Central and peