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NOT JUST DRYNESS: A REVIEW OF PERIPHERAL NEUROPATHY IN PRIMARY SJÖGREN'S SYNDROME

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ABSTRACT

Introduction: Primary Sjögren's syndrome (pSS) is a chronic systemic autoimmune disease primarily affecting exocrine glands, but it can also involve the peripheral nervous system (PNS). Peripheral neuropathy (PN) is a diverse extraglandular manifestation of pSS, with distal axonal polyneuropathy and sensory neuronopathy (ganglionopathy) being the most prevalent subtypes. PN symptoms often precede the diagnosis of pSS, posing a diagnostic challenge.
Materials and methods: An electronic literature search was performed using PubMed. Search terms included 'primary Sjögren's syndrome (pSS)', 'peripheral neuropathy', 'neurological involvement', 'Neuro-Sjogren', 'polyneuropathy', 'small fibre neuropathy' as keywords. This review focused on articles published in English from their inception until 2025.
Conclusions: Diagnostic approaches combine clinical evaluation, electrophysiological testing, and other procedures such as nerve and skin biopsies. Treatment remains challenging due to the heterogeneity of neuropathic presentations and limited evidence guiding clinical decisions. Corticosteroids are primarily effective in neuropathies associated with vasculitis. Immunosuppressive agents and intravenous immunoglobulin (IVIG) are also commonly used. In addition, effective symptomatic management of neuropathic pain plays an important role in the overall care of the patient. As evidence on the treatment of PN in pSS is limited further research is needed. Early detection and individualized treatment are essential to improve patients' quality of life.

KEYWORDS

Primary Sjögren's Syndrome (pSS), Peripheral Neuropathy, Neuro-Sjogren, Polyneuropathy, Small Fibre Neuropathy

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Introduction and purpose

Primary Sjögren's syndrome (pSS) is a chronic, autoimmune disease causing inflammation of the exocrine glands, particularly salivary and lacrimal glands. Lymphocytic infiltrates in the glands impair their function, resulting in sicca symptoms such as dryness of the mouth (xerostomia) and dryness of the eye (xerophthalmia). Dryness, fatigue and pain are the three central clinical symptoms of the pSS [1]. However, the disease can also involve other organs, including the peripheral nervous system (PNS) and the central nervous system (CNS). Neurological manifestations may precede the diagnosis of pSS causing diagnostic difficulties [2,3]. The most common neurological disorder in pSS is peripheral neuropathy (PN) which can present with symptoms such as tingling sensation, numbness and pain. Liampas et al. estimated that PN affects approximately 15% of patients with pSS (with a 95% confidence interval ranging from 10.7% to 20.7%) [4].The aim of this review is to comprehensively analyse and synthesize the latest evidence on peripheral neuropathy in pSS, focusing on subtypes, prevalence, diagnostic approach and treatment outcomes.

Materials and Methods

A comprehensive literature search was conducted using the PubMed database for studies published between 2010 and 2025. Keywords included "neuropathy OR polyneuropathy OR mononeuropathy" AND "Sjogren OR Sjögren OR pSS". Inclusion criteria were full-text studies including systematic reviews, meta-analyses, and case series with a focus on peripheral neuropathy in pSS. Studies not available in English or not related to human subjects were excluded. Articles were selected based on relevance and methodological quality. Information was collected regarding prevalence, neuropathy subtypes, diagnostic methods, potential pathomechanisms, and treatment options. As this review was not designed as a meta-analysis, no statistical methods were applied. Although this review primarily focused on studies published between 2010 and 2025 to ensure relevance to current clinical practice, some older research was also included. This was necessary when data from earlier studies was cited in the more recent publications. As a result, a certain degree of heterogeneity may be present, reflecting changes in diagnostic criteria, clinical outcomes, and treatment approaches over time.

