Neuroinflammation and Sjogren's Syndrome

Pasquale Annunziata

Abstract Sjogren's syndrome (SS) is a chronic organ-specific autoimmune disease mainly involving exocrine glands such as lacrimal and salivary glands. SS may also involve central and peripheral nervous system with variable prevalence due to differences in diagnostic criteria and in time length to reach diagnosis. Clinical features of the central nervous involvement share similarities with multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD), two major neuroimmune disorders. SS may even coexist with MS or NMOSD. Sensory neuropathy, chronic polyradiculoneuropathy, cranial neuropathies as well as small fibre neuropathy are the main manifestations of the peripheral nervous system involvement. The pathogenic mechanism underlying neuro-SS is unclear even though molecular mimicry and epitope spreading have been hypothesized for central nervous involvement, whereas vasculitis with or without direct damage to nerve could account for peripheral nervous involvement. Treatment is mainly based on immunosuppressive therapies requiring a close cooperation between neurologists and rheumatologists to achieve the best management.

Keywords Sjogren's syndrome · Multiple sclerosis · NMOSD · Polyneuropathy · Autoimmunity

Introduction

Sjogren's syndrome (SS) is a chronic organ-specific autoimmune disease that is characterized by lymphocytic infiltrate and progressive degeneration of the exocrine glands such as lacrimal and salivary glands. This disorder may present with both an isolated syndrome named primary SS (PSS) and a secondary SS in association with other connective tissue diseases such as rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis (reviewed in [1]). SS may also involve central/

P. Annunziata (✉)
Department of Medicine, Surgery and Neurosciences, Clinical Neuroimmunology Unit, University of Siena, Siena, Italy
e-mail: annunziata@unisi.it

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peripheral nervous system (CNS/PNS) and likely represents the connective disorder with most intriguing features (mainly regarding the central nervous system manifestations) that, sometimes, raise doubts in diagnosis and thus in treatment for both rheumatologists and neurologists.

Epidemiology

Data on the prevalence of PSS are heterogeneous, ranging from 0.2% in a Danish population to 3.9% in a population-based study in United States (reviewed in [2]). However, the prevalence of PSS coexisting with CNS clinical features and consistent with the diagnosis of inflammatory nervous disorders such as multiple sclerosis (MS) is questionable ranging from 0% to 16.7% [3–7]. Conversely, the prevalence of peripheral nervous system (PNS) features in SS ranges from 25% to 59% of PSS patients [8–10]. This heterogeneity is due to a number of reasons including the criteria used in performing diagnosis of SS as well as the long time needed to reach a diagnosis of SS sometimes requiring an average of 10 years [11]. Table 1 summarizes the most relevant epidemiological findings.

Clinical Manifestations

Clinical Features of Sjogren's Syndrome

The classical clinical features of PSS involve lacrimal and salivary glands and are part of the 'sicca syndrome complex' including xerophthalmia and xerostomia as well as recurrent salivary gland enlargement. However, the disease may involve other organs and systems such as the lung, liver, kidney and circulation [12]. Respiratory symptoms such as cough or rarely interstitial pneumonitis and fibrosis may be present [13]. Mild hepatitis or intestinal malabsorption occurs, while glomerulonephritis, rarely progressing towards a nephrotic syndrome, may develop [14]. SS may occur in association with other connective disorders such as

Table 1 Epidemiology of Sjogren's syndrome with nervous involvement

	Prevalence	References
CNS	5.8%–38%	[9, 20, 21]
MS	0%–16.7%	[3–7]
PNS	25%–59%	[8–10]
	1.8%[a]	[27]

CNS central nervous system, *MS* multiple sclerosis, *PNS* peripheral nervous system

[a]supported by electrophysiological findings

rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis consisting with secondary SS. Arthralgias and myalgias occur in 53% and 22% of patients, respectively [12]. The severity of clinical features is variable extending from benign course characterized by clinical remission stages up to rare severe manifestations when being associated with peripheral blood alterations such as purpura, reduced complement levels and monoclonal cryoglobulinemia that may increase mortality [15]. Other secondary symptoms are part of the various SS clinical scenario. Fatigue is present in nearly 50% of PSS patients, sometimes debilitating, and often associated with hypothyroidism [16]. Another symptom is pain that may represent one characterizing sign of fibromyalgia detected in more than 20% of PSS [17]. A mild Raynaud's phenomenon also occurs in nearly 30% of SS patients, and different skin alterations such as dryness or burning are detected. When skin ulcerations are present, vasculitis of small- or medium-sized vessels is observed [18].

