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Recent Updates on Neurological Manifestations of Sjögren Syndrome

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Introduction

Associated with a spectrum of extra glandular manifestations, primary Sjögren syndrome (pSS) is a chronic autoimmune disorder affecting primarily exocrine glands, causing xerophthalmia and xerostomia. First described by Sjögren in 1933 followed by Jönköping in 1935 [1], it has been well established that central and peripheral nervous systems involvement is one of the most serious complications of pSS. Based on many studies, 1.8%-70% of pSS patients may suffer from neurological manifestations [2-17]. Different study designs, selection bias depending on rheumatology or neurology specialty conducting the study, and degree of investigation on patients' signs and symptoms may contribute to this significant disparity. Studies with lower prevalence focused on the general population [2,3 and 5], while the higher prevalence series are based on patients who present with neurological symptoms [16,17]. Indeed, the definition and classification criteria of pSS have been changed frequently making it difficult to compare different cohorts [18,19].

Neurologic manifestations may predate pSS diagnosis [10], not only delaying diagnosis but also clarifying the natural history of pSS challenges. This article will focus on both peripheral and central nervous system manifestations of pSS along with a pathological and immunological review.

Peripheral nervous system (PNS)

Peripheral neuropathy is one of the most frequent extra glandular manifestations of pSS [5,6,10 and 20]. PNS involvement is heterogeneous, and no single mechanism may explain its pathogenesis. Although different mechanisms have been suggested, no definite answer has been found and possibly more than one mechanism is involved in nerve injury.

Vasculitis

Vasculitis is probably the best-described pathomechanism of neurological manifestations and particularly a common finding in pSS patients [20,21]. Several studies described cutaneous vasculitis involvement that seems to be a frequent finding in neurologic pSS suggesting a relationship between vasculitis lesions and neurologic complications.

A retrospective study of 54 patients with sicca syndrome and peripheral neuropathy found necrotizing vasculitis is responsible for mononeuropathy [22]. In this study, 33 patients (73%) had positive minor salivary gland biopsy and 50% underwent nerve biopsy. Although nonspecific epineurial and perivascular inflammation was present in 70% of nerve biopsies, 3 patients had more severe inflammation with probable mural extension without specific changes sufficient for a diagnosis of necrotizing vasculitis [22]. In another retrospective study of 40 patients with pSS-related neuropathy, there was no vasculitis in 18 patients. However, 8 patients had lymphocytic and 14 patients had necrotizing vasculitis [23].

Autoantibodies

In a study comparing pSS individuals with and without neuropathy [24], patients with vasculitic neuropathy and normal volunteers were

catalogued for the pathogenic role of antiganglion neuron antibodies. It was found that pSS patients with neuropathies had autoantibodies specific to ganglion neurons. Lack of antiganglion neuron antibodies in vasculitic neuropathy group suggests that antigen exposure to the immune system during nerve/neuronal degeneration is not the cause of these autoantibodies. The presence of autoantibodies reacting with both the salivary gland and peripheral nervous tissue might be necessary for developing neuropathies. In another study [25], 25 out of 45 pSS patients had neurologic complications of whom antineuronal antibodies were found in 55% of those with major neuropsychiatric complications but only in 11% of patients with minor neuropsychiatric complications. No antineuronal antibodies were found in sera of control groups. These findings suggest a link between antineuronal antibodies and the pathogenesis of pSS neuropathy.

Epidemiology and risk factors

Owing to different classification criteria used by different authors, finding the most frequent type of neuropathy is difficult and is a source of prevalence disparity. Most authors used sensorimotor polyneuropathy in their classification since it is difficult to quantify analyzing pure sensory neuropathies (Table 1). Sensorimotor polyneuropathy is the most frequently reported type if all different classifications of sensory neuropathies are combined. In a retrospective study of 563 pSS patients, 158 patients underwent nerve conduction studies, suggesting a classification of peripheral neuropathies by electrodiagnostic patterns provides more accurate cataloging of types and possible causes of neuropathy and may provide more specific treatment options [5].

Table 1: Most frequent types of primary Sjogren's syndrome neuropathies. (AN: autonomic neuropathy, APN: ataxic polyneuropathy, CNN: cranial nerve neuropathy, CTS: carpal tunnel syndrome, MG: myasthenia gravis, MMN: multiple mononeuropathy, MNS: motor neuron syndrome, MPN: pure motor polyneuropathy, NAP: non-ataxic painful polyneuropathy, PRNP: polyradiculoneuropathy, PSA: pure sensory polyneuropathy, axonal EMG pattern, PSP: pure sensory polyneuropathy, no EMG pattern, SMN: sensorimotor polyneuropathy, SMP: small fiber polyneuropathy, SN: sural neuropathy, TA: trigeminal affectation).
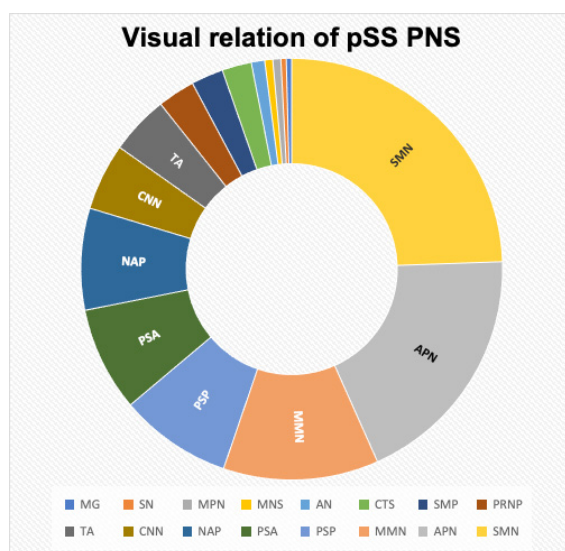
There are many reported risk factors for developing pSS neuropathy. More than one study [5,20] revealed that cryoglobulinemia is frequently related to neuropathy. While one study [5] showed that men affected by pSS were more likely to develop neurologic manifestations, other studies do not support this finding as most case series includes a small number of men. Hypocomplementemia, vasculitis, and monoclonal gammopathy were also reported to have links with peripheral neuropathy.

One study found [23] that patients with vasculitis have a higher prevalence of acute neuropathy at onset, multiple mononeuropathies, and sensorimotor involvement. Another study suggests that patients with vasculitis have a significantly lower prevalence of profound sensory involvement compared to those without vasculitis. Ganglionopathy, even associated with other forms of neuropathy, was not associated with vasculitis [23]. A large cohort of 1010 Spanish pSS patients revealed that peripheral neuropathy is more prevalent in disease duration of over 10 years, 24% compared with 8% in incidental cases [7]. In a study of 120 pSS patients, 30 (25%) were diagnosed with pSS-associated peripheral neuropathy. In this study, positive serum markers of monoclonal B-cell proliferation such as mixed cryoglobulinemia, monoclonal gammopathy, and non-Hodgkin lymphoma were more likely to have pSS-associated sensorimotor neuropathy suggesting that all patients with pSS-associated sensorimotor neuropathy should be assessed for benign or malignant B-cell proliferation [12].

PNS syndromes

- **Peripheral neuropathies (PN)**

☐ **Sensorimotor polyneuropathy (SMP):** Sensorimotor polyneuropathy is the most common type of neurologic manifestation of pSS (Table 1). The typical presentation is the symmetrical distal motor with or without sensory deficits that typically have a graded increase in severity distally and distal attenuation of reflexes. Sensory and motor deficits generally follow a length-dependent stocking-glove pattern symmetrically with an axonal pattern in nerve conduction studies found in 4-55% of case series (Table 1). In a retrospective study of 82 pSS patients with neurologic manifestations, sensory-motor neuropathies were the most frequent type of neuropathies, with similar frequency in CNS and PNS involvement.

Only PNS patients presented with predominantly sensory symptoms had positive cryoglobulinemia suggesting the possible pathophysiologic role of cryoglobulinemia in sensory-motor neuropathy [20]. In a study of 120 pSS patients, SMP patients had more monoclonal B-cell proliferation markers such as mixed cryoglobulin with monoclonal gammopathy and B cell non-Hodgkin lymphoma than pSS patients without peripheral neuropathy [12]. In agreement with this finding, in a retrospective study of 40 biopsy-proven peripheral neuropathy pSS patients, sensorimotor neuropathy was more frequent in patients with vasculitis, monoclonal gammopathy, and cryoglobulinemia [23].

