologic features of pSS and its mechanisms of involvement in the nervous system are not fully understood.[16,17] It has been reported that progressive lymphocytic infiltration of the exocrine salivary and lacrimal glands occurs in pSS.[18,19] However, the precise mechanism by which pSS affects the nervous system remains unclear.[20] Although several studies have investigated potential treatment options for pSS, the lack of information regarding the molecular mechanisms leading to PNS and CNS complications in pSS has hindered the development of effective targeted therapies.[21,22] It is well-established that lymphocytes and dendritic cells play a critical role in cytokine secretion, which triggers vasculitis through inflammatory responses. Furthermore, some studies have identified specific antibodies reactive to nervous tissue.[23]

This review aims to provide a comparative analysis of the PNS and CNS complications observed in pSS patients, elucidate the molecular mechanisms underlying the pathogenesis of pSS, and discuss the currently available treatment options. By examining the existing literature, this review seeks to offer an inflammation-centric perspective on the neurological manifestations of pSS, providing a comprehensive understanding of the underlying mechanisms and their medical implications.

## General Features of Disease

pSS is an intricate autoimmune disorder primarily affecting adult women, characterized by lacrimal and salivary gland dysfunction. As pSS progresses, it may damage additional organs, such as the lungs, kidneys, musculoskeletal system, and nervous system.[24] The clinical presentation of pSS varies

widely, from a mild, gradually progressing condition to severe systemic complications with significant consequences.[25] A defining characteristic of pSS is the hyperactivity of B-cells, coupled with the progressive infiltration of B- and T-cells into the exocrine salivary and lacrimal glands.[18] The detection of specific autoantibodies, such as anti-Ro (anti-SSA), anti-La (anti-SSB), and/or antinuclear antibodies (ANA) in patients' serum, is a critical diagnostic feature of pSS.[26] Approximately one in five pSS patients may experience significant organ involvement, which can lead to severe end-organ damage.[27] Systemic autoimmune diseases, including pSS, often exhibit complex or overlapping molecular profiles, categorized into four clusters: inflammatory, lymphoid, interferon (IFN), or healthy-like patterns.[28] The upregulation of IFN-related genes, known as the IFN signature, is a common feature observed in many patients with systemic autoimmune disorders.[29] Increased serum concentrations of circulating free DNA (cfDNA), a potential factor for autoimmune disorder diagnosis, are associated with disease progression in pSS patients.[30] pSS chronicity increases the risk of severe complications, such as cryoglobulinemic vasculitis and B-cell lymphoma.[31] The diagnosis requires a minor salivary gland biopsy or the presence of autoantibodies. Objective tests for oral and ocular dryness can be helpful.[32] Disease progression is associated with extraglandular manifestations and impairment of other organs.[6] Recent research has shed light on the metabolic underpinnings of pSS through preclinical and clinical studies. In a mouse model, early-stage pSS is dominated by glycolytic metabolism, transitioning to amino acid metabolism in later stages. A parallel metabolic profile was observed in human patients: those in early-stage pSS relied on glycolysis and mitochondrial respiration, while patients with long-standing disease predominantly utilized amino acid metabolism.[33] These findings highlight the dynamic metabolic shifts in pSS and their potential implications for targeted therapeutic strategies.

## Neurological Symptoms

### *Peripheral Nervous System Symptoms*

The prevalence of pSS-PNS complications ranges from 2% to over 50% based on different studies.[34,35] This impressive variability can possibly be attributed to three major reasons: 1) methodological veracity in diagnosing neurological complications; 2) different criteria used for patient stratification; and 3) study design heterogeneity.[36] The PNS manifestations of pSS exhibit a diverse range of clinical features, encompassing multiple mononeuropathies, axonal sensorimotor polyneuropathies, and cranial nerve involvement, notably affecting cranial nerves III, V, VI, VII, IX, X, and XII.[37] Notably, facial nerve neuropathy has been documented in a cohort of 11 patients who tested negative for pSS-specific autoantibodies but were diagnosed with pSS through minor salivary gland biopsy.[38] Abnormal morphology of the corneal sub-basal nerve plexus, which is responsible for tear production, has been observed in pSS. It was shown that PNS involvement manifested as sensorimotor polyneuropathies and pure sensory neuropathy, which were the most frequent pSS complications.[39] Another study reported that a considerable proportion of all PNS symptoms was attributed to pure sensory neuropathies, especially dorsal root ganglionopathy and painful small-fiber neuropathy. It is likely that pSS represents one of the leading causes of pure sensory neuropathy among immune-mediated disorders.[40,41] It was shown that axonal sensorimotor polyneuropathies have poor prognosis, but pure sensory neuropathies may have a mild clinical course.[24] Hypokalemic paralysis, stemming from renal tubular acidosis associated with pSS, has been documented in clinical reports[42] Acute or chronic inflammatory demyelinating polyradiculoneuropathy, multiplex neuritis, and dysautonomia have been described.[43,44] Severe neuropathy with limb weakness related to pSS has been reported.[45] Small-fiber neuropathy also emerges as a relevant clinical concern.[46]