General overview of Sjögren Syndrome

Sjögren's syndrome is a chronic systemic autoimmune disease characterized by lymphocytic infiltration of exocrine glands, leading to hallmark symptoms of dry eyes and dry mouth. It is classified as “primary” when it occurs independently, without being associated with any other autoimmune diseases. Although glandular involvement is a defining feature, pSS frequently presents with a range of systemic complications, including musculoskeletal, pulmonary, renal, and neurological manifestations [1,5]. Sjögren syndrome is also associated with an increased risk of non-Hodgkin lymphoma due to chronic B-cell stimulation [6]. Moreover, the disease significantly impairs patients' daily functioning, as fatigue, depression and anxiety are commonly reported [7]. The disease primarily affects middle-aged women. Diagnosis is typically made in the fifth decade of life [8]. However, initial symptoms may manifest several years before the diagnosis. Diagnosis of pSS is based on characteristic symptoms, tests including salivary gland biopsy and the presence of specific autoantibodies such as anti-SSA (anti-Sjögren’s-syndrome-related antigen A, also known as anti-Ro) and anti-SSB (anti-Sjögren’s-syndrome-related antigen B, also known as anti-La). Other tests, like Schirmer’s test or salivary flow measurement, may also help. Treatment typically involves symptomatic therapies such as artificial tears or saliva substitutes and systemic medications, including disease-modifying agents and biological drugs. To evaluate disease activity in pSS, the EULAR Sjögren’s Syndrome Disease Activity Index (ESSDAI) is commonly used [9]. This validated tool covers 12 organ-specific domains, including the PNS and CNS, to assess systemic disease activity and help guide clinical decisions.

Clinical subtypes

Peripheral neuropathy can be broadly divided into two subcategories, based on pathological (e.g. biopsy) and electrophysiological findings. There is pure small fiber neuropathy (SFN), that primarily impacts unmyelinated C fibers and thinly myelinated Aδ fibers. Meanwhile, large fiber neuropathy (LFN) involves damage to the myelinated Aα and Aβ fibers, often accompanied by some level of small fiber impairment. Thicker axons are responsible for transmission of vibratory sensation, proprioception, motor function and light touch, so their involvement may impair these functions. The pooled prevalence of LFN in pSS is estimated to be 15.0% (95% confidence interval= 10.7%-20.7%), with high heterogeneity across the studies [4]. LFN is primarily pure-sensory but can also occur as sensorimotor neuropathy. It poses a clinical challenge to distinguish sensory LFN from SFN, so more testing is required to assess the type of neuropathy [10].

1. Distal Axonal Polyneuropathy

The most common type of pSS-related neuropathy is distal axonal polyneuropathy. It is responsible for almost 80% of cases involving LFN associated with pSS (calculation based only on studies classifying peripheral neuropathy as either distal axonal neuropathy or sensory ganglionopathy) [4]. Not only does it occur in pSS but axonal polyneuropathy is also the most prevalent type of peripheral neurologic manifestations in other rheumatic diseases, including rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) [11,12]. The symptoms include symmetric paraesthesias such as numbness or tingling sensation, especially in distal parts of lower limbs and stocking-and-glove-pattern pain. Lower limbs are far more affected than upper limbs [2]. Symptoms may be either just sensory or sensorimotor. Clinical manifestations differ depending on which type of fibers is affected. Involvement of Aδ and C fiber results in typically burning pain, itching or allodynia. Motor symptoms, such as muscle weakness, occur with the progression of the disease [13]. Nerve biopsy reveals axonal degeneration along with signs of remyelination, but with no evidence of necrotizing inflammation in the blood vessels (contrary to the multiple mononeuropathy) [2]. Electrodiagnostic tests show a symmetrical pattern of sensory fiber damage consistent with axonal loss.