☐ **Mononeuritis multiplex:** Different pSS series show a relationship between acute mono neuritis multiplex and systemic vasculitis. In a retrospective study of 82 pSS patients with neurologic involvement, 7 patients had multiple mononeuropathies as a severe systemic complication [20]. Acute onset of tingling sensation or painful dysesthesia in distal portions of limbs was described as the initial presentation of neuropathy [26]. Subsequently, motor and sensory symptoms episodically occurred and extended to multiple mononeuropathy patterns mostly restricted to limbs. Several studies report acute or subacute presentation in half of the patients with vasculitic lesions associated with perivascular cellular invasions as the most prominent histological feature. Although affected nerves are acutely and more profoundly damaged, prognosis tends to be better as it responds well to immunosuppressive therapy [5,23 and 26]. In a study of 158 patients with pSS and neuropathy, 15 patients had mono neuritis multiplex; all had lower extremity involvement, however, only 7 individuals had upper extremity neurological symptoms [5].

• **Sensory neuropathy**

☐ **Small fiber neuropathy:** Small fiber neuropathy is diagnosed by skin biopsy to assess epidermal nerve fiber density (ENFD) and morphology. This particular category of neuropathy has probably been underdiagnosed since patients with large-fiber involvement may also have small fiber damage. In a study of 20 pSS patients with neuropathy, the most frequent complaint was a burning sensation insole. Although electrophysiology findings were suggestive of large fiber disease, skin biopsy revealed decreased epidermal nerve fiber density or abnormal nerve morphology [27]. This study suggests that small fiber neuropathy is a frequent finding in pSS patients and might be the cause of presenting symptoms even in patients with large fiber neuropathy. In a cross-sectional study of 62 pSS patients, leg epidermal fiber densities were significantly lower in only 2 pSS individuals, suggesting small fiber neuropathy is not a frequent occurrence [6].

☐ **Sensory axonal PN:** Bilateral symmetrical pain and dysesthesia are the most frequent complaints. It has been reported that non-ataxic sensory neuropathy is associated with the presence of ANA and CNS involvement [12]. In one study, axonal neuropathy had the lowest rate of positive serology markers and recommended salivary gland biopsy to confirm pSS [5]. In 82 patients with pSS and neurologic manifestations, 53% of patients had distal axonal sensory-motor neuropathy while 25% had pure axonal sensory neuropathy [20].

☐ **Cranial neuropathy:** May present with single or multiple nerve involvements. In a retrospective study of 92 pSS patients, the trigeminal nerve was the most frequently compromised cranial nerve presenting with neuralgia or sensory deficits in both unilateral and bilateral fashion [26]. Facial nerve involvement is less frequently reported [28]. There are reports of isolated cranial nerve involvement, but CN XI involvement has never been reported. Although the pathophysiology of cranial nerve neuropathy is not clear, the possibility of vasculitic changes in affected nerves is the most likely pathomechanism and might explain unilateral or isolated cranial nerve involvement in most cases.

• **Neuronopathies**

☐ **Ganglionopathy (sensory ataxic neuropathy):** Sensory ataxic neuropathy is a rare form of neuropathy that results from dorsal root ganglia injury. Different studies report that pSS is one of the most frequent etiologies of ataxic neuronopathy [26,29-31]. In a retrospective study, 36 out of 92 pSS patients with neuropathy had sensory ataxic neuropathy characterized by sensory ataxia due to deep sensory impairment with no major motor symptoms [26]. Nerve involvement was mostly deep sensory impairment. Positive Romberg's signs, generalized areflexia, and pseudoathetosis were seen in all patients. Facial and truncal sensory involvement was observed in some patients and autonomic symptoms including Adie's pupils were observed in more than half of the patients. Nerve conduction studies revealed mostly axonal features with also central rami of sensory ganglion neuron involvement. Increased signal intensity in the posterior column was observed in T2 weighted MRI. Sural nerve biopsy in 31 patients exhibited chronic vasculitis of arterioles in epineurial space with mild perivascular lymphocytic infiltrates in small vessels. In a cohort of 13 patients with ataxic neuropathy, dorsal root ganglion biopsy revealed sensory ganglionitis with T-cell infiltration and sensory neuron destruction [29]. Although this is not the most frequent form of neurological involvement, it is one of the most debilitating ones.