The occurrence of peripheral neuropathy in pSS has been significantly correlated with elevated levels of immunoglobulin G (IgG), α-Fodrin IgG (α-FIgG), and platelet count (PLT), all of which independently predict PNS complications. Interestingly, the presence of xerostomia (dry mouth) has been inversely correlated with neuropathy. High PLT and elevated anti-SSB antibody titers have been associated with an increased risk of both motor and sensory nerve damage in patients with pSS-related peripheral neuropathy.[47] Pathophysiological mechanisms involve M2-predominant CD68+ macrophages, which infiltrate small vessels and nerve bundles, engulf myelin and axons, and contribute to nerve fiber swelling, axonal degeneration, and separation of the myelin-axon membrane—leading to both demyelination and axonal injury.[48] Clinically, patients with pSS and peripheral neuropathy often have a longer disease duration and a higher prevalence of Raynaud's phenomenon, anti-SSB antibodies, rheumatoid factor (RF), and hyperglobulinemia compared to those without neuropathy. Multivariate analyses have identified RF, hyperglobulinemia, and anti-SSB antibodies as independent risk factors for the development of peripheral neuropathy in pSS.[49]

### *Central Nervous System Symptoms*

The features and pathogenesis of CNS involvement in pSS (pSS-CNS) are not well understood,[11] which explains the absence of formal classification standards for CNS complications of pSS.[50] The involvement of the CNS is a rare complication in pSS patients. It is characterized by a spectrum of symptoms, including seizures, migraines, meningitis, dementia, chorea, chronic myelopathies, acute cerebral infarction, encephalopathy, cognitive dysfunction, and psychiatric disorders.[51–53] The complications of pSS-CNS were described in a group of eight patients for the first time in 1982. pSS-CNS manifestations were related to focal or diffuse symptoms, including focal cerebral deficits, aseptic meningoencephalitis, and spinal cord defects. Three forms of chronic progressive myelopathy, acute transverse myelitis, and spinal subarachnoid hemorrhage were observed in the spinal cord of such patients. A direct correlation between vasculitis severity and anti-Ro antibody serum levels was reported.[54]

According to the literature, the global complications of pSS-CNS include acute or subacute encephalopathy, aseptic meningitis, narcolepsy, psychosis, atypical headache, cognitive impairments, dementia, psychiatric disorders. The focal or multifocal complications are sensory and/or motor dysfunctions, dysarthria/aphasia, hemiparesis, brainstem syndrome, seizure disorders, multifocal vascular encephalopathy, Parkinson-like syndrome, and cerebellar atrophy. The spinal cord-related complications include Brown-Séquard syndrome, chronic progressive myelitis, transverse myelitis, neurogenic bladder, lower motor neuron disease. Additionally, optic neuropathy and multiple sclerosis-like disorders have been

detected. Among all pSS-CNS complications, global defects are the most common manifestation.[32,51] Brain scanning techniques have revealed both cerebral atrophy and white matter abnormalities in pSS patients.[52,55] Diffuse, small, and punctate white matter hyperintensities (WMHs) are a frequent but nonspecific finding in aging, atherosclerosis, diabetes mellitus, and hypertension.[56–58]

Multiple WMHs have been observed in more than 80% of pSS patients with focal patterns of CNS involvement and in 50% of patients with diffuse types.[51,59] Subcortical and periventricular white matter involvement is common, but brainstem involvement is uncommon in pSS patients.[51] Involvement of the basal ganglia, corpus callosum, and corona radiata has been reported in pSS patients.[60] Neuroimaging studies confirm that white matter abnormalities are usually due to vascular brain involvement in pSS patients. These abnormalities may present as multiple small focal involvements, the beginning of confluent lesions, diffuse involvement of one major area, or MS-like lesions.[52] Furthermore, neuroimaging studies suggest that cognitive disorders, including memory and attention deficits, may result from subcortical foci in the fronto-parietal area and hypoperfusion regions in the temporal and frontal lobes.[61–63] In addition to neurological involvement, patients with pSS may exhibit psychiatric and cognitive impairments, including, in rare cases, psychosis. Although depressive symptoms are frequently reported and considered a common comorbidity in pSS, psychotic episodes remain uncommon.[9] Neurological signs of pSS may include CNS vasculitis-related symptoms, such as dysphagia, facial paralysis, and cortical blindness. Magnetic resonance imaging (MRI) often reveals white matter and vascular abnormalities. Combined with systemic features and autoantibodies, these findings illustrate the diverse and complex nature of pSS.[64]

## Pathologic Mechanisms of Neuropsychiatric Complications

The pathologic mechanisms causing neurological complications of pSS are not well understood, although genetic and environmental factors, autoimmunity against nervous tissue, neuroimmunoendocrine network dysregulation, and post-traumatic stress have been suggested.[65] PNS and CNS involvement in pSS is primarily a consequence of direct immunological damage to nervous tissue and vasculitis.[66] Moreover, treatment with corticosteroids and immunosuppressive medications may increase the risk of neurological disorders in pSS.[67] Table 1 and Figure 1 summarize the pathological mechanisms involved in PNS and CNS complications of pSS.

