Published in final edited form as:

Curr Treatm Opt Rheumatol. 2017 December ; 3(4): 275–288. doi:10.1007/s40674-017-0076-9.

Neurological Complications of Sjögren's Syndrome: Diagnosis and Management

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Abstract

Purpose of review—Neurologic disease is a common extraglandular manifestation of Sjögren's syndrome (SS), the study of which has been hampered both by the lack of uniform definitions for specific neurologic complications and by the imprecision of the tools used to diagnose SS. There is a great need to develop consensus criteria for classifying these varied neurologic manifestations, as has been done in systemic lupus erythematosus (SLE) "Arthritis and rheumatism 42:599-608, 1999". SS patients with certain forms of neurologic involvement, such as small fiber neuropathy and sensory ataxic ganglionopathy, frequently lack anti-SSA and anti-SSB antibodies and other serologic abnormalities. In these patients, neurologic disease is often their presenting manifestation, triggering a search for underlying SS. Given the frequent seronegativity of such patients, their diagnosis of SS rests heavily on the interpretation of a labial gland biopsy. However, these biopsies are prone to misinterpretation "Vivino et al. J Rheumatol 29:938-44, 2002", and "positive" ones are found in up to 15% of healthy volunteers "Radfar et al. Arthritis Rheumatism 47:520-4, 2002". Better diagnostic tools are needed to determine if the frequent seronegative status of these SS patients may be related to a unique disease pathogenesis.

Recent findings—Recent advances in diagnostic techniques have served to define a likely pathogenetic basis for certain neurologic manifestations of SS. The advent of punch skin biopsies to analyze intraepidermal nerve fiber density and morphology has helped define pure sensory small fiber neuropathy as common in SS and the basis for both length- and non-length-dependent patterns of neuropathic pain. New protocols for magnetic resonance imaging (MRI) have enabled the recognition of dorsal root ganglionitis, a finding originally detected in pathologic studies. The advent of the anti-aquaporin-4 (AQP4) antibody test in 2004 has led to the appreciation that demyelinating disease in SS is often related to the presence of neuromyelitis optica spectrum disorder. The anti-AQP4 antibody is considered to be directly pathogenic in the brain, targeting the primary water channel proteins in the brain, expressed prominently on astrocytic foot processes.

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Compliance with Ethical Standards

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest

Sara McCoy, MD declare that they have no conflict of interest.

Alan Baer, MD declare that they have no conflict of interest.

Summary—There are no clinical trials evaluating the efficacy of systemic immune suppressive therapy for peripheral or central nervous system involvement. With the recent increase in clinical trials of biologic agents for SS, which utilize systemic disease manifestations as standardized outcome measures, there is an urgency to develop appropriate definitions of neurologic complications of SS and clear parameters for clinical improvement.

Keywords

Sjögren's syndrome; Autoimmune disease; Central nervous system; Peripheral nervous system; Neurologic

Introduction

Sjögren's syndrome (SS) can occur alone (so-called primary SS) or in association with a second well-established systemic rheumatic disease, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), or systemic sclerosis (so-called secondary SS). This distinction is imperfect, since patients with SS often have overlap features of other rheumatic diseases but not enough to allow formal classification as secondary SS. In addition, they may develop features of other rheumatic diseases during longitudinal follow-up. Consequently, attribution of a neurologic manifestation to SS alone or to a partially expressed overlapping autoimmune disease can be problematic. In this review, the focus will be entirely on primary SS (pSS).

Neurologic manifestations of pSS arise from involvement of the peripheral nervous system (PNS) and/or CNS, are diverse in presentation (Table 1) [1, 2], and often predate the diagnosis of pSS [3-5]. The overall prevalence of neurologic disease in pSS is approximately 20% [6]. However, there is a wide range reported in the literature, likely due to the varying definition and method for detection of the particular PNS and CNS manifestations, differing classification criteria for pSS, and selection bias of the patient cohorts used for study. PNS involvement is the more common of the two, with a prevalence of approximately 5-20% [7, 8], while that of the CNS is 1-5% [7, 9, 10, 11•]. The neurologic manifestations often arise in an individual not previously recognized as having pSS [3, 12-14, 15•]. The cause may thus be listed as "idiopathic" until a diagnosis of pSS is specifically sought or sicca and other manifestations supporting this diagnosis accrue during longitudinal observation [12].

Diagnosis

Peripheral nervous System involvement

The PNS manifestations include small-fiber sensory neuropathy, sensory ataxic neuronopathy (also known as sensory ganglionopathy), axonal sensory and sensorimotor polyneuropathies, cranial neuropathy (including trigeminal neuropathy), radiculoneuropathy, autonomic neuropathy, muscular disease (ranging from myalgias to myopathy), and motor neuron disease. Of these, small fiber sensory neuropathies and axonal sensorimotor polyneuropathies are the most common [3, 5, 8, 10, 16]. Different forms of these PNS manifestations may coexist in the same individual.

The clinical and diagnostic test findings which differentiate various types of peripheral nerve involvement in pSS are shown in Table 2. The first step is a careful neurologic examination, seeking evidence of muscle weakness, deficits in vibration, position, and pinprick sensation, and impairment of deep tendon reflexes.

Individuals affected by small-fiber sensory neuropathy commonly describe their pain as burning, shooting, or prickly [17]. The neuropathy is frequently associated with allodynia and hyperalgesia. The sensory symptoms are most often in a symmetrical length-dependent distribution, starting in the feet or hands and extending proximally. However, some individuals may have a non length dependent distribution, with patchy involvement of their face, scalp, trunk, or proximal limbs. Autonomic symptoms may also occur, including alterations in sweating, micturition, accommodation, or bowel function. Examination demonstrates loss of pinprick and temperature sensation with preserved large nerve fiber modalities, including muscle strength, light touch and vibratory sensation, proprioception, and deep tendon reflexes [3]. Electrodiagnostic studies are normal unless there is a coexistent large fiber neuropathy. A diagnosis of small fiber neuropathy is confirmed by quantitative sensory testing or punch skin biopsies demonstrating reduction in intraepidermal nerve fiber density. The distribution of abnormal nerve fiber density in skin biopsies obtained in proximal and distal sites of the same limb can help differentiate length vs non-length dependent neuropathies. Other diagnostic tests include quantitative sensory testing for thermal sensations, laser evoked potentials, sympathetic skin response, and electrochemical skin conductance [18].

Sensory ataxic neuronopathy is a rare yet devastating form of PNS disease in pSS. Affected individuals present with asymmetric sensory involvement in a non-length-dependent distribution, often without a pre-existing diagnosis of pSS [13]. Many also demonstrate autonomic insufficiency with manifestations of Adie's pupils, fixed tachycardia, hypohydrosis or anhidrosis, and orthostatic hypotension [19]. These individuals have marked loss of kinesthesia and proprioception leading to ataxia and difficulty with fine motor skills. They may demonstrate pseudoathetosis, an inability to localize the extremity in space and an abnormal Romberg's test. There is widespread loss of deep tendon reflexes, along with proprioception and vibration sensation. There may be slight reduction in pain and thermal sensation, but strength is preserved [19, 20]. Trigeminal nerve abnormalities have also been associated with ataxic neuropathy [20, 21]. Electrodiagnostic studies typically show a non-length-dependent decrease or absence of sensory nerve action potentials in clinically affected extremities with minimal, if any, abnormalities of motor nerve conduction [22, 23]. MRI of the spinal cord may demonstrate hyperintensity of T2 signal in the posterior columns [23]. Patients presenting with sensory ataxic neuronopathy should be evaluated for underlying cancer and HIV.

Individuals with pSS and small fiber sensory neuropathy or ataxic sensory neuronopathies tend to be older and have a lower frequency of anti-SSA and anti-SSB antibodies than those who are non-affected [15•, 24].

