Review

The kaleidoscope of neurological manifestations in primary Sjögren's syndrome

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Key words: primary Sjögren's syndrome, central nervous system, peripheral nervous system, autonomic system

ABSTRACT

Neurologic involvement is a common extraglandular manifestation of primary Sjögren's syndrome (pSS), is varied and can be divided anatomically into 3 categories: central nervous system, peripheral neuropathies and autonomous nervous system manifestations. According to different study cohorts, neurological manifestations can occur in 18-45% of pSS patients, with the peripheral nervous system being the most frequent site of involvement compared to the central nervous system and autonomic system. Some neurologic complications share convergent pathophysiology, although the pathological basis of other conditions, namely cognitive impairment in pSS, is less clear. The heterogeneity of neurologic manifestations in pSS complicates the diagnosis and approach to treatment, which should be directed toward the underlying neuropathologic mechanism. The diagnosis and treatment of these manifestations must be optimised in order to avoid severe disability. However, for the majority of the complications, evidence for treatment efficacy is limited and requires further investigation.

Introduction

Primary Sjögren's syndrome (pSS), is a systemic autoimmune disease characterised by chronic inflammation of exocrine glands (1, 2). Despite the tropism for glandular tissue, leading to a clinical picture dominated by mucosal dryness, a consistent proportion of patients with pSS can also experience extra-glandular manifestations. Any organ and system can be affected with different features according to ethnicity, serological features and age at disease onset. In particular, up to 75% of pSS patients experience any extraglandular manifestation ranging from mild arthralgia to life-threatening vasculitis (3-5). Although pSS is not associated with an increase in all-cause mortality as compared with the general population, a subset of patients with extraglandular involvement, vasculitis, hypocomplementaemia and cryoglobulinaemia may be at increased risk of mortality (6). According to different study cohorts, neurological manifestations can occur in 18–45% of pSS patients with the peripheral nervous system (PNS) being the most frequent site of involvement (4, 7) compared to the central nervous system (CNS) and autonomic system. In the majority of cases, neurological manifestations occur in association with other extra-glandular manifestations; interestingly, cryoglobulinaemia, low complement fractions, and male gender predict not only neurological involvement, but also a more severe clinical picture (8, 9). Finally, a higher focus score in the minor salivary gland biopsy correlate with extraglandular manifestation in pSS, including neurological involvement (10).

The purpose of this review article is to summarise the features on pSS-associated neurological clinical spectrum and their management based on the available literature (Table I). In particular, we designed a comprehensive search of literature on this topic, by a review of reported published articles in indexed international journals until April 30, 2019, following proposed guidelines for preparing biomedical narrative review (11).

Central nervous system involvement in pSS

Initially considered as associated conditions rather than extraglandular manifestations within the clinical spectrum of pSS, CNS manifestations have now been properly recognised (12). In 1981 Alexander *et al*. described for the first time 8 cases of CNS involvement

Table I. Most relevant manifestations of central, peripheral and autonomous nervous system involvement in primary Sjögren's syndrome.

Central nervous system	Peripheral nervous system	Autonomous nervous system
Focal/multifocal involvement	Distal axonal sensory polyneuropathy	Adie's pupils
– Stroke	Small fibre neuropathy	Disorders of gastrointestinal motor activity
– NMOSD	Sensorimotor polyneuropathy	Bladder dysfunction
– MS-like syndromes	Multiple mononeuropathy	Orthostatic hypotension
– ALS-like syndrome	Sensory ganglionopathy	Heart arrhythmia
Diffuse abnormalities	Cranial nerve neuropathies	Secretomotor dysfunction
– Cognitive dysfunction	CIDP	Anhidrosis
– Dementia	Motor neuron diseases	
– Psychiatric abnormalities		
– Aseptic meningoencephalitis		

NMOSD: neuromyelitis optica spectrum disorders; MS: multiple sclerosis; ALS: amyotrophic lateral sclerosis; CIPD: chronic inflammatory demyelinating polyneuropathy.

in pSS patients, with no explanation for neurological symptoms other than anti-Ro/SSA-mediated small vessel vasculitis (13). Small vessel lymphocytic inflammatory and ischaemic vasculopathy of the brain could be subsequently demonstrated by angiography and histopathology and patients with CNS vasculitis often display concomitant active vasculitis in other organs and systems, in particular the skin (14, 15). A few years later, Bakchin *et al.* observed for the first time a large lymphocytic infiltrate in the brain at *post-mortem* examination of a pSS patient with multiple CNS manifestations (16). In agreement with an immunological aetiology of CNS involvement, Sanders *et al.* provided evidence of intrathecal activation of the complement system by detecting downstream fractions in the cerebrospinal fluid (CSF) from pSS patients with CNS manifestations (17). A recent study added that also a slightly elevated cell count, increased total CSF protein content and identical oligoclonal IgG bands in CSF and serum can be observed in pSS CSF, but Authors ruled out intrathecal synthesis of IgM or IgA (18).

The prevalence of CNS manifestations in pSS ranges from 2.5 to 60%, likely due to the lack of a unified definition, leading to major differences across studies and the variability of the clinical picture, from clinically apparent conditions *versus* asymptomatic lesions identified with electrophysiologic studies or imaging methods (19). However, a 10-year follow-up study in a large cohort of pSS patients revealed that, after lymphoma, CNS involvement was the most frequent severe/life threatening extraglandular manifestation with a complete treatment response observed in only 29% of patients (20). To note, CNS symptoms may also precede the diagnosis of pSS by up to 2 years in 80% of the patients, and have a worse prognosis leading to more severe disability compared to PNS manifestations (21-22). pSS-CNS manifestations can be classified into focal or multifocal involvement of the brain and spinal cord and diffuse abnormalities.

Focal/multifocal involvement of the brain and spinal cord

Focal encephalic involvement is the most frequent CNS manifestation in pSS and can occur with an insidious onset (23). Focal symptoms mostly present with stroke-like features with motor or sensory deficits, including haemiparesis, aphasia, dysarthria, haemiplegia, movement disorders, and cerebellar syndromes. The different symptoms reflect the site of the focal CNS vasculitis (cryoglobulinaemia-related or not). Several other focal neurologic manifestations have been described in pSS including seizures, chorea, dystonia internuclear ophthalmoplegia, nystagmus, intention tremor, L-dopa resistant Parkinsonism, athetosis and spastic tetraparesis (22, 24-27). Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory conditions of the CNS characterised by severe, immune-mediated demyelination and axonal damage predominantly targeting optic nerves and spinal cord. Traditionally considered a variant of multiple sclerosis (MS), NMO is now recognised as a distinct clinical entity based on the discovery of disease-specific anti-aquaporin-4 (AQP4) antibodies (28). A recent study assessed anti-AQP4 antibodies in pSS patients reported that they could be detected only in patients with NMOSD, putting forward the hypothesis that NMOSD may not be a direct central nervous system manifestation of SS but rather an associated condition (29). NMO typically presents with acute attacks of bilateral or rapidly sequential optic neuritis (leading to severe visual loss) or transverse myelitis (often causing limb weakness, sensory loss, and bladder dysfunction) with a typically relapsing course (30-32). Subacute transverse myelitis identified by magnetic resonance imaging (MRI) is rare but it was described in pSS (33). It has been postulated that in pSS optic neuritis is the result of both demyelination and ischaemic vasculitis (22). Bilateral retrobulbar optic neuritis has been extensively described in pSS with blindness due to bilateral optic neuritis being the first symptom in some cases. However, NMO is asymptomatic/paucisymptomatic in the majority of cases in pSS and is diagnosed through the visual evoked potentials (34). In addition to NMOSD, multiple sclerosis (MS)-like lesions have been also identified in the white matter of the brain and the spinal cord of pSS patients The clinical picture includes limb paresis, internuclear ophthalmoplegia, ataxia and aphasia with a chronic, relapsing-remitting course as in MS (22, 34). CSF analysis reveals oligoclonal bands typical of MS (35). As for the NMOSD, the relationship between MS and pSS

is a subject of ongoing debate and it has been therefore suggested to always verify if patients with MS-like features actually satisfy MS diagnostic criteria and can be diagnosed with both conditions (36).

Finally, a multifocal form including involvement of the lower motor neuron imitating amyotrophic lateral sclerosis (ALS) and a form including involvement of the upper motor neuron have also been described (37, 38).