☐ **Autonomic neuropathy:** Autonomic involvement as the main manifestation has been reported in several series of pSS patients with PNS. In one study, severe autonomic neuropathy has been reported in 3 out of 92 patients with pSS and neuropathy [26]. All 3 patients had Adie's pupils, severe orthostatic hypotension with syncope, hypohidrosis, or anhidrosis in the trunk and all four limbs. Limb and truncal sensory involvement with sensory ataxia without motor involvement were reported in these patients. In a retrospective study of 54 patients with pSS and neuropathy, a subclinical autonomic compromise was more common than symptomatic autonomic neuropathy [22]. Although only one patient had autonomic neuropathy on presentation, 14 of 21 patients had abnormal reflexes and most patients had sensory neuropathy or polyganglionopathy. In a prospective study of 154 Korean patients with pSS, resting heart rate variability (HRV) was present in 35.7% of individuals suggesting that Raynaud's phenomenon might increase the risk of autonomic dysfunction. Although pSS autonomic dysfunction was associated with generalized fatigue and may sometimes be mistaken with fibromyalgia, it was poorly associated with exocrine involvement in pSS [32].

☐ **Motor neuropathy:** Although motor neuropathy is an infrequent finding, in one series of 184 patients presenting with severe motor symptoms (exclusive sensory symptoms were excluded), 44 were diagnosed with pSS. 93% were diagnosed with pSS after neurologic diagnosis, and gender distribution was equal with 50% of patients being men. The most common reported symptoms were paraesthesia, weakness, and gait disturbance. All patients developed limb weakness in the course of the evaluation. The main diagnoses before pSS discovery were polyneuropathy of unknown origin (36%), primary chronic inflammatory demyelinating polyneuropathy (CIDP) (28%), paraproteinemia associated polyneuropathy (10%), multifocal motor neuropathy (8%), Guillain-Barre syndrome (GBS) (8%), motor neuron disease (5%), and multifocal acquired demyelinating

sensory and motor (MADSAM) neuropathy (5%) [33]. The previous series have reported similar findings, emphasizing the need for further characterization of neuropathies on diagnosis and including pSS as part of diagnostic evaluation.

In summary, clinicopathological features of neuropathies associated with pSS are highly variable. Future studies implementing collaboration between neurologists and rheumatologists are required to further understand the association.

Central nervous system (CNS)

Pathophysiology: Although the pathology of CNS involvement in pSS is unknown, CNS complications might be a direct invasion by immune cells or result from immune-mediated vasculitis. In a study of 16 pSS with CNS involvement, biopsy-confirmed peripheral and visceral vasculitis in 12 patients [34]. Brain histopathologic studies revealed meningitis, small to medium size vessel vasculitis, vasculopathy, and mononuclear cell infiltration without evidence of demyelination [35]. The same study revealed elevated IgG index in one or more clonal bands in 2/3 of pSS patients with CNS involvement and mild pleocytosis with reactive lymphoid cells in cerebrospinal fluid (CSF) studies. It has been suggested that two-thirds of pSS patients with biopsy-proven vasculitis may have concomitant PNS or CNS involvement and share many pathologic features with unusual vasculopathy of neuropsychiatric systemic lupus erythematosus (NPSLE) [20,21].

In a cohort of 52 pSS patients with CNS involvement, anti-SSA antibodies were detected in 28 patients (54%), especially in patients with focal CNS manifestations, suggesting a potential role in the immunopathogenesis of CNS disease. Anti-SSA antibodies were also more frequent in patients with established active and progressive CNS disease, although anti-SSA negative pSS patients may develop significant CNS disease [36].

It has been demonstrated [37] that there is a correlation between neurologic and psychiatric symptoms and brain MRI findings; patients with neuropsychiatric symptoms were more likely to have CNS lesions, and white matter changes were the most common findings seen in MRI. Another study of 82 pSS patients with CNS [20] revealed that white matter lesions are more frequently seen in patients with CNS involvement. In a study of 424 pSS patients, 25 patients (5.8%) had CNS involvement, and small punctate white matter hyperintensities (WMHs) mainly in subcortical and periventricular areas were detected in the brain MRI of most patients [3]. Two different studies [38,39] have found WMHs in patients presenting with neuropsychiatric symptoms. In both studies, diffusion tensor imaging (DTI) revealed significant differences between pSS-CNS and healthy volunteers, suggesting an anatomical abnormality may present in pSS-CNS patients with neuropsychiatric manifestations.