The distinction between small-fiber sensory neuropathy and sensory ataxic neuronopathy may be imperfect in some individuals. Mori et al. described 18 patients with "painful

sensory neuropathy without sensory ataxia” [3]. These patients had predominant features of a small fiber neuropathy, including symptoms consistent with autonomic neuropathy in 11, but also had evidence of large fiber involvement on electrodiagnostic studies and sural nerve biopsies. In an autopsy study of two pSS patients, one with painful sensory neuropathy and the other with sensory ataxic neuronopathy, common features included prominent CD8+ lymphocytic infiltration of the dorsal root ganglia and reduction of dorsal root ganglion neurons [25]. This suggested that these two forms of sensory neuropathy both stem from a dorsal root ganglionitis, with variable involvement of large versus small neurons. In a separate study, Birnbaum et al. demonstrated abnormalities of the dorsal root ganglia on high-resolution magnetic resonance neurography in five often SS patients with proximal neuropathic pain [26]. Interestingly, these patients with dorsal root ganglion abnormalities had increased intraepidermal nerve fiber density compared to those without, suggesting a novel mechanism for neuropathic pain generation involving trophic mediators, perhaps early in disease course.

Axonal sensory and sensorimotor neuropathies are characterized by impairment of large nerve fibers leading to abnormal nerve conduction studies [13]. They are typically symmetric in involvement and predominantly affect the distal lower extremities. Affected individuals usually report distal paresthesia [3, 8]. Examination demonstrates distal sensory deficits, including those of light touch, proprioception, and vibratory sensation. Motor weakness, if present on exam, allows classification as a sensorimotor neuropathy [27]. It is generally mild, with involvement of toe and foot extensors. Deep tendon reflexes may be diminished or absent, particularly in the Achilles tendon. Nerve conduction studies primarily show reduced amplitude of the sensory nerve action potential with or without a reduction in compound muscle action potential in the setting of relatively preserved conduction velocity [28]. The axonal large-fiber neuropathies may co-exist with a small fiber sensory neuropathy, with diminution in intra-epidermal nerve fiber density [29]. The presence of a length-dependent sensory neuropathy may require evaluation for other diseases such as sarcoidosis, paraproteinemia, diabetes, thyroid and renal impairment, toxins, and infection.

The majority of patients with axonal sensorimotor polyneuropathies have active systemic disease, defined variably by the presence of cutaneous vasculitis, renal involvement, non-Hodgkin lymphoma, and serum markers of monoclonal B cell proliferation, including serum cryoglobulins [8, 15, 24]. In some patients, an apparent distal sensorimotor polyneuropathy can actually represent the confluence of multiple mononeuropathies [30]. Findings pointing to a frank vasculitic neuropathy include severe pain, rapid stepwise progression of the neuropathy, asymmetry of examination and/or electrodiagnostic findings, and concomitant features of vasculitis in other organs, such as the kidneys or skin. A nerve biopsy may be required for definitive diagnosis.

Mononeuritis multiplex in SS, invariably a manifestation of vasculitis, is strongly linked to the presence of serum cryoglobulins and needs prompt diagnosis, since affected patients require treatment with immunosuppressive agents (see below).

Additional neurologic involvement in pSS includes trigeminal and other forms of cranial neuropathy, radiculoneuropathy, chronic demyelinating inflammatory neuropathy, muscular disease, autonomic neuropathy, and motor neuron disease [12].

Central nervous system involvement

The CNS manifestations of pSS include diffuse abnormalities (psychiatric changes, encephalopathy, aseptic meningitis, and cognitive difficulties/dementia) and focal or multifocal involvement of the brain and spinal cord leading to motor and sensory deficits, seizures, aphasia, and optic neuropathy [12, 31]. Spinal cord involvement can range from transverse myelitis to progressive myelopathy. Attribution of the CNS abnormality to pSS requires careful evaluation to exclude infection, manifestations of a co-existing rheumatic disease (such as SLE), small vessel disease related to hypertension or hyperlipidemia, and adverse effects of medications. Certain diseases can affect the salivary glands and central nervous system and be misdiagnosed as pSS, such as IgG4-related disease and sarcoidosis.