Clinical Features of Central Nervous Involvement

The neurological involvement in SS consists of symptoms and signs affecting both PNS and CNS [19], but it is still matter of discussion whether central or peripheral nervous involvement may be predominant. Isolated CNS involvement was found to vary between 5.8% and 38% of PSS patients [9, 20, 21]. Brain, spinal cord and optic nerve may be affected in percentages variable and not necessarily in the same patient. The clinical features are secondary to location of inflammatory lesions in the brain and spinal cord white matter and include aphasia, hemiparesis, cerebellar symptoms, brainstem symptoms, sensory impairment, acute myelitis, chronic myelopathy, aseptic meningitis as well as optic neuritis [9, 20, 22]. The neurological manifestations in SS occur in various times developing prior to or after SS onset (reviewed in [1]) and thus leading to delay in diagnosis assessment. However, CNS involvement preceding SS diagnosis seems to be predominant ranging from 52% to 80% of subjects [9, 20, 22].

Two major inflammatory nervous disorders characterizing central nervous involvement in SS are MS and neuromyelitis optica (NMO). Clinical and laboratory features of PSS may develop during the course of MS with various diseases duration ranging from 9.3 to 13 years [5, 6] and with higher prevalence in progressive MS supporting the need to perform screening for SS in all patients with primary progressive MS [7]. An important issue is the occurrence of clinical signs or symptoms of sicca syndrome in the course of MS. This issue was addressed in a large multicentre study in Italy. Sicca syndrome occurred in 9.6% of MS patients and was detected at onset of disease in 2.3% of cases [4]. However, the presence of sicca syndrome was not related to SS development and tended to arise in progressive forms of MS patients displaying a higher disability and higher frequency of cognitive disturbances with a low inflammatory disease activity as assessed at magnetic resonance imaging (MRI). This finding suggests a different pathogenic mechanism underlying xerophthalmia and xerostomia in MS from that known in SS, linking the

Table 2 Clinical features of central nervous involvement in Sjogren's syndrome

Optic neuritis
Aphasia
Hemiparesis
Brainstem symptoms
Cerebellar symptoms (ataxia, dysmetria)
Acute transverse myelitis
Aseptic meningitis
Sensory impairment

development of sicca complex symptoms in MS to autonomic dysfunction involving both parasympathetic and sympathetic systems, previously demonstrated in this disorder [23]. Moreover, PSS may develop during MS course under immunomodulatory therapy with Interferon beta, both in non-responder and in good responder patients after a few months from MS onset [24] or after a very long time up to 29 years from MS onset [25]. Currently, a pathogenic role of immunomodulatory therapies in developing SS in course of MS has not been demonstrated. SS was found to be part of clinical onset of NMO and is currently included in NMO spectrum disorders appearing as acute transverse myelitis with MRI lesions involving one or more spinal cord segments [26]. The main clinical features are paraparesis, hypoesthesia or anaesthesia with cervical or thoracic sensory level associated or not with sphincter dysfunction. Table 2 summarizes the most frequent clinical features of central nervous involvement in SS.

Clinical Features of Peripheral Nervous Involvement

PNS involvement based on clinical assessment ranges from 25% to 59% of PSS patients [8–10]. This frequency dramatically decreased when electrophysiological assessment was used showing the prevalence of peripheral neuropathy reaching only 1.8% in a large cohort of patients with PSS [27]. The most common neuropathies reported in PSS patients include sensory neuropathy with or without ataxia, sensory-motor neuropathy, mononeuritis multiplex, chronic polyradiculoneuropathy, cranial neuropathies as well as small fibre neuropathy [8–10]. The neuropathy is mainly axonal. These patients may have extraglandular manifestations including purpura and vasculitis and laboratory features such as monoclonal cryoglobulinemia. The related clinical features include distal symmetric sensory loss, sensory ataxia due to loss of proprioceptive large fibres associated with ganglionopathy and painful dysesthesias characterizing small fibre sensory neuropathy and due to degeneration of cutaneous axons. Table 3 summarizes the main clinical features of peripheral involvement in SS.