Diffuse CNS abnormalities
Diffuse CNS involvement encompasses cognitive dysfunction, dementia, psychiatric abnormalities and aseptic meningoencephalitis (23). Cognitive dysfunction in pSS is rather frequent and characteristic of a fronto-subcortical alteration with memory, attention, and executive disorders (39, 40). Patients with mild cognitive impairment referred to as "brain fog" are often not classified as pSS with CNS manifestations, since cognitive deficits can arise from depression/anxiety. However, both cognitive and affective disorders could also be the result of immune mediated brain dysfunction, and therefore require prompt identification and treatment. A recent study outlined that a certain degree of cognitive impairment can be observed in up to 80% of patients with pSS, with half of them being moderate or severe (41). With regard to the pathological basis of cognitive impairment in pSS, this has been ascribed to a combination of pain, depression and immune-mediated endothelitis (42-45). Compared to the many studies exploring the effects of depression on cognition, those exploring the relationship between pain and cognitive status are rather few. However, most of them agree that pain has a role in this process and that the intensity of pain correlates with the performance of executive functions (39, 42, 46, 47). To note, cognitive impairment is not associated with any variable related to the disease (*e.g.* disease activity/damage, serological status, disease duration) but adjusting for depression, verbal memory is a significant predictor of cognitive symptoms (43). Brain MRI is normal in 80% of pSS patients with cognitive impair-

ment, or it may show subcortical foci in the fronto-parietal region. Single-photon emission computed tomography (SPECT) may show hypoperfusion areas in the frontal and temporal lobes (22, 44, 48). Dementia is observed in a very small proportion of overall pSS patients since in the majority of cases cognitive impairment remains stable overtime and does not evolve in overt dementia The prevalence increases between 7.5 and up to 33% when selecting elderly pSS patients (49, 50). Psychiatric diseases such as depression, anxiety, and sleep disorders are rather prevalent in pSS. However, given that patients with chronic diseases are at higher risk for these conditions, it is unclear whether pSS confers an independent increased risk of psychiatric diseases (51, 52). Aseptic meningitis/meningoencephalitis are relatively common in pSS and have been linked to inflammation of meningeal vessels. The clinical features include headache, meningeal signs and flu-like symptoms at onset and could evolve with focal neurological symptoms such as seizures, cranial nerve palsy or cerebellar syndromes. Fever is not necessarily present. Brain MRI may be either normal or show hyperintense inflammatory lesions in the cerebral white matter and cortex or vasculitis (12, 53).

Peripheral nervous system involvement in pSS
PNS manifestations within the spectrum of pSS occur in 5.3 to 21% of patients and encompass different types of neuropathies and myopathies (4). Interestingly, peripheral neuropathies is the presenting symptom in 25% of pSS patients (54), and most (93%) of patients with Sjögren-associated neuropathy had clinical manifestations of neuropathy that preceded either the development of sicca symptoms or laboratory findings consistent with pSS (55). Neuropathies include distal axonal sensory polyneuropathy, small fibre neuropathy, sensorimotor polyneuropathy, multiple mononeuropathy, sensory ganglionopathy, cranial nerve neuropathies chronic inflammatory demyelinating polyneuropathy (CIDP) and motor neuron diseases (56). All these periph-

eral neuropathies can be differentiated according to clinical presentation and results from electromyography and nerve-conduction studies, evoked potentials, and nerve/muscle biopsy. Skin biopsy may provide useful information to diagnose small fibre neuropathies by assessing for the intraepidermal nerve fibre density of unmyelinated nerves. Different pathogenic mechanisms have been suggested based on the histological and serological findings such as vasculitis of the vasa nervorum, lymphocytic infiltration of the dorsal ganglia, necrotising vasculitis and anti-neuronal antibodies and depend on the type of nerve involved (22, 57-61). The most common PNS manifestation is distal axonal sensory polyneuropathy followed by sensimotor neuropathy (7). Sensory axonal neuropathy is characterised by symmetric distal paresthesias and sensitive signs with prevalence on the lower limbs and may be accompanied by burning feet pain. Sensory loss in a stocking distribution is typically associated with cryoglobulinaemia. Small fibre neuropathy occurs from damage to the A-δ small myelinated fibres and/or unmyelinated C fibres which conduct nociceptive stimuli and temperatures and is characterised by very painful, burning paraesthesias involving proximal parts of limbs, trunk or face. Typically, small fibre neuropathy has non–length-dependent features in the majority of cases which allows to differentiate it from other forms of neuropathy such as diabetes where the 'distal-to-proximal' gradient is followed (62). Axonal dysfunction can be elicited at physical examination and electrodiagnostic study with non-necrotic axonal degeneration observed at nerve biopsy. Conversely, physical examination and electrodiagnostic studies are usually normal in patients with small fibre neuropathy and only a skin biopsy to assess the reduction of intra-epidermal nerve fibre density (IENFD) can aid the diagnosis. The denervation pattern observed in the biopsy usually reflects the non-length dependent symptoms. Given the difficulty to perform the above mentioned biopsy in routine practice, a recent study explored and compared quantitative sensory tests