Demyelinating CNS disease in pSS is often related to the presence of neuromyelitis optica (NMO) or neuromyelitis optica spectrum disorder (NMOSD). NMO is an autoimmune disease defined by recurrent episodes of longitudinally extensive transverse myelitis and optic neuritis, frequently associated with anti-aquaporin-4 (AQP4) IgG antibodies. Individuals with anti-AQP4 antibodies who do not have the full clinical expression of classic NMO are classified as having NMOSD [32]. They may have brain lesions in anatomic areas distinct from those in multiple sclerosis (MS), such as the hypothalamus, brainstem, and periventricular regions, and have fewer associated neurologic deficits. AQP4 IgG antibodies are highly specific for NMO and NMOSD, including among individuals with pSS and other connective tissue diseases [33, 34]. Anti-SSA antibodies are present from 11 to 19% of individuals with NMOSD, with increasing frequency in those with anti-AQP4 antibodies [35, 36]. Among individuals with pSS and myelitis, up to 50% will have positive anti-AQP4 antibodies [37]. There are conflicting data as to whether the co-existence of both diseases modulates the clinical expression of either one [38, 39, 40, 41].

The relationship between MS and pSS is a subject of ongoing debate. In 1986, Alexander et al. reported that pSS patients could have CNS manifestations that closely mimic MS [9]. Following this report, efforts to identify an enrichment of unrecognized pSS patients among MS cohorts were unsuccessful. pSS has been identified among MS patients in rates from 0 to 3% [42-44]. Anti-SSA antibodies have been found in up to 7% of MS patients; however, labial gland biopsies in one study were negative in 67% of patients, indicating that positive serology may not reflect the actual presence of pSS [45]. In retrospect, some of the pSS patients with MS-like CNS disease reported by Alexander et al. may actually have had NMOSD, a disease not recognized until the discovery of anti-AQP4 antibodies in 2004 [46]. In a study of 12 pSS patients with recurrent focal CNS manifestations, all had brain lesions in areas characteristic of NMO and 75% had anti-AQP4 antibodies; nine patients met criteria for NMOSD or NMO [47].

Demyelinating CNS disease in pSS maybe difficult to differentiate from MS, but CSF analysis and imaging may aid in this endeavor. Approximately 30% of pSS patients with focal or multifocal CNS involvement have increased oligoclonal bands in their CSF [12]

compared to 95% of MS patients [48]. Those pSS patients with demyelinating disease and CSF oligoclonal bands tend to have fewer of them (more commonly one or two), while active MS patients have a median of 5 bands [9, 49]. Infections, including aseptic meningitis and spirochetal infections, may also be associated with CSF oligoclonal bands, so these should be considered in the differential diagnosis [48].

In pSS, there is an increased prevalence of non-specific T-2 weighted hyperintensities (e.g. white matter lesions) on MR imaging of the brain, most often in the absence of corresponding neurologic findings [50, 51]. In the absence of localizing symptoms, these white matter lesions occur at similar rates between pSS patients and age- and sex-matched controls [52] and correlate more with age and cardiovascular risk factors, such as hypertension and hyperlipidemia than the underlying disease [53]. These lesions most likely represent an ischemic microangiopathy not related to immune causes. In contrast to MS, the white matter lesions of this non-specific ischemic microangiopathy (1) do not demonstrate enhancement, (2) tend to spare the corpus callosum subcortical U-fibers and spinal cord, (3) commonly affect the basal ganglia with lacune formation, and (4) affect the central rather than peripheral portions of the brainstem [54].