## Peripheral Nervous Systems

In pSS-PNS individuals, axonal loss or demyelination was associated with increased levels of anti-Ro/anti-La antibodies and rheumatoid factor, respectively.[68] Serological findings include elevated erythrocyte sedimentation rate, C-reactive protein, and cryoglobulinemia levels.[69] The key mechanism proposed for the progression of pSS neuropathies is vasculitis of the vessels supplying blood to nerves (vasa nervorum), which results in significant nerve infarction and necrosis

Table 1. **Mechanisms underlying neuropsychiatric manifestations in pSS**

| Author (year) | CNS/ PNS | Sample size | Complications | Findings |
|---|---|---|---|---|
| Alexander et al. (1986) (92) | CNS | *N* = 30 CNS disease<br>*N* = 20 No CNS disease | -CNS involvement | -Increased levels of total protein, IgG level, IgG/total protein ratio, and IgG index in CSF<br>-Abnormal cytologic findings in the CSF, including: Lymphoblastoid cells, atypical mononuclear cells, and plasma cells |
| Malinow et al. (1986) (74) | PNS | A case | -Sensory NP (Trigeminal NP) | -Involvement of the trigeminal and DRG<br>-Infiltration of lymphocytic into the thoracic DRG and degeneration of ganglion cells |
| Griffin et al. (1990) (121) | | *N* = 13 | -Sensory and autonomic NPs<br>-Ataxia and kinesthetic loss. | -Degeneration of sensory neurons<br>-Loss of large myelinated fibers<br>-Perivascular mononuclear infiltrates without necrotizing arteritis in cutaneous nerve samples<br>-Infiltration of lymphocytes (T-cell) into the DRGs with focal clusters around neurons. |
| Inoue et al. (1991) (122) | PNS | Two cases | -Peripheral NP | -Increased anti-endothelial cell antibody<br>-Deposits of IgG and C3 component in the vasa nervorum |
| Alexander et al. (1994) (123) | CNS | Four groups<br>I: 54<br>II: 53<br>CNS disease<br>III: 24<br>IV: 10<br>No CNS disease | -CNS involvement | -Association between seropositivity to anti-Ro and serious CNS disease and frank cerebral angiopathy |
| Tuominen et al. (2003) (80) | PNS | *N* = 10 | -Corneal subbasal nerve involvement ((4/10) | -Abnormal morphology in subbasal nerve fiber bundles |

(Continued)

Table 1. **Mechanisms underlying neuropsychiatric manifestations in pSS—Continued**

| Author (year) | CNS/ PNS | Sample size | Complications | Findings |
|---|---|---|---|---|
| Delalande et al. (2004) (62) | PNS/ CNS | *N* = 82 | -CNS involvement mostly focal or multifocal (56)<br>-Spinal cord involvement (29):<br>-Acute myelopathy (12)<br>-Chronic myelopathy (16)<br>-Motor neuron disease (1)<br>-Brain involvement (33)<br>-MS (10)<br>-Primary progressive MS (13)<br>-Diffuse CNS symptoms:<br>-Seizures (7)<br>-Cognitive dysfunction (9)<br>-Encephalopathy (*n* = 2)<br>-Optic NP (13)<br>-PNS involvement (51)<br>-Pure sensory NP (28)<br>-Cranial nerve involvement (trigeminal, facial, or cochlear nerves) (16)<br>-Multiple mononeuropathy (7),<br>-Myositis (2),<br>-Polyradiculoneuropathy (1) | -MRI findings:<br>-White matter lesions (70%)<br>-Radiologic criteria for MS (40%)<br><br>Lab findings:<br>-Seropositivity to anti-Ro or anti-La (21%) |
| Yadav et al. (2011) (78) | PNS | *N* = 6 | -Peripheral sensori-motor NP and sensory ataxic NP (3/6)<br>-Mononeuritis multiplex (2/6)<br>-Cranial NP (2/6)<br>-Autonomic NP (1/6)<br>-Myelopathy (4/6)<br>-Optic NP (2/6)<br>-Classical sicca properties (5/6) | -Vasculitis<br>-Chronic nonuniform axonopathy<br>-Seropositivity to anti-Ro or anti-La (5/6) |
| Estiasari et al. (2012) | CNS | *N* = 22 Positive for anti-AQP4 | -CNS involvement | -MRI findings:<br>-Discrete lesions in the in the brainstem, cerebrum, and optic nerve<br>-Posterior column lesions in the cervical spinal cord |
| Lauvsnes et al. (2013) | CNS | *N* = 66 | -Memory dysfunction<br>-Reduced volume of hippocampi | -Association between CSF anti-NR2 antibodies and memory and learning deficits |
| Lauvsnes et al. (2014) (103) | CNS | *N* = 50 | -CNS involvement<br>-Reduced volume of hippocampi | -Association between CSF anti-NR2 antibodies and hippocampal gray matter atrophy |
| Park et al. (2015) (95) | CNS | *N* = 106 with NMO | -NMO spectrum disorder | -Association between seropositivity to anti-Ro and presence of AQP4-Ab |
| Li et al. (2018) | CNS | A case | -Recurrent cerebral infarctions | -Seropositivity to anti-Ro, anti-nuclear antibodies, anti-β2-glycoprotein antibodies, protein S activity, IgG, and C-reactive protein |
| Lauvsnes et al. (2018) (109) | CNS | *N* = 93 | -Cerebral involvement | -Increased levels of TWEAK<br>-Increased levels of S100B<br>-No relationship between serum or CSF levels of TWEAK or S100B and neuropsychiatric symptoms<br>-Association between anti-NR2 antibodies and impairment in visuospatial processing and motor functioning |
| Bårdsen et al. (2019) (106) | CNS/ PNS | *N* = 49 | -Fatigue, depression, and pain | -Association between CSF levels of IL-1β-related molecules (IL-1Ra, IL-1RII, and S100B) and clinical manifestations of depression and pain<br>-Association between CSF levels of Hcrt1 and fatigue, independently of IL-1β |
| Perzyńska-Mazan et al. (2020) (50) | PNS | *N* = 61 | -Axonal loss or demyelination (63.9%)<br>-Peripheral NP, mainly axonal type (47.5%) | -Association between seropositivity to Anti-Ro and axonal neuropathy<br>-Association between seropositivity to RF and demyelination. |