Epidemiology: The same as PNS, CNS involvement frequency has not been well studied in pSS individuals and compared to PNS, there are fewer reports on this topic. CNS involvement ranges from 7-73% in different series. Depending on different diagnostic pSS criteria, the definition of neurologic involvement, and selection criteria by different disciplines, the prevalence of CNS involvement in pSS is highly heterogeneous [20]. The higher prevalence is found in series that included headache and migraine as part of CNS involvement, while others only catalogued more serious complications of pSS.

pSS-CNS manifestations are broad and include migraines, seizures, aseptic meningitis, cognitive impairment, and neuropsychiatric manifestations while focal manifestations include MS-like syndrome, neuromyelitis optica spectrum disorders (NMOSD), and non-specific white matter lesions. Compared with non-CNS-pSS, mean age at disease onset was significantly lower in CNS-pSS in one study (42.1 vs 48.4 years). Other independent factors correlated with CNS involvement were longer disease duration, pulmonary manifestations, and low C4 levels [3].

CNS syndromes

- **Aseptic meningitis:** A low incidence in different series, it starts as an acute or subacute febrile process with headaches, meningismus, and clouded sensorium. There are case reports [20] of aseptic meningitis with cranial nerve and cerebellar involvement, and another report of diplopia with aseptic meningitis [10]. CSF exam characteristically reveals pleocytosis and increased protein level, with conflicting findings of lymphocyte or polymorphonuclear predominance.

- **Cognition impairment:** In a retrospective study of 424 pSS patients, CNS involvement was detected in 5.8% of patients. Mild recurrent subacute encephalopathy characterized by memory loss, cognitive dysfunction, visual disturbances, dizziness and impaired concentration and attention were the most common findings. All patients had brain MRI abnormalities, mainly small punctate WMHs in subcortical and periventricular areas [3]. It was also demonstrated that cerebral hemispheres are involved in a subcortical fashion in patients with psychiatric and cognitive dysfunction [35]. Using 99mTc ECD brain SPECT, one study compared 17 female pSS patients without neuropsychiatric symptoms or signs with 32 female pSS patients with neuropsychiatric symptoms or signs. This study revealed hypoperfusion regions in 56.3% of pSS patients and definite neuropsychiatric symptoms or signs with only 17.6% in pSS patients without neuropsychiatric symptoms or signs. In addition, there were significantly higher positive rates of anti-SSA antibody, antiphospholipid antibodies, and antineuronal antibodies in patients with definite neuropsychiatric symptoms or signs than in patients without neuropsychiatric symptoms or signs [40]. In a cohort of 39 pSS patients, prevalence of self-reported depression, fatigue and pain was higher in pSS group compared to control individuals [41].

- **Multiple Sclerosis (MS):** A study of 82 pSS patients revealed that 10 (12.1%) patients with pSS and neurologic manifestations had recurrent deficits mimicking relapsing-remitting MS, including the brain, spinal cord, and optic features [20]. Although WMHs were compatible with MS in 40% of patients, lesions were localized in areas such as corpus callosum or basal ganglia. In a retrospective study of 424 pSS patients, 5.8% (25 pSS patients) had CNS involvement, and although 20% [5] of them had demyelinating MS-like syndrome, only 2 of them (8%) fulfilled MS criteria [3]. In a study of 16 pSS patients with active CNS disease, 6 of them were indistinguishable from MS by neurologic manifestations, electrophysiological studies, and CSF analyses results, and 5 patients had multiple WMHs that were indistinguishable in size and distribution from plaques seen in MS [37]. In another study, 60 primary progressive MS patients underwent screening for pSS and found that 16.7% of patients also had pSS suggesting MS and pSS are related disorders [42]. However, in a prospective study of 64 MS patients, only 3.1% of MS patients also had

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pSS, suggesting this incidence is not greater than the general population [43]. Authors recommend it is prudent to screen primary progressive MS patients for pSS.

- **Neuromyelitis optica spectrum disorders (NMOSD):** A fairly recently described syndrome, was initially believed to be a precursor of MS and later identified as a separate disease after the discovery of Aquaporin 4 IgG antibodies (AQP4-IgG). Optic neuritis and longitudinally extensive spinal cord lesions (LESLs) are the main manifestations. Although there is a relationship between NMOSD and pSS, the exact frequency of NMOSD in pSS patients is not clear [44]. It has been suggested that Aquaporin 5 (AQP5) is expressed at a high level in salivary glands and bears protein sequence identity with AQP4. As a result, patients may have a subset of autoreactive immune cells that recognize AQP5 homologous portions, causing inflammation of salivary glands. It is recommended to search for AQP4-IgG in patients with pSS who develop longitudinally extensive spinal cord lesions. In a retrospective study of 12 pSS patients with CNS involvement, AQP4-Ab was positive in six of eight patients, and brain MRIs of all six seropositive patients showed extensive brain lesions, five (83.3%) of them had cavity-like lesions [45]. Although all patients with LESL were positive for AQP4-Ab, one of two patients had only brain involvement. In a retrospective 22 pSS patients with CNS manifestations, 7 (31.8%) patients were positive for anti-AQP4 antibody, visual involvement was more common in these individuals (71.4% vs. 0.0%), and more likely to have an acute presentation (100% vs. 26.7%) [46]. Also, anti-AQP4 antibody-positive pSS patients responded better to corticosteroids than Anti-AQP4 antibody-negative individuals (55.6% vs. 9.1%).

- **Vasculitis:** Has been documented in case reports and case series. In one case series [36] of 20 pSS-CNS patients with abnormal cerebral angiography, 18 had radiographic findings of stenosis, dilatation, or occlusion of small cerebral blood vessels, compatible with small-vessel vasculitis. There was a significant association between SSA antibody positivity and abnormal angiography. In a case report [47], of a patient presenting with right hemiparesthesia, hemihypoesthesia, and positive anti-SSA antibodies, she had an abnormal angiogram with disruption of MCA and ACA. There is another case report [48] of lower thoracic cord anterior spinal artery necrotizing arteritis with fibrinoid changes and infiltration of small and medium vessels with spinal subarachnoid hemorrhage observed in an autopsy after the patient presented with progressive lower extremity weakness and eventually death. A crescendo transient ischemic attack due to MCA stenosis caused by vasculitis in a patient with positive SSA antibodies has been described [49]. Depending on affected vessels and the presence of increased inflammatory markers, vasculitis manifestations may vary. Aggressive immunosuppression and possible vessel-directed therapies are treatment mainstay.

Diagnosis

There is no single diagnostic test for pSS. Serologic tests are the first step in pSS diagnosis. Although SSA (anti-Ro) and SSB (anti-La) are widely used for diagnosis, their low sensitivity makes them less helpful.

A relatively simple procedure first described in 1968, labial salivary gland biopsy (LSGB), also known as lip biopsy, helps pSS diagnosis, and management (Figures 1 and 2) [50]. A relatively large study showed that 53% of patients with negative anti-SSA and anti-SSB antibodies had positive lip biopsy [51]. Considering close to half of the pSS patients may have negative anti-SSA and anti-SSB, there is a need for better diagnostic

Figure 1: Minor salivary gland biopsy, also known as lip biopsy. Black arrows point to two minor salivary glands after a small lower lip incision.
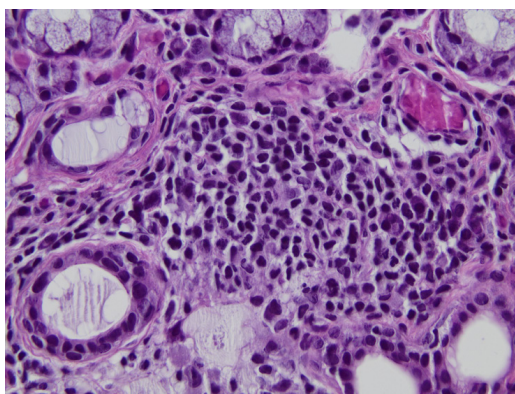

Figure 2: Salivary gland Biopsy H & E X 40 consistent with lymphocytic sialadenitis. Lymphocytic sialadenitis is considered the histologic hallmark of Sjögren's syndrome.

tools. It is unclear whether anti-SSA and anti-SSB antibodies are associated with false-negative results in the early stages of pSS. Although LSGB is the method of choice for diagnosis, there are no established guidelines concerning biopsy procedures. Furthermore, some studies have questioned lip biopsy utility based on the high frequency of equivocal findings and the invasive nature of the procedure [52].

Also, determining who requires a lip biopsy can be difficult and controversial. Two major groups of patients who may benefit from the biopsy are:

- Those who lack the classic pSS presentation of sicca syndrome, but include other systemic symptoms, such as idiopathic peripheral neuropathy and joint pain.

- Those who have classical xerostomia/sicca with undiagnosed peripheral neuropathy or cranial nerve involvement, specifically the Vth cranial nerve.

Treatment

The same as diagnosis, pSS treatment poses a challenging dilemma. Hydroxychloroquine is frequently used based on observational studies. In a retrospective study of 13 pSS patients with sensory neuropathy, 11 patients received several medications including corticosteroids, hydroxychloroquine, IVIG, mycophenolate mofetil, and cyclophosphamide, and followed for 3 years [31]. Seven patients received corticosteroids plus a second agent with a response rate of 92%, mycophenolate mofetil 92%, cyclophosphamide 80%, hydroxychloroquine 67%, and IVIg 50%. The study revealed mixed results with unsatisfactory outcomes [30]. In a retrospective study of 82 pSS with neurologic manifestations, 73 patients received corticosteroids that resulted in a durable neurologic amelioration or stabilization in 45% of patients. Corticosteroids were ineffective in 13 patients, mostly in individuals with polyneuropathies. Patients with spinal cord compromise and multiplex mononeuropathy received intravenous cyclophosphamide every 30 days for half or a full year with improvement or absence of progression [20].

In a series of 3 anti-SSA/SSB positive pSS patients [53] with ataxic neuronopathy, interferon-alpha showed symptomatic improvement in disability level, sicca symptoms, and antibody levels. In another case series of 5 patients with painful sensory neuropathy, intravenous immunoglobulin (IVIG) pain improvement was achieved even after relapses in 2 patients [54]. In a retrospective study of 8 pSS patients with neurologic symptoms, all patients received pulse methylprednisolone, 6 received pulse cyclophosphamide, and 3 patients received IVIG [55]. All 8 patients responded favourably with improvement or stabilization of symptoms. In another study, although IVIG and corticosteroids were effective for neuropathic symptoms of 92 pSS patients [26], the response was depending on the type of neuropathy. For instance, cranial nerve compromise responded better to corticosteroids whereas IVIG was more effective for sensory neuropathies. In a study of 40 pSS-related neuropathy patients, necrotizing vasculitis responded better to cyclophosphamide [23] than patients without vasculitis. Rituximab is recommended by ACR treatment guidelines [56] for systemic manifestations of pSS, including peripheral neuropathy. This was based on a prospective study of 86 pSS patients where 74 individuals had systemic organ involvement, and 18 had nervous system disorder [53,57] with an efficacy of 44% for central and 50% for peripheral nervous compromise.

Based on available evidence and expert opinion of a multidisciplinary EULAR [58] task force, systemic treatment depends on the type of organ involvement. Glucocorticoids followed by oral immunosuppressant's or rituximab are the first choice for mono neuritis multiplex and vasculitis mediated axonal PN. However, IVIG is the first-line recommendation for ganglionopathy and CIDP. Regarding CNS syndromes, for CNS vasculitis and NMOSD, glucocorticoids are first-line treatment with cyclophosphamide as second choice and MS-specific treatments are recommended for MS-like syndromes.

Conclusion

Neurologic manifestations of autoimmune disorders, including pSS are well known for both rheumatologists and neurologists. However, most studies focus on PNS, namely painful sensory neuropathy. CNS and cranial nerve involvement, particularly trigeminal nerve involvement that may present with facial pain or headaches, as the main pSS presenting manifestation have been underestimated and under-looked. A detailed history and review of the system for a constellation of dry eye, dry mouth, multiple dental caries, miscarriage, or unexplained fatigue might be a clue for a proper diagnosis.

Although different case series and observational studies tried to find the most effective treatment for pSS-CNS and PNS, there is no high-quality evidence-based study supporting a treatment. Most series used corticosteroids with good results. No study reports therapeutic agents' side effects, and there is scarce evidence to support biological agents' benefits. Further investigation is warranted to establish the best treatment for these patients. Improvement of our understanding of pathophysiology, diverse manifestations, and neurological complications of pSS may help to develop a standard treatment for pSS-related neuropathies.

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