2. Sensory Neuronopathy (Ganglionopathy)

The second, most common neuropathy among pSS patients is sensory neuronopathy, also known as ganglionopathy [2,4]. It is yet another example of LFN. It affects the cell bodies of the sensory neurons located in the dorsal root ganglia. As type Ia large sensory fibers transmit signals from muscle spindles through the dorsal root ganglia, symptoms are typically characterized by signs of impairment in the type Ia sensory fibers. The most noticeable clinical manifestation is the impaired balance with gait unsteadiness [14]. Balance disorder can be severe and reduce patients’ mobility, forcing them to use a wheelchair [2]. Moreover, vibratory sensation might be diminished and tendon reflexes may be absent (with maintained muscle strength). Symptoms in sensory neuronopathy tend to be asymmetrical, however not always is it a rule [15]. Electrodiagnostic testing reveals decreased or even missing sensory nerve action potentials. Abnormalities can

also be seen in somatosensory evoked potentials- a test measuring how sensory signals travel through the nerves to the CNS. Nerve biopsy reveals T-lymphocyte infiltration in the dorsal root ganglia and a loss of large nerve fibers. However, motor conduction studies and needle electromyography results are normal [16].

3. Other Types of Neuropathy

According to Liampas et al. other types of neuropathy are rare and account for <1% of pSS- related neuropathies [4]. Multiple mononeuropathy (mononeuritis multiplex) is characterized by the damage of at least two separate peripheral nerves in different areas of the body. Symptoms vary depending on the region innervated by the affected nerve. When symptoms from different nerves overlap it may imitate polyneuropathy. Multiple mononeuropathy occurs in pSS patients with concurrent vasculitis [17]. Inflammation of the blood vessels supplying the nerves causes ischemia and nerve damage. Since vasculitis also affects other organs, systemic symptoms may be present. Electrophysiological studies typically show axonal damage and "pseudo-blocks," reflecting regions of nerve ischemia [18]. Histopathological examination of these areas reveals necrosis of the blood vessels supplying the nerve, along with infiltration by T cells and macrophages. Laboratory tests often show the presence of cryoglobulins, proteins (usually composed of immunoglobulins) that precipitate at temperatures below 37 °C in small- to medium-sized blood vessels, leading to inflammation and organ damage. Consequently, an elevated erythrocyte sedimentation rate (ESR) and increased C-reactive protein (CRP) levels are often observed [19,20]. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is uncommon in pSS and has only been reported in a few studies [6,21]. Its clinical presentation includes proximal and/or distal muscle weakness, sensory deficits, and reduced deep tendon reflexes. Electrophysiological studies show evidence of demyelination (detailed diagnostic criteria have been established by the European Academy of Neurology/Peripheral Nerve Society and are beyond the scope of this review) [18]. A distinguishing feature of CIDP is elevated protein levels in the cerebrospinal fluid, found in approximately 90% of patients [2,22].

4. Small Fiber Neuropathy (SFN)

One of the most common neuropathies that occur in pSS is small fibre neuropathy (SFN). According to Sène et al., patients with pSS and SFN were mostly female (approximately 90%) [23]. SFN results from damage to A-δ small myelinated fibres and unmyelinated C fibres, which are primarily responsible for transmitting pain and temperature signals to the central nervous system. Therefore the most striking symptom of SFN is neuropathic pain. Apart from the very painful burning paresthesias, sensation of numbness, tingling, pins and needles, and allodynia can occur [23,24]. Manifestations can be distal and symmetrical or asymmetrical [25,26]. It has also been observed that restless leg syndrome (RLS) is more prevalent in patients with SFN. Pain might be aggravated at rest while moving can reduce it [27]. As noted by Liampas et al., these observations might suggest that small fiber involvement could be an early sign of subsequent large fiber PN [4]. In pSS-related pure SFN symptoms usually precede the diagnosis of pSS [23]. Neurological examination often appears normal or may reveal reduced response to pinprick and impaired temperature sensitivity. Standard sensory nerve conduction testing usually does not detect any abnormalities. The absence of clinical signs and normal conduction studies may lead to a mistaken assumption of a psychosomatic disorder [2]. Diagnosis of SFN can be challenging and is typically based on reduced intraepidermal nerve fiber density on skin biopsy or abnormal results in quantitative sensory testing (QST). QST evaluates the function of small fibers by measuring the patient’s responses to different types of sensory stimuli like temperature, vibration, or light touch. QST is a psychophysical method, which means that it relies on the patient's perception and responses. As a result, its accuracy and reliability can be influenced by the patient's cognitive abilities and level of cooperation during the test. According to Seeliger et al., skin biopsy results show that nerve damage is more severe in patients with small fiber neuropathy linked to Sjögren’s syndrome, as they have lower intraepidermal nerve fiber density (IENFD) compared to those with idiopathic SFN [13].