(Continued)

Table 1. **Mechanisms underlying neuropsychiatric manifestations in pSS—Continued**

| Author (year) | CNS/ PNS | Sample size | Complications | Findings |
|---|---|---|---|---|
| Tetsuka et al. (2020) (124) | CNS | Two cases | Case 1: Cerebellar degeneration<br>Case 2: CIDP | -Anti-Ro in both serum and CSF<br>-Loss of Purkinje cells<br>-Expression of Ro52/TRIM21 in the cerebral cortex, hippocampus, and cerebellum<br>-Expression of Ro52/TRIM21 in Purkinje cells |
| Barcelos et al. (2021) (81) | PNS | *N* = 55 | -Corneal subbasal nerve involvement | -Reduced nerve length and density associated with IL21$^{+}$CD8$^{+}$T-cells and B-cell subgroups (total memory, unswitched memory, and CD24HiCD27+ B-cells) |
| Cafaro et al. (2021) (24) | PNS | *N* = 1695 | -PNS involvement (3.7%)<br>-Pure sensory NPs and axonal sensorimotor polyneuropathies (most common) | -Higher rate of other organ involvement, purpura, lowed levels of complement (C4), and cryoglobulinemia in patients with PNS involvement |
| Zheng et al. (2023) (47) | PNS | *N* = 108 | -pSS-PNS | -A notable association between IgG, α-FIgG, PLT, and dry mouth<br>-High levels of α-FIgG, IgG, and PLT were identified as independent risk factors<br>-Increased PLT and high anti-SSB antibody titers were linked to a greater risk of motor and sensory nerve damage. |
| Zheng et al. (2023) (48) | PNS | *N* = 12 | -pSS-PN<br>biopsies on 12 patients (4 men, 8 women; age 50.4 ± 16.3 years; disease duration 4.43 ± 4.06 months). | -Reduction in large and small myelinated fibers<br>-Decrease in non-myelinated fibers (mild in 4, moderate in 5, severe in 3)<br>-Inflammatory infiltration with mixed peripheral neuropathy predominantly axonal in nature<br>-Presence of CD68$^{+}$ macrophages in small vessels and nerve bundles, with dominance of M2 subtype<br>-Macrophage activity around nerve fibers with engulfment of myelin and axons, leading to swelling, axonal atrophy, and axon-myelin separation |
| Wu et al. (2023) (49) | PNS | *N* = 60 | -pSS-PNS | -Longer disease duration<br>-Higher frequency of Raynaud's phenomenon, anti-SSB antibodies, RF, and hyperglobulinaemia<br>-Hyperglobulinaemia, RF, and anti-SSB antibodies identified as independent risk factors for PN<br>-Clinical improvement and reduced mRS scores in 10 out of 14 pSS-PN patients following immunosuppressive therapy |
| Afzali et al. (2023) (125) | CNS | *N* = 194 | -CNS demyelinating disease in pSS | -CNS involvement observed in 22 patients, with demyelinating patterns in 19<br>-Lower prevalence of glandular symptoms, higher frequency of anti-SSA/Ro antibodies in CNS group<br>-Frequent misdiagnosis as MS due to atypical onset age and clinical course<br>-Poor response to MS therapies; improved outcomes with B-cell-depleting agents |
| Yilmaz et al. (2024) (126) | CNS | A case | -A 16-year-old female pSS with CNS involvement | -Severe headache<br>-Neurological symptoms unresponsive to multiple immunosuppressants, but improved with rituximab |
| Bandler et al. (2024) (127) | CNS | A case | -Diplopia (double vision)<br>-Eye pain<br>-Periorbital swelling<br>-Right abducens nerve (CN VI) palsy<br>-61-year-old | -Enlarged extraocular muscles and optic nerve compression.<br>-Treated successfully with steroids and cyclophosphamide |

(Continued)

Table 1. **Mechanisms underlying neuropsychiatric manifestations in pSS—Continued**

| Author (year) | CNS/ PNS | Sample size | Complications | Findings |
|---|---|---|---|---|
| Mihai et al. (2023) (128) | PNS | *N* = 121 | pSS with PNS neuropathy | -Development of neurological symptoms in 25.61% during follow-up.<br>-Elevated disease activity in 80.64% of PN cases higher pain levels<br>-Increased neutrophil counts and NLR, along with decreased lymphocytes, monocytes, and MLR<br>-Lower levels of gammaglobulins, complement C3 and C4, total proteins, and vitamin D |

AQP4: Anti-aquaporin-4, Anti-NR2 antibodies: NR2 subtype of the N-methyl-D-aspartate receptor, CIDP: Chronic inflammatory demyelinating polyradiculoneuropathy, CNS: Central nervous system, CSF: Cerebrospinal fluid, DRG: Dorsal root ganglion, IL-1β: Interleukin-1β, MLR: Monocyte-to-lymphocyte ratio, MS: Multiple sclerosis, NLR: Neutrophil-to-lymphocyte ratio, NMO: Neuromyelitis optica, NP: Neuropathy, PN: Peripheral neuropathy, PNS: Peripheral nervous system, RF: Rheumatoid factor, TWEAK: Tumor necrosis factor (TNF)-like weak inducer of apoptosis, Hcrt1: Neuropeptide hypocretin-1.