Table 3 Clinical features of peripheral nervous involvement in Sjogren's syndrome

Sensory neuropathy with or without ataxia (dysesthesias in arms or legs, with or without pain)
Sensory-motor neuropathy (dysesthesias or hypoesthesias, limb weakness)
Mononeuritis multiplex
Cranial neuropathies (facial or oculo-motor neuropathies)
Small fibre neuropathy (painful dysesthesias)
Chronic polyradiculoneuropathy (progressive limb weakness, gait impairment with or without dysesthesias)

Pathogenesis

Immunopathogenesis of Sjogren's Syndrome

Currently, there is a wide agreement on the concept that a combination of genetic susceptibility and environmental factors may account for the pathogenesis of SS (reviewed in [1]). The role of several viral infections in the SS induction has been investigated. The list of viruses includes cytomegalovirus (CMV) and Epstein-Barr virus (EBV). An association with retroviruses such as HTLV-1 and HIV has also been reported (reviewed in [28]). Dendritic and epithelial cells of the salivary glands could be activated by viral antigens, leading to upregulation of pro-inflammatory and anti-viral genes resulting in presentation of the MHC class 2 molecules and secretion of several pro-inflammatory cytokines, mainly type-1 interferon (IFN-1) but also including B-cell-activating factor (BAFF), interleukin (IL)-6, IL-21 and IL-12 (reviewed in [1]). This strong inflammatory response results in the breakdown of innate response leading to activation of the adaptive immune response involving both T- and B-lymphocytes. These cells could migrate from peripheral blood entering the salivary gland parenchyma where they interact with antigen-presenting cells (APCs). It is likely that SSA and SSB represent the most important antigens presented by APCs. A second step of the pathogenic pathway is characterized by infiltration of lacrimal and salivary glands by $CD4^+$ but also $CD8^+$ T cells playing a role in the glandular injury. B-cell immunity also participates in the glandular injury through production of autoantibodies against M3 muscarinic receptors largely expressed on salivary gland epithelial cells (reviewed in [1]).

Immunopathogenesis of Nervous Involvement

The pathogenesis of the nervous system involvement in SS remains unclear and, to date, is mainly speculative. However, two major immunological mechanisms could be hypothesized to play a role: molecular mimicry and epitope spreading. T- and B-cell response could be triggered by a putative molecular mimicry mechanism between glandular epithelium antigens and CNS antigens that remain to be identified. This molecular mimicry could lead activated T-cell clones recognizing salivary

and lacrimal gland antigens to also recognize any putative nervous myelin antigen or, alternatively, any cerebral endothelial antigen at the blood-brain barrier (BBB) facilitating their passage into the brain parenchyma. B-lymphocytes also significantly contribute to intrathecal immune response producing antibodies reacting with specific myelin antigens. However, although IgG oligoclonal bands may be rarely detected in cerebrospinal fluid of SS patients, there is still no clear evidence for any myelin antigen recognized by these IgGs in SS. The passage of T and B cells across BBB could also be due to an epitope spreading mechanism [2] leading, in a subject with MS or SS, the immune response to extend from the peripheral blood compartment and salivary glands, respectively, to brain parenchyma. These concepts appear less appropriate for explaining the PNS involvement in SS. SS patients with clinical evidence of neuropathy do not display any circulating antibody directed against anti-myelin antigen [8]. However, vasculitis involving neural vessels is rarely present in SS patients and mainly, when peripheral blood alterations including purpura or cryoglobulinemia are found [12]. Moreover, alterations of the endoneural microvessels were observed in SS patients with neuropathy [29]. Figure 1 shows the main mechanisms underlying central nervous involvement in SS.