Many individuals affected by pSS report mild cognitive difficulties, often referred to as “brain fog.” The physiologic basis for this is not known but has been postulated to be multifactorial due to pain [55•], depression [56], and possibly an immune-mediated endothelitis [11•, 57-59]. Although pSS patients frequently report impaired memory, abnormalities on objective neuropsychiatric testing are not definite, with some studies showing reduced psychomotor processing, verbal reasoning, memory, attention, and concentration ability among other deficits [56, 60-62], while others have failed to show consistent differences between pSS patients and controls [56]. Dementia is less commonly described in the literature. In one series, pSS was diagnosed in up to 7.5% of elderly patients with dementia, and in another series, 33% of pSS patients with cognitive impairment had some level of dementia. However, in the general pSS population, dementia is a relatively uncommon finding [63]. Characteristic imaging in pSS patients with cognitive disease and the role of these findings in the pathogenesis of disease are disputed [4]. Overall, most pSS patients with cognitive difficulty remain stable and do not decline over time [64].

Treatment

Peripheral nervous system

Small-fiber neuropathy

Treatment of small-fiber neuropathy is aimed initially at symptomatic relief of the associated pain. First-line therapeutic agents include gabapentin and pregabalin [65, 66]. Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine or venlafaxine may be substituted or added to first-line therapy if pain control is inadequate [65]. Tri-cyclic antidepressants (TCA) may also be effective for treatment of neuropathic pain but can cause significant dryness, potentially compounding existing sicca symptoms. For this reason, the secondary amine TCAs, nortriptyline and desipramine, are preferred over amitriptyline. Opiate analgesics may be required to control pain but should be used judiciously given the

potential for addiction and questionable efficacy of these agents in chronic medical conditions.

A trial of immunomodulatory or immunosuppressive therapy is appropriate in patients in whom sensory deficits are rapidly progressive or severe or in those who have failed symptomatic therapy. Intravenous immunoglobulin (IVIG), in a dose of 0.4 g/kg for 5 days, is generally recommended, based on beneficial results in anecdotal case reports and several small series, although duration of therapy is not clear. A limitation of these studies is that patients with small fiber neuropathy were not distinguished from those with axonal sensory neuropathy [3, 67, 68]. Small fiber neuropathies may not respond to corticosteroid therapy [3]; however, this observation is limited by the coexistence of multiple forms of peripheral neuropathy in the studied populations. Small studies evaluating rituximab in painful sensory neuropathy have had disappointing results [69].

Sensory ataxic neuropathy

Data to assess treatment of sensory ataxic neuropathy are limited to case reports and series. The recommended first line of treatment for recent-onset sensory ataxic neuropathy is corticosteroids and IVIG, most frequently used together. Corticosteroid therapy is the most widely reported therapeutic modality for sensory ataxic neuropathy. Overall, reports of the use of corticosteroids are varied in terms of their benefit and in many the corticosteroids are used in conjunction [70•, 71, 72]. Response to IVIG has been mixed, but nevertheless has been recommended as the first line of treatment [73]. In a series of five patients, marked improvement with IVIG was seen in four patients [74]. A second series showed a variable response, with two patients improving, three stabilizing, and four worsening while on IVIG, 2 g/kg of body weight [75]. Other series have been less optimistic with improvement in three of 13 patients in one series and one of six patients in another series [3, 70•]. These conflicting reports of response to IVIG may be explained by delayed therapy, which has been postulated to lead to poor therapeutic response [76].

After IVIG, mycophenolate mofetil (MMF) at a dose of 2 g per day is the most frequently reported effective treatment of sensory ataxic neuropathy [70].

However, MMF was not effective in an earlier report [77]. Several reports have documented success with rituximab [77, 78] while others, in the absence of cryoglobulinemia or vasculitis, have been disappointing [69]. Other reported therapies include hydroxychloroquine, cyclophosphamide, tacrolimus, azathioprine, plasmapheresis, d-penicillamine, infliximab, and interferon alpha [19, 70•, 71, 79, 80].