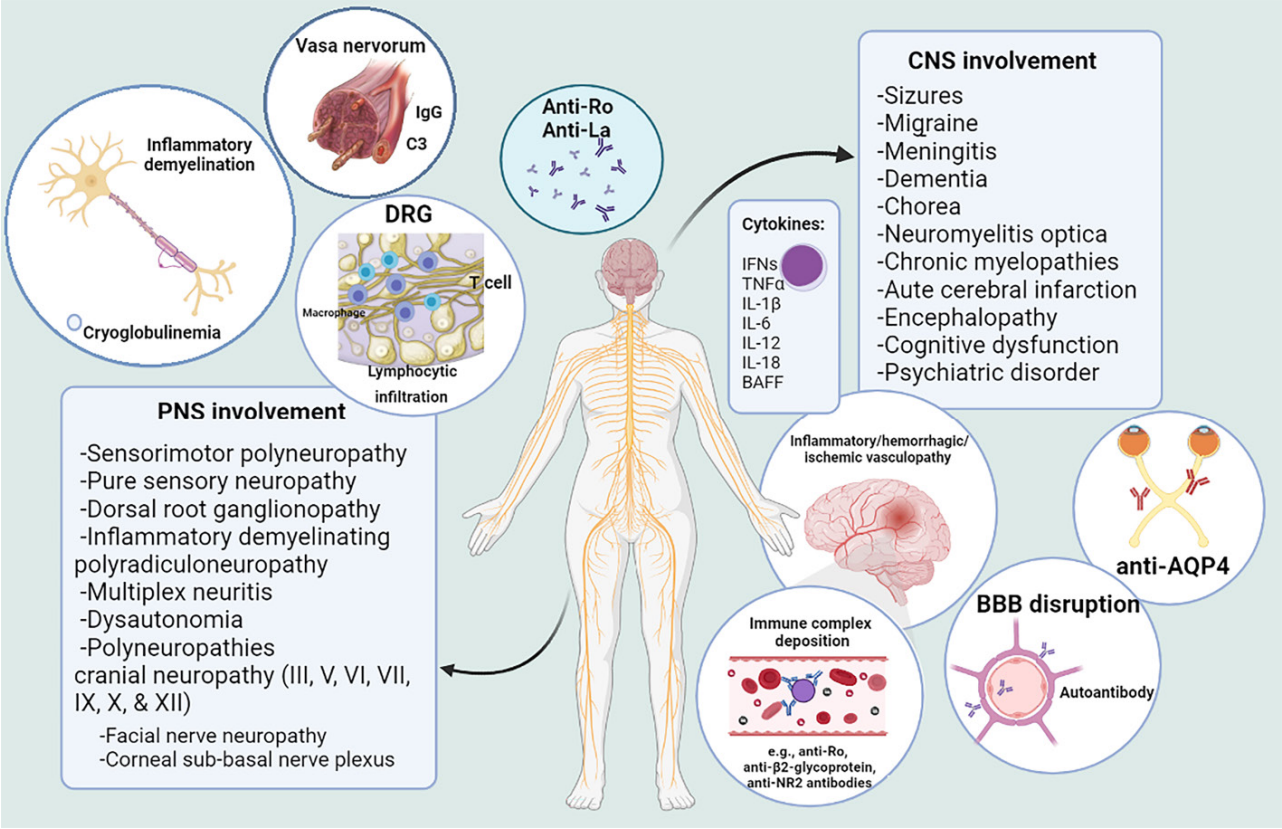


Fig. 1 **Neurological Manifestations and Underlying Mechanisms of Central and Peripheral Nervous System Involvement in pSS. This illustration depicts the spectrum of neurological features associated with central (CNS) and peripheral (PNS) nervous system involvement in pSS, highlighting key immunopathogenic mechanisms, such as autoantibody production, vasculitis, and immune-mediated neuronal damage. (Created with BioRender.com)**