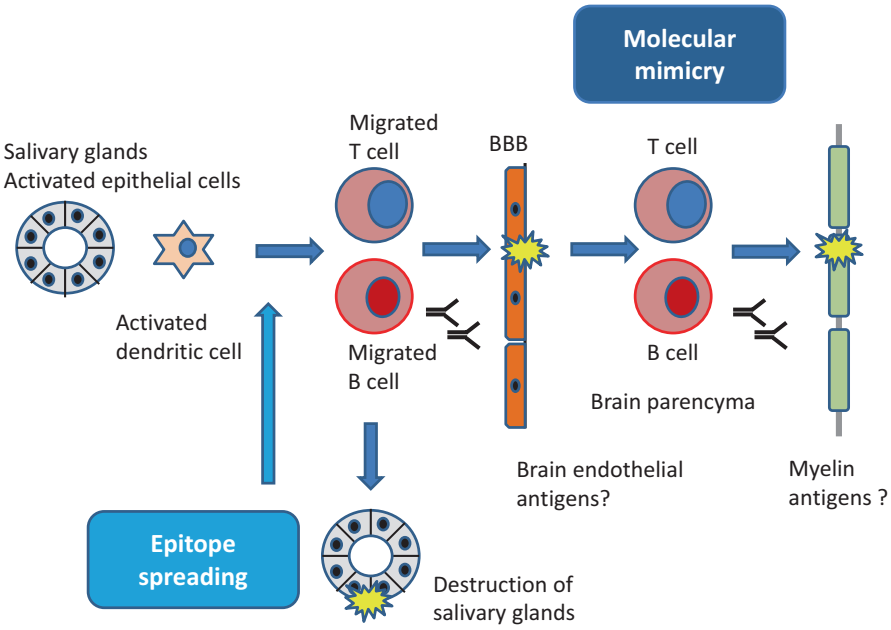

Fig. 1 Pathogenesis of the central nervous involvement in Sjogren's syndrome

Diagnosis

Currently, SS is diagnosed based on the presence of ocular and/or oral symptoms and ocular signs according to the items listed by the American-European Consensus Group (AECG) for SS as classification criteria [30]. These items also comprise a number of laboratory tests such as serum anti-Ro (SSA) and SSB antibodies as well as instrumental diagnostic tests including testing for dry eye (Schirmer's test), salivary test and minor salivary gland biopsy. The diagnosis of neurological involvement in course of SS does not appear clear at any time as due to various temporal intervals elapsing from the onset of neurological features to the SS diagnosis. This interval may take out up to 5 years [9]. Further problems come from detection of subclinical cerebral white matter lesions at MRI in PSS with no appearance of clear clinical neurological features. These lesions are not easily distinguishable from those typical of MS and thus nurture further pathogenic questions [31]. Another question is raised when, in definite MS, sicca syndrome signs and symptoms occur supporting the hypothesis of SS development. However, serum anti-Ro (SSA) and SSB antibodies are not sufficient for establishing a diagnosis even though a low frequency (7% only) of SSA antibodies has been detected in MS patients [32]. If pathogenic tests for diagnosing MS in the course of SS are lacking, more help is available for NMO diagnosis in the course of SS based on the identification of serum NMO-IgG antibody binding to aquaporin-4 (AQP4), as reliable laboratory biomarker of the NMO spectrum disorders (NMOSD) [26]. Recently, a diagnostic algorithm helping for practical managing of SS and MS has been proposed [33]. Search for sicca symptoms (xerophthalmia and xerostomia) should be performed in all patients with MS. In the presence of these symptoms, diagnostic tests (Schirmer's test) and serological screening (serum anti-SSA and anti-SSB antibodies) for SS are recommended. In case of positive findings, the diagnostic work-up should be concluded with a biopsy of minor salivary glands (Fig. 2). Conversely, in patients with PSS, a brain MRI is useful to search for any white matter lesions (mainly active as suggested by gadolinium enhancement) that should lead to perform evoked potentials and cerebrospinal fluid analysis. The positivity of these tests could support MS diagnosis according to the current revised diagnostic criteria (reviewed in [34]). Moreover, the detection of spinal cord lesions at MRI in patients with PSS requires serum anti-aquaporin-4 antibody assay to exclude a diagnosis of NMO spectrum disorder (reviewed in [35]) (Fig. 2).

On the other hand, the diagnosis of peripheral nervous involvement in course of PSS appears easier, based on clinical and neurophysiological parameters. Clinical features of PNS involvement such as sensory disturbances associated or not with pain may account for a suspected neuropathy. Electrophysiology tests such as nerve conduction studies and somatosensory evoked potentials could confirm the clinical suspicion.