Axonal sensory/sensorimotor neuropathy

Treatment of axonal polyneuropathies is dictated by the presenting symptoms and signs. For patients with mild and stable sensory or motor symptoms, initial treatment may be symptomatic as discussed above [27, 65]. A trial of immunosuppressive therapy is warranted if symptoms are rapidly progressing, severe, or include significant motor deficits. IVIG, at a dose of 0.4 g/kg for 5 days, has been reported to be successful in small numbers of pSS patients [3, 75]. Few small studies have evaluated rituximab in painful sensory neuropathy with disappointing results [69]. Despite a lack of supportive data, a trial of therapy with a

disease-modifying agent such as azathioprine or mycophenolate mofetil may be pursued, but the results are often disappointing [69].

Multiple mononeuropathies due to vasculitis should be treated with high-dose corticosteroids (prednisone 1 mg/kg/day) and cyclophosphamide (oral or IV) [81]. Response of pSS patients with mononeuritis multiplex to therapy with cyclophosphamide is generally robust with rates as high as 100% [12]. Rituximab can be used for treatment of cryoglobulinemic vasculitis-related PNS manifestations of pSS [69]; in a series of six patients with pSS-related PNS disease, all of the patients with vasculitis (3 of 3) responded to rituximab therapy.

Other peripheral nervous system manifestations

Multiple cranial neuropathies related to vasculitis should be treated as described above. Multiple cranial neuropathy has been reported to have favorable response to corticosteroids (three of four patients improving) [3]. However, a similar response is not observed in isolated trigeminal neuralgia [3]. Radiculoneuropathy may respond to IVIG as demonstrated in small series [3]. Autonomic neuropathy may be treated supportively. Series of patients with autonomic neuropathy treated with IVIG and prednisone have not demonstrated a response [3]. Chronic Inflammatory Demyelinating Polyneuropathy is rare in pSS; it is treated with corticosteroids, plasmapheresis, and IVIG.

Central nervous system

The relative rarity of CNS manifestations of pSS has not permitted clinical trials, and thus, treatment recommendations are based on expert opinion and case series. Pharmacologic therapy is largely empiric. In general, acute or rapidly progressive CNS manifestations require treatment with high-dose corticosteroids [intravenous (IV) methylprednisolone 1 g daily for 3-5 days, then 1 mg/kg/day of prednisone for 1 month with gradual taper] and monthly IV cyclophosphamide (700 mg/m²) [12, 82]. As with other serious manifestations of systemic rheumatic diseases treated in this fashion, the goal is to taper the prednisone to 10 mg daily within 2-3 months, but no studies detail the success rates of this protocol in pSS CNS disease. Alternative therapy options include azathioprine and mycophenolate mofetil. Overall, the benefits of rituximab for the treatment of CNS manifestations of pSS have been unimpressive in small case series [83].

NMO with or without pSS is treated with corticosteroids (IV pulse methylprednisolone for 5 days) [84, 85]. If the patient fails to respond to high-dose corticosteroid therapy, then plasmapheresis should be instituted. Remission may be maintained with azathioprine, rituximab, or mycophenolate mofetil [84, 85]. Because it may be neither clinically feasible nor clinically relevant to distinguish between NMO and NMOSD from pSS-related myelopathy, presumptive therapy of NMO and NMOSD is favored.

For indolent manifestations such as psychiatric changes or mental fog, monitoring with supportive therapy is appropriate. One case report documented improvement of pSS-related dementia with high-dose corticosteroid therapy [86]. Immunosuppression in pSS patients with dementia should only be pursued after alternative and more common causes of dementia have been excluded. Neuropsychiatric testing should be performed before and after

a corticosteroid trial to ensure objective improvement has occurred prior to initiation of steroid-sparing therapy.

Conclusions

Peripheral and central nervous system manifestations of pSS are common and may be the presenting sign of pSS. The clinician should maintain a low threshold to initiate prompt diagnostic assessment of pSS patients who exhibit symptoms or signs of PNS or CNS disease. Treatment of PNS and CNS pSS is largely supportive, but in cases of progressive or debilitating disease, immune-suppressive or immunomodulatory therapy is utilized.

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Table 1.