typical of perivascular inflammatory infiltration.[70,71] IgG and complement 3 (C3) deposits in the vasa nervorum have been observed in pSS-PNS.[72] Lymphocytic infiltration of dorsal root ganglia may lead to sensory ganglionopathy.[73,74] Histopathological studies suggest necrosis of the nerve wall vasa nervorum, along with T-cell and macrophage infiltration.[69] Macrophages are a prominent immune cell population within the salivary glands (SG) of patients with pSS, and their abundance correlates with the degree of glandular lymphocytic infiltration, as measured by the focality index. These cells contribute to tissue damage by releasing proinflammatory cytokines that harm salivary gland epithelial cells (SGECs).[75] Notably, macrophages possess functional plasticity, enabling them to polarize into either proinflammatory M1 or anti-inflammatory M2 phenotypes in response to microenvironmental signals. M1 macrophages amplify inflammatory responses, promote matrix breakdown and apoptosis, and facilitate Th1 immune activation. Conversely, M2 macrophages are involved in dampening T-cell responses, supporting Th2 immunity, and promoting tissue repair. A dysregulated M1/M2 polarization dynamic is considered a key factor in pSS pathogenesis.[76] Additionally, T-cell infiltration and associated damage to the dorsal root ganglia have been implicated in sensory ataxic neuropathy observed in pSS patients.[77] Inflammation and obstruction of the vasa nervorum and vasculitic involvement of epineurial vessels were observed in pSS patients with

sensorimotor neuropathy.[6,78] Cryoglobulinemia has been shown to be related to the PNS EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI).[79] Abnormal morphology of the corneal sub-basal nerve plexus was observed in pSS patients.[80] Reduced nerve length and density were associated with IL21+ CD8+ T-cells and B-cell subgroups.[81] Mixed cryoglobulinemia has been identified in approximately 36.6% of pSS patients exhibiting neurological involvement.[62] This condition is particularly prevalent among those with sensorimotor polyneuropathy and is frequently associated with more severe extraglandular manifestations. The presence of cryoglobulins not only reflects heightened systemic disease activity but also correlates with an increased risk of lymphoproliferative disorders, including lymphoma.[82]

### *Central Nervous System*

The pathological events related to CNS involvement are associated with abnormal microRNA expression, DNA demethylation, imbalanced levels of IFN I (α and β) and II (γ), vasculitis, and secretion of anti-neuron autoantibodies.[83–86] The direct effects of antibodies on the progression of neuropathy are not well established.[87] Neuropathological analyses of brain tissue from pSS patients with CNS involvement have revealed evidence of inflammatory and ischemic-hemorrhagic vasculopathy, predominantly affecting small vessels and characterized by mononuclear cell infiltration.[88] In particular, vasculitis of the vasa nervorum is considered a critical contributor to CNS pathology in pSS.[89] A notable association has been reported between elevated anti-Ro (SSA) antibody titers and cerebral angiographic abnormalities consistent with small-vessel vasculitis, suggesting a pathogenic role for anti-Ro antibodies in CNS vascular injury.[90] This may be mediated by immune complex deposition within the cerebral microvasculature, driven by B-cell hyperactivity and autoantibody overproduction—hallmarks of the systemic autoimmune response in pSS.[91] Furthermore, the presence of specific antibodies against nervous tissue has been noted. The detection of antibodies in the cerebrospinal fluid (CSF) of pSS patients confirms the migration of lymphocytes to the CNS.[92] Along with demyelination, the pathogenesis of optic neuritis is associated with ischemic vasculitis.[35] A key immunopathological mechanism underlying neuromyelitis optica (NMO) involves the production of autoantibodies targeting aquaporin-4 (AQP4), a water channel protein abundantly expressed on astrocytic end-feet. This mechanism has also been observed in patients with pSS and other systemic autoimmune disorders.[93] Elevated AQP4 antibody titers in pSS are strongly linked to neurological syndromes, such as optic neuritis and transverse myelitis, which clinically mimic multiple sclerosis.[94] Retrospective analyses have demonstrated a robust correlation between AQP4 seropositivity and the presence of non-organ-specific autoantibodies, including anti-Ro, anti-La, ANA, and anti-dsDNA, suggesting shared immunological pathways among overlapping autoimmune conditions.[95] Anti-AQP4 antibodies are believed to mediate CNS injury by targeting astrocytic structures at the blood-brain barrier (BBB), thereby initiating inflammation and tissue damage.[35] Furthermore, increased levels of anti-β2-glycoprotein I antibodies—known contributors to thrombotic events—have been implicated in ischemic cerebrovascular complications in pSS.[96] Additional reports have highlighted an association between serum anti-Ro antibodies and limbic encephalitis in pSS, with detection of these antibodies in CSF indicating BBB disruption driven by autoantibody activity.[97–99] The anti-Ro and anti-La antibodies can target three types of cellular proteins, including Ro52, Ro60, and La48.[100] In a recent study, autopsy findings revealed that cerebellar atrophy due to degeneration of Purkinje cells was associated with the presence of Ro52 protein in these cells. Additionally, the synthesis of this protein in neurons of the hippocampus and cortex was confirmed.[101] Neuropsychiatric symptoms in pSS may stem from the production of autoantibodies targeting the NR2 subunit of N-methyl-D-aspartate (NMDA) receptors, known as anti-NR2 antibodies.[102–104] These antibodies, which specifically target the NR2 component of NMDA receptors, are crucial for cognitive functions, such as learning, memory, and emotional regulation.[105–107] Elevated levels of anti-NR2 antibodies in the CSF have been linked to hippocampal gray matter atrophy, as demonstrated by MRI imaging.[108] These antibodies appear to contribute to neuronal damage, leading to significant reductions in hippocampal gray matter volume in pSS patients.[103] Moreover, increased levels of tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) in the CSF of pSS patients have led to the hypothesis that anti-NR2 antibodies secreted by resident B-cells bind to neurons and induce TWEAK secretion. The binding of TWEAK to Fn14 may increase the permeability of the BBB. However, no relationship was found between serum or CSF levels of TWEAK and neuropsychiatric symptoms in pSS patients.[109] Higher levels of CSF S100B, a biomarker of activated astrocytes, were reported in pSS patients. It appears that B-cells can stimulate astrocytes to secrete S100B, which can bind to various cells, such as neurons. However, no association was found between markers of BBB integrity or astroglial activity and neuropsychiatric symptoms.[109] Although the role of B-cell hyperactivity via antibody secretion has been highlighted, the contribution of T-cell subtypes, including innate T cells, CD4+ T cells, and CD8+ tissue-resident memory (TRM) cells, has been implicated due to their roles in eliciting inflammatory cell infiltration, activating B-cells, secreting pro-inflammatory mediators, and inducing tissue damage and metabolic alterations in pSS.[110]