5. Cranial Mononeuropathies

Trigeminal neuropathy is the most common cranial neuropathy in the pSS. It typically presents unilaterally and most frequently involves the maxillary branch of the trigeminal nerve. However, involvement of other cranial nerves has also been documented, including the optic, oculomotor, abducens, facial, vestibulocochlear, glossopharyngeal, and vagus nerves. According to Liampas et al., the pooled prevalence of cranial nerve involvement in unselected populations of patients with pSS was 5.4% (95% CI: 3.3%–8.9%),

based on a meta-analysis of 16 studies encompassing a total of 1,430 patients [4]. Nevertheless, substantial heterogeneity was observed across the included studies.

Table 1. Description of clinical symptoms and diagnostic tests used to diagnose different subtypes of peripheral neuropathy. ENMG- electroneuromyography; MRI- magnetic resonance imaging; CSF- cerebrospinal fluid

TYPE OF NEUROPATHY	CLINICAL SYMPTOMS	TESTING
Axonal sensorimotor neuropathy	Distal, symmetrical paresthesias and sensory deficits, progressively accompanied by distal symmetrical muscle weakness, with diminished or absent deep tendon reflexes.	ENMG: axonal polyneuropathy affecting motor and sensory fibers Nerve biopsy: recommended only in case of suspected vasculitis
Sensory neuronopathy (ganglionopathy)	Impaired proprioception and vibratory sensation. Positive Romberg. Absent deep tendon reflexes and normal strength	ENMG: reduced or absent sensory nerve action potentials Nerve biopsy: loss of large myelinated axons MRI: high intensity signal of the posterior columns on T2-weighted
Mononeuritis multiplex	Acute or subacute onset of symptoms, often painful, sensory and/or motor deficits in the areas innervated by individual nerves.	ENMG: axonal dysfunction and pseudo-blocks (caused by cryoglobulins) Nerve biopsy: vasculitis Laboratory tests: increased CRP and ESR; presence of cryoglobulins
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Proximal and distal muscle weakness. Sensory deficits and diminished deep tendon reflexes.	ENMG: signs of demyelination CSF: elevated protein
Small fibre neuropathy	Painful paresthesias. Physical examination most frequently reveals a patient with pinprick and thermal sensation loss and preserved motor functions.	Skin biopsy: reduced nerve fiber density Quantitative sensory testing
Cranial neuropathy	Symptoms differ depending on the affected nerve	

Diagnostic process

Diagnosing peripheral neuropathy involves a thorough clinical assessment of the patient's symptoms, followed by confirmation through electrodiagnostic testing. For all types of peripheral neuropathy, excluding cranial nerve involvement and small fiber neuropathy, evidence of peripheral neurological impairment should be confirmed by at least one nerve conduction study (NCS) [9]. Some additional tests may be required in certain subtypes of peripheral neuropathy. In case of the small fiber neuropathy, diagnosis should be confirmed using one or more of the following methods: skin biopsy demonstrating reduced intraepidermal nerve fiber density, altered or absent laser-evoked potentials, abnormal quantitative sensory testing (QST), and/or abnormal results in autonomic or sympathetic sensory function tests. For proximal demyelinating neuropathy, supportive findings may include an elevated protein level in the cerebrospinal fluid (CSF) and/or abnormalities in sensory evoked potentials. These diagnostic evaluations are also essential for the proper assessment and scoring of PNS involvement in the ESSDAI, ensuring standardized evaluation of disease activity.