Frequency of PNS and CNS manifestations in symptomatic pSS patients

Clinical manifestation	N (%)
Peripheral nervous system ^a	51 (62)
Neuropathy ^a	36 (44.5)
Small-fiber neuropathy ^b	9 (9.8)
Sensory ataxic neuropathy ^b	36 (39)
Sensorimotor polyneuropathy ^{a,c}	19 (53), 1 (6)
Multiple mononeuropathy/mononeuritis multiplex ^{a,b,c}	7 (19), 11 (12), 3(18)
Cranial nerve neuropathy ₁ ^c	16 (19.5), 7 (41)
Multiple cranial neuropathy ^b	5 (5.4)
Trigeminal neuropathy ^{b,c}	15 (16.3), 2 (12)
Radiculopathy ^a	2 (2.4)
Autonomic neuropathy ^b	3 (3.2)
Muscular disease ^a	2 (2.4)
Central nervous system ^a	56 (68)
Focal or multifocal brain involvement ^a	33 (40.2)
Spinal cord involvement ^a	29 (35.4)
Optic neuritis ^{a,c}	13 (15.9), 3(9.4)
Cognitive impairment ^a	9 (11)
Seizures ^a	7 (8.5)
Encephalitis ^{a,c}	2 (2.4), 3 (9.4)
Motor neuron disease ^a	1 (1.2)
Aseptic meningitis ^c	2 (6.4)

^aDelalande, S et al. Medicine (Baltimore). 2004;83(5):280-911;^bMori, K et al. Brain: a journal of neurology. 2005;128:2518-342^cGono, T et al. Clinical rheumatology. 2011;30(4):485-903

Table 2.**Diagnosis of PNS manifestation of pSS**

	Small fiber sensory neuropathy	Sensory ataxic neuropathy	Sensorimotor axonal neuropathy
Exam	Variable length dependence Abnormal pinprick/temperature Sensation DTR normal Vibratory sense normal	Non-length-dependent Pseudoathetosis Abnormal proprioception Abnormal vibration Reduced DTR Abnormal Rombergs Test	Length-dependent mild distal weakness Decreased or absent DTR
Neurodiagnostics	NCS/EMG: Normal	NCS: Low amplitude or unelicitable SEPs and SNAPs involving central/peripheral rami of sensory neurons Motor nerve conduction normal (may be more frequently abnormal in paraneoplastic syndromes)	NCS: CMAP/SNAP amplitude reduction Conduction velocity: normal/slightly prolonged
Other	Skin biopsy Quantitative sensory test for thermal sensations Laser evoked potentials Electrochemical skin conductance Sympathetic skin response	MRI: T2 hyperintensity of posterior columns	Further evaluation Nerve biopsy Cryoglobulins
Differential diagnosis ^{a,b,c}	Diabetes mellitus or impaired glucose tolerance Hyperlipidemia Celiac disease Infection (ie HIV) Toxins (drugs, alcohol) Other autoimmune (ie amyloidosis) Hereditary Monoclonal gammopathy or Paraneoplastic syndrome Idiopathic	HIV Malignancy/paraneoplastic Bickerstaffs brainstem encephalitis Drugs (cisplatin, pyridox'ne)	Diabetes Mellitus Thyroid disease Uremia Tox'ns (alcohol, drugs) Vitamin deficiency (B1, B12) Vasculitis Sarcoidosis Other autoimmune (SLE) Paraneoplastic syndrome Infection (HIV, Lyme disease, Leprosy) Porphyria

DTR deep tendon reflexes, *NCS* nerve conduction studies, *EMG* electromyography, *SEP* somatosensory evoked potential, *SNAP* sensory nerve action potential, *CMAP* compound muscle action potential

^a Birnbaum J. Peripheral nervous system manifestations of Sjogren syndrome: clinical patterns, diagnostic paradigms, etiopathogenesis, and therapeutic strategies. *Neurologist*. 2010;16(5):287-97

^b Mauermann ML et al. The evaluation of chronic axonal polyneuropathies. *Semin Neurol*. 2008;28(2):133-51

^c Lauria G. Small fiber neuropathies. *Curr Opin Neurol*. 2005;18(5):591-7