such as determination of warm and cold detection thresholds (WDT, CDT), recording of laser-evoked potentials (LEP), recording of sympathetic skin responses (SSRs), and measurement of electrochemical skin conductance (ESC) to diagnose small fibre neuropathy. LEP, WDT, and ESC have a better diagnostic sensitivity compared to SSR and CDT and their combination further improves diagnostic accuracy (63). The question remains on how accurate and cost-effective these tests are compared to the gold standard. Sensorimotor polyneuropathy occurs when in addition to axonal sensory polyneuropathy, motor nerve fibres are also involved. Clinical features are those mentioned above and weakening of distal muscles of the limbs which is usually mild and limited to the toe or foot extensors, but in rare cases can be severe and impair ambulation. Deep tendon reflexes may be diminished or absent. Electrodiagnostic studies reveal reduced sensory nerve action potential and features of acute or chronic denervation. Nerve biopsy is not recommended, unless the presence of vasculitis is suspected (64). Of interest, sensimotor polyneuropathy is associated with cryoglobulinaemia, low C4 and the development of lymphoma (54). Multiple mononeuropathy is defined by the simultaneous or consecutive asymmetric damage of at least two nerves which do not form a continuity with each other. It is the results of an underlying necrotising vasculitis of the vasa nervorum with concomitant T cell and macrophage infiltration leading to ischaemia-induced nerve damage (65) In these patients, vasculitis is not limited to the nerves but also present in other extraglandular sites therefore multiple mononeuropathy is often part of a more complex clinical picture.

Sensory and motor deficits involving the area of the ischaemic nerves, along with pain, deeply located in the proximal part of the affected limb and painful paraesthesias are the main clinical features and may have acute or subacute onset. The longest nerves in the body are affected first, therefore foot drop is the most common manifestation of multiple mononeuropathy and in some cases, weakness of the affected limb

may be more invalidating than pain (66). Axonal damage and pseudoblocks corresponding to the areas of nerve ischaemia are the hallmark that are detected at electrophysiological studies. Sensory ganglioneuronopathy recognises dorsal root ganglia as main target and is probably due to lymphocytic infiltrates with or without vasculitis of large and small fibres on posterior roots and spinal ganglions. According to some Authors, autoantibodies may also be involved in this process (55, 60, 67). Unsteadiness of gait is the main clinical feature along with dysfunction of vibration sensation, areflexia and, in some cases, pseudoathetoid movements of limbs (68, 69). Electrodiagnostic studies shows reduced/absent sensory nerve action potentials and somatosensory evoked potential abnormalities while motor conduction studies are normal in most cases (55, 67, 68). Dorsal root ganglionitis may also selectively affect small neurons and present with painful dysesthesias in an asymmetric, patchy, non-length dependent distribution (70).

Cranial nerve neuropathies can occur in pSS with trigeminal neuropathy being the most frequent followed by the involvement of facial and oculomotor nerves (71, 72). Trigeminal nerve dysfunction is caused by damage to the ganglion, and usually affects the middle (maxillary) branch (73). Gasser ganglion damage can be at least in part explained by the observation that trigeminal neuropathy may be associated with dorsal roots ganglionitis (60, 74). In the majority of patients it presents as a pure sensory neuritis, either uni- or bilateral, but in some cases it occurs within multiple cranial neuropathy patterns. The facial nerve is the most frequently targeted motor cranial nerve and the first case of bilateral neuropathy was described by Henrik Sjögren in 1935. Unilateral neuropathy is more frequent and is seldomly associated with other cranial nerve neuritis (75). Selective or combined neuropathy of the oculomoter nerves results in diplopia (75). Involvement of the optic nerve has been already discussed with regard to NMOSD, and the involvement of other cranial nerves is anectodical.