Treatment of pSS-related neuropathies

The pathogenesis of pSS-related neuropathies is not fully understood. Therefore, there are no standardized guidelines for their treatment [2,4,28]. The choice of therapy also depends on the type of neuropathy and must be adapted to each patient's case. So far, no treatment has been clearly proven to stop the progression of pSS-related neuropathies, except when necrotizing vasculitis is identified in the biopsy samples [20]. In other situations, therapies that can stabilize or reduce neurological symptoms would be beneficial.

1. Glucocorticoid Therapy

Glucocorticoid treatment is the most extensively studied approach for managing neuropathy caused by pSS. In a retrospective study, Terrier et al. described patients treated with either oral prednisone (16 patients) or intravenous methylprednisolone pulses (22 patients) as initial therapy [20]. They found that patients with vasculitis responded significantly better after six months compared to those without vasculitis ($p < 0.001$). Similarly, Mori et al. evaluated 51 pSS patients who received prednisone at 1 mg/kg/day for the treatment of neuropathy. The greatest improvement was observed in those with multiple mononeuropathy, suggesting that these patients may have had underlying vasculitis affecting the peripheral nervous system [29]. Delalande et al. observed different therapeutic responses in different neuropathies: poor efficacy of corticosteroids in axonal polyneuropathies and neuronopathies, whereas both cyclophosphamide and corticosteroids proved effective in multiple mononeuropathies, suggesting these treatments should be used in the latter cases.

2. Immunosuppressive Agents

The role of immunosuppressive agents in pSS-related neuropathy needs further research as there is still little data available in this field. Delalande et al. evaluated the use of cyclophosphamide combined with corticosteroids in a small group of pSS patients with multiple mononeuropathy ($n = 7$), resulting in partial recovery or disease stabilization in all cases. In another retrospective cohort study, mycophenolate mofetil was used alongside glucocorticoids in a small group of patients with sensory ganglionopathy ($n = 7$), showing favorable outcomes [3].

3. Intravenous Immunoglobulin (IVIG)

Rist et al. made a conclusion that intravenous immunoglobulin (IVIG) may be useful in the treatment of pSS-related sensorimotor neuropathies or sensory neuropathies without any necrotizing vasculitis. They tested IVIG in 19 patients with pSS-related neuropathy who did not have necrotizing vasculitis. All patients received monthly IVIG infusions at a dose of 2 g/kg, administered over either 2 or 5 days. The treatment was well tolerated, with clinical improvement observed in about half of the patients. However, the effectiveness of this treatment in pSS-related ataxic neuropathy (which affects balance and coordination) appears to be uncertain. It was also indicated that additional research is needed to determine the optimal number of IVIG courses in a treatment, making it possible to evaluate whether the treatment is effective or not [30]. In a separate study by Mori et al., 13 pSS patients received IVIG at the same dosage over 5 days. Those with polyradiculoneuropathy (such as CIDP) and painful sensory neuropathy responded best, whereas patients with sensory ataxic neuropathy showed less favorable outcomes [29]. Pereira et al. tested IVIG in six patients with sensory ganglionopathy, used either alone or with other treatments, but results were poor [15]. Pindi Sala et al. reported on 12 pSS patients with pure small fiber neuropathy (SFN) treated with IVIG. In 75% of these patients, pain medications were discontinued, and in the remaining 25%, their need was reduced. The median treatment duration was 21 months (ranging from 2 to 51 months). Notably, the benefits of IVIG persisted even after treatment ended, with an average follow-up of 25 months [31]. These findings suggest that IVIG may provide long-term relief in SFN, although larger, controlled trials are needed to establish optimal dosing for both initial and maintenance therapy.