Overproduction of inflammatory cytokines from T-cells and dendritic cells plays a significant role in the pathogenesis of neural disorders in pSS. The key pro-inflammatory cytokines contributing to pSS pathogenesis include IFNs, TNF-α, interleukin (IL)-1β, IL-6, IL-12, IL-18, and B-cell activating factor (BAFF).[111] A relationship exists between chronic inflammation and neurological manifestations, such as pain and neuropathic disorders.[112] Elevated levels of IL-1β in the CSF, capable of bypassing the BBB, show a significant association with depression and pain in pSS. Additionally, an association between CSF levels of the neuropeptide hypocretin-1 (Hcrt1) and fatigue has been demonstrated.[106] In the pathogenesis of pSS, dysregulation of the 2'–5' oligoadenylate synthetase 1 (OAS1) gene results in decreased responsiveness to IFN-γ.[113] Overexpression of IFN-γ and a subsequent imbalance in the tryptophan/kynurenine pathway have been shown to play a critical role in the pathogenesis of severe neurological manifestations, such as fatigue and chronic neuropathy.[65] Depression and other neuropsychiatric complications of pSS may also be related to elevated levels of IFN-γ.[69] Increased levels of albumin in the CSF/serum index indicate a disrupted

BBB in pSS cases.[104] Additionally, cfDNA has been considered a biomarker of BBB disruption in neurological diseases.[114] While high levels of cfDNA in the serum of pSS patients are associated with impaired DNase I activity, no reports confirm the role of cfDNA in pSS-related CNS involvement.[115] Methylation patterns of cfDNA may reflect pathophysiological events in the brain, and this biomarker has been proposed as a predictor of multiple sclerosis in several studies.[116,117] Aseptic meningitis may be associated with reactions to certain substances (e.g., viral proteins or drugs), the presence of oligoclonal bands, elevated IgG levels, and antibodies in the CSF. These CSF antibodies can induce meningeal cell damage, leading to the secretion of autoantibodies and lymphocyte infiltration of the CNS.[118] Inflammation of meningeal vessels can also contribute to meningitis.[119] According to a recent study, salivary gland-derived fibroblasts (SGF) in pSS exhibit heightened pro-inflammatory characteristics. The research demonstrated that SGF from pSS patients proliferate at higher rates compared to controls and respond robustly to pro-inflammatory stimuli, such as IL-1 and poly(I:C). RNA sequencing analysis revealed significant activation of key inflammatory signaling pathways, including NF-κB, JAK-STAT, and interferon response pathways. Additionally, the study found increased expression of non-coding enhancer RNAs (eRNAs) in SGF, and treatment with a bromodomain inhibitor (I-BET) effectively suppressed both eRNA and inflammatory cytokine expression.[120]

## Therapeutic Approaches for Disease Management

No consensus exists regarding the specific treatment of neurological manifestations in pSS. Corticosteroids and immunosuppressive drugs are commonly prescribed for managing patients with either PNS or CNS involvement.[14,67] Typically, pSS patients with peripheral neuropathy show poor responses to pharmacological treatment.[62,129,130] Treatment is generally recommended based on the severity of manifestations. In some patients with PNS involvement, immunosuppressive drugs, including corticosteroids, azathioprine, cyclophosphamide, and plasmapheresis, have shown only mild effectiveness.[131,132] Corticosteroids are considered beneficial for treating multiple neuropathy and multiple cranial neuropathy.[130] High doses of corticosteroids are usually initiated in patients with CNS symptoms, with exceptional outcomes in some cases. For example, treatment with high-dose corticosteroids remarkably improved dementia in one patient.[133] In cases where progressive symptoms lead to neurological deterioration, a combined regimen of cyclophosphamide and corticosteroids, or other immunosuppressive agents such as azathioprine or chlorambucil, is recommended to manage the condition.[134] One study documented that a combination of steroids and monthly cyclophosphamide was effective in managing acute and chronic myelopathies.[135]