Diseases affecting the anterior horn cells, namely, motor neuron diseases occur rarely in pSS and are characterised by paresis, atrophies and fasciculations mainly in distal parts of limbs. Electrodiagnostic studies detect abnormalities of motor nerve conduction with signs of acute denervation. The pathogenic mechanism seems an inflammatory response characterised by mononuclear cell infiltration without signs of vasculitis (26, 76)

A condition that is rarely observed in pSS, but should be mentioned for the sake of completeness is chronic inflammatory demyelinating polyneuropathy (CIDP). From a clinical point of view, CIDP is characterised by symmetric weakening of proximal and/or distal muscles of upper and lower limbs with sensory dysfunctions and reduced/absent deep tendon reflexes. Electrodiagnostic studies demonstrate prolonged distal motor latency, slowed conduction velocity, abnormal temporal dispersion or partial conduction block, and absent F-wave or prolongation of its latency (77).

Autonomous nervous system involvement in pSS

The prevalence of dysautonomias in pSS ranges between 2 and 50% but the exact burden of these conditions is not known due to different definitions and diagnostic workouts (55, 78). In this regard, some Authors did not observe any difference in the prevalence of autonomic dysfunction in pSS compared to the general population (79). Autonomic dysfunction has been ascribed to a combination of ganglioneuronopathy and vasculitis. In addition, antibodies against the type 3 muscarinic receptor, which are able to inhibit neuron-mediated contraction throughout the gastrointestinal tract have been described in pSS and may explain at least in part some of the manifestations resulting from autonomic dysfunction in pSS (80). Antibodies against acetylcholine receptor have also been detected in patients with pSS and autonomic symptoms (81). Finally, yet importantly, patients with pSS display high levels of cholinesterase, allowing to speculate that interference with cholinergic neu-

rotransmission may be an additional pathogenic mechanism (82) Adie's pupils disorders of gastrointestinal motor activity, bladder dysfunction, orthostatic hypotension, heart arrhythmia, secretomotor dysfunction and anhidrosis are the most commonly observed manifestations of autonomic neuropathy (55).

Management of neurological manifestations in pSS

Solid evidence to support therapeutic decision in pSS patients with extraglandular manifestations is currently lacking. The European League Against Rheumatism (EULAR) recently formulated guidelines for pSS management (83) which represent a milestone in rheumatology and will allow clinician to have for the first time in history such support in daily practice. Currently, the use of immunosuppressive and biologic agents in pSS is mainly based on their efficacy in other autoimmune disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), expert opinion, and uncontrolled studies (84). High-dose glucocorticoids and other immune suppressant drugs are used empirically for CNS manifestations involving the spinal cord. In selected patients with NMO high doses of corticosteroids can be used to induce remission and then maintenance therapy is performed with mycophenolate mofetil or azathioprine. Other drugs that can be used for CNS manifestations include rituximab, plasma exchange, azathioprine, methothrexate and mycophenolate mofetil and are used according to the severity of the condition (85, 86). Peripheral neuropathies are usually treated with oral corticosteroids and immunosuppressive agents may be used to maintain remission, along with intravenous immunoglobulins (IVIG), rituximab or plasma exchange for refractory cases (87-89). Plasma exchange, IVIg, rituximab, glucocorticoids and cyclophosphamide should be used for sensory ganglioneuronopathy keeping in mind that pseudo-athetoid movements of the fingers and toes are often refractory to treatment (90-92). The treatment of autonomic dysfunctions in only symptomatic and based

on the empirical use of anti-cholinergic agents, antidepressants and gabapentinoids (93).

Conclusions

Neurologic involvement in pSS is common and may be the presenting sign of pSS. There is a great need to develop consensus criteria for classifying these varied neurologic manifestations. In fact, according to different study cohorts, neurological manifestations can occur in 18–45% of pSS patients; this wide range reported in the literature reflects the varying definition and method for detection of the neurologic manifestations, differing classification criteria for pSS, and selection bias of the patient cohorts used for study. The heterogeneity of neurologic manifestations in pSS complicates diagnosis and approach to treatment, which should be directed toward the underlying neuropathologic mechanism. The diagnosis and treatment of these manifestations must be optimised in order to avoid severe disability. However, for the majority of complications, evidence for treatment efficacy is limited and requires further investigation.

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