4. Symptomatic Treatment

Treating neuropathic pain may pose a challenge due to the heterogeneity of its underlying mechanisms and the frequent involvement of psychological and emotional factors that often accompany chronic pain. In the management of neuropathic pain, antiepileptic drugs such as gabapentin are used. Symptomatic treatment may also include tricyclic antidepressants and opioids. Coexisting depression and anxiety can interfere with effective pain control and should be recognized and addressed with appropriate, targeted interventions [32]. Although evidence-based guidelines for the management of neuropathic pain have been established, a comprehensive discussion of symptomatic treatment exceeds the scope of this review.

Pathogenesis and risk factors

The exact mechanism responsible for nervous system involvement in pSS remains unclear. Sène et al. described a connection between sensorimotor neuropathy associated with pSS and a higher occurrence of markers indicating B-cell monoclonal proliferation, along with signs of chronic B-cell activation. Chronic activation of B cells is characterized by increased levels of serum gamma-globulins, primarily IgG, and the presence of various serologic markers produced by B cells—such as antinuclear antibodies (ANA), anti-Ro/Sjögren's-syndrome-related antigen A (anti-Ro/SS-A), anti-La/Sjögren's-syndrome-related antigen B (anti-La/SS-B) antibodies, and rheumatoid factor (RF). However, patients with pSS-related sensorimotor neuropathy exhibited a similar B-cell activation profile to those without peripheral neuropathy, showing comparable rates of ANA, anti-SSA/Ro, anti-SSB/La antibodies, and RF. Compared to patients without peripheral neuropathy, those with pSS-associated sensorimotor neuropathy more frequently had positive serum markers of monoclonal B-cell proliferation. These markers included mixed cryoglobulins, monoclonal gammopathy, and B-cell non-Hodgkin lymphoma (B-NHL). Nonataxic sensory neuropathies are characterized by a lower prevalence of markers associated with chronic B-cell activation [24]. Jamilloux et al. identified cryoglobulinemia as a predictive factor for the development of neurological complications, particularly sensorimotor neuropathies and mononeuritis multiplex. Conversely, sensory neuropathies, especially ganglioneuronopathy, were described as not associated with cryoglobulinemia and were suggested to be related to lymphocytic infiltration instead [18]. Likewise, Sène et al. reported a correlation between sensorimotor neuropathies and the presence of mixed cryoglobulins, supporting the hypothesis that vasculitis may play a role in the pathogenesis of peripheral neuropathy associated with pSS. Liampas et al. also noted that the presence of beta-2 glycoprotein antibodies, perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA), and older age may be risk factors for peripheral neuropathy in patients with pSS [4]. However, larger-scale studies are required to verify these findings.

Conclusions

Peripheral neuropathy is a significant extraglandular manifestation of primary Sjögren’s syndrome, occurring with a diverse range of clinical presentations and underlying pathophysiological mechanisms. The most prevalent subtypes include distal axonal polyneuropathy and sensory neuronopathy (ganglionopathy). Neuropathy can be the first sign of pSS, even without accompanying sicca symptoms. It usually starts with sensory involvement and can later develop into a sensorimotor neuropathy. The diagnostic process should be subtype-specific and may require a combination of clinical symptoms, electrodiagnostic studies, nerve and skin biopsies and some additional tests. Treatment remains challenging due to the heterogeneity of the condition and a lack of standardized protocols. Corticosteroids are frequently used, particularly in cases associated with vasculitis (e.g., mononeuritis multiplex), with better outcomes reported in this subgroup. Immunosuppressive agents like cyclophosphamide and mycophenolate mofetil show promise, especially when combined with glucocorticoids. Intravenous immunoglobulin (IVIG) has demonstrated potential benefit, particularly in sensorimotor and SFN subtypes. Long-term outcomes and optimal treatment durations remain poorly defined, highlighting the need for randomized controlled trials and more robust long-term data. Early diagnosis and personalized treatment are key to slowing disease progression and improving patients’ quality of life.

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