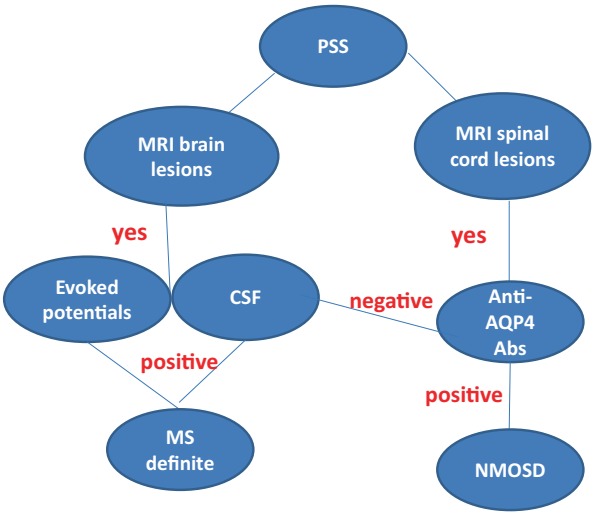

Fig. 2 Flowchart for the diagnosis of multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) in primary Sjogren's syndrome (PSS) (Modified from Masi and Annunziata [33])

Treatment

Treatment of CNS and PNS involvement in SS aims to reduce signs and symptoms related to both SS and definite neurological disorders appearing in the course of or pre-existing to SS development. When sicca syndrome occurs in MS patients, symptomatic treatment is based on the same recommendations as PSS such as hydration, avoiding anticholinergic drugs and artificial tears. Rarely, sicca symptoms are severe in the course of MS and do not require the use of muscarinic agonists employed in PSS such as pilocarpine or cevimeline [36]. When the central nervous involvement satisfies the criteria of MS, the first-line disease-modifying therapies including intramuscular or subcutaneous interferon beta 1a or beta 1b are the established choice. Due to their well-known gastrointestinal side effects, oral immunomodulators such as dimethylfumarate appear not suitable. However, in case of MS diagnosis in the course of PSS, the treatment resembles that of definite MS and the acute clinical relapses occurring during the disease are treated with standard high-dose intravenous methylprednisolone (IVMP). In central nervous involvement not satisfying the diagnostic criteria for definite MS, clinical features may be treated with oral corticosteroids or, more frequently, with IVMP. Cyclophosphamide has been used in resistant cases. When adverse events occur or in case of low efficacy, intravenous immunoglobulins (IVIG) may be employed. In the presence of frequent relapses, other immunosuppressive drugs such as azathioprine or methotrexate have been used. In SS with severe systemic symptoms such as recurrent severe arthralgias, rituximab, an anti-CD20 monoclonal antibody, can be administered. In SS occurring in the course of NMO, IVMP could be efficacious at the first clinical manifestations. However, in the presence of relapses, azathioprine or, in case of inefficacy, rituximab may be used (reviewed in [37]). In SS patients with sensory neuropathy, dysesthesias and pain may be treated with gabapentin/pregabalin or with IVIG in absence of response. Chronic polyradiculoneuropathy is treated with

Table 4 Treatment of Sjogren's syndrome with nervous involvement

Clinical feature	Drug	Administration route	Dose
CNS	Prednisone	Os	1 mg/kg/die
	IVMP	Intravenous	1 g/die per 3–5 days
	IVIG	Intravenous	0.4 g/kg die 5 days
	Cyclophosphamide	Os	50–100 mg/die
	Rituximab	Intravenous	750 mg on day 1 and day 15
MS	Interferon beta 1a	Subcutaneous	22–44 μg (3 days a week)
	Interferon beta 1a	Intramuscular	30 μg/week
	Interferon beta 1b	Subcutaneous	250 μg each other day)
	IVMP	Intravenous	1 g/die per 3–5 days (for relapses)
NMO	IVMP	Intravenous	1 g/die per 3–5 days
	Azathioprine	Os	2 mg/kg/die
	Rituximab	Intravenous	750 mg on day 1 and day 15
PNS	Prednisone	Os	1 mg/kg/die
	Gabapentin	Os	900–1600 mg/die
	Pregabalin	Os	300–600 mg/die
	IVIG	Intravenous	0.4 g/kg die 5 days

CNS central nervous system, *MS* multiple sclerosis, *NMO* neuromyelitis optica, *PNS* peripheral nervous system, *IVMP* intravenous methylprednisolone, *IVIG* intravenous immunoglobulins

oral corticosteroids or with IVIG in severe or relapsing cases. An efficacious treatment of SS with nervous involvement requires a close cooperation between neurologists and rheumatologists to achieve the best management of all symptoms and signs appearing in the course of the related disorders. Table 4 summarizes the main treatments and related doses in SS with nervous involvement.

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