Although randomized studies are essential, this treatment should be considered for patients with progressive pSS and CNS involvement. In a case series, immunosuppressive treatment, particularly with cyclophosphamide, resulted in more favorable outcomes for pSS patients with necrotizing vasculitis compared to those with lymphocytic vasculitis.[136] Historically, the management of pSS has focused primarily on symptom relief, with limited evidence supporting the efficacy of systemic therapies. However, advancements in understanding the pathophysiology of pSS have facilitated the development of novel biologic agents targeting specific disease mechanisms, offering new therapeutic options for managing progressive disease.[129] B-cell-targeted drugs, such as rituximab and epratuzumab, and anti-TNF agents, such as infliximab and etanercept, are used in pSS; however, their effectiveness for CNS symptoms remains uncertain.[137] Infliximab, a monoclonal antibody against TNF-α, has been shown to improve sensory ganglioneuronopathy.[138] Additionally, rituximab (a type I anti-CD20 antibody) may be useful for systemic complications in pSS patients and in some cases of refractory neuropathy.[139] In a clinical study, rituximab was effective in treating pSS patients with PNS symptoms, particularly those with vasculitis or cryoglobulinemia-mediated PNS involvement.[139] A report detailing four cases of pSS suggests that a treatment regimen starting with rituximab, followed by obinutuzumab (a glycoengineered, humanized type II anti-CD20 antibody), could be effective for alleviating psychotic symptoms.[140]

Several studies have confirmed the efficacy of oromucosal IFN-α in the management of pSS.[141–143] In a report on three cases, treatment with oral IFN-α was shown to be effective in improving pSS-related sensory ataxic neuronopathy and axonal sensorimotor neuropathy with demyelinating features.[144] However, the mechanisms underlying IFN-α-induced neurological improvement in pSS remain unclear. The beneficial effects of intravenous immunoglobulin (IVIG) have been demonstrated in the treatment of pSS cases with painful sensory neuropathy and radiculoneuropathy, though less so for ataxic neuropathy.[145–148] Additionally, plasma exchange (PE) has been used in the treatment of pSS patients.[149] PE was reported as an effective rescue therapy for neuromyelitis optica after the failure of high-dose steroid therapy. In a retrospective study, nine patients with neuromyelitis optica were followed up for management through PE. The results revealed that PE was a potential rescue therapy for neuromyelitis optica patients with autoantibodies against AQP4.[135] Furthermore, RCI001 effectively inhibits inflammation and oxidative stress, demonstrating a promising therapeutic effect in a pSS mouse model, and it may serve as a novel treatment option for this condition.[150] Recent research indicates that mesenchymal stem cells (MSCs) and their exosomes can alleviate pathological alterations associated with pSS in salivary and lacrimal glands, primarily by inhibiting T- and B-cell-associated inflammation in animal models. MSCs have been shown to enhance saliva flow, reduce salivary gland damage, and inhibit pulmonary inflammation by downregulating IL-17-producing γδ T cells. They also decrease IL-12 production, preventing the activation of Th1 cells and the subsequent generation of autoantibodies.[151] Studies have demonstrated that MSC-produced IFN-β promotes IL-27 production in dendritic cells (DCs), which helps restore the balance between regulatory T cells (Tregs) and Th17 lymphocytes, alleviating pSS symptoms. Additionally, intravenous administration of umbilical cord MSCs (UC-MSCs) and their exosomes enhanced the Tregs/Th17 ratio in inflamed tissues, improving inflammation and symptoms.[152] Exosomes derived from labial gland MSCs (LG-MSC-Exos) promoted the differentiation of naïve T cells into TGF-β-producing Tregs while suppressing their transformation into inflammatory Th17 cells, leading to reduced

inflammatory cytokines and improved tear secretion in pSS models.[153] Overall, the evidence highlights the promising potential of MSCs in treating pSS, harnessing their immunosuppressive and regenerative properties to mitigate inflammation, enhance tissue repair, and restore immune equilibrium.[151]

## Conclusion

Neurological manifestations, including PNS and CNS involvement, are frequently reported in patients with pSS. This review highlights the diversity of neurological complications associated with pSS. Although CNS involvement is less frequent than PNS involvement, pSS patients should be evaluated for CNS complications. Neuroimaging techniques and serological biomarkers can be used to predict disease progression and CNS involvement. The pathogenesis and features of PNS and CNS involvement are varied and remain elusive. However, the critical role of immunologically mediated events has been confirmed. Among several mechanisms, vasculitis is considered a key pathogenic feature for both PNS and CNS involvement. Additionally, a disrupted blood-brain barrier (BBB), lymphocyte infiltration, and secretion of antibodies against brain tissue may contribute to CNS complications. With deeper insight into the biology underlying disease mechanisms and the development of predictive biomarkers, more effective treatment approaches can be established. Conventional immunosuppressive medications and cutting-edge biologic antibodies are among the reported therapeutic approaches for pSS patients with CNS or PNS involvement. Randomized, multicenter investigations are needed to confirm the efficacy of these therapeutic approaches, which have shown promise in case studies or small series.

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### *Disclosure of Potential Conflicts of Interest*

The authors declare that they have no conflict of interest.

### *Research Involving Human Participants and/or Animals*

N/A

### *Informed Consent*

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### *Consent to Publish*

N/A

### *Authors' Contributions*

FM and TM conceived the study idea. All authors contributed equally to drafting the manuscript. MS provided critical revisions for important intellectual content. All authors reviewed and approved the final version of the manuscript and any subsequent revisions for submission.

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### *Availability of Data and Materials*

No datasets were generated or analyzed during the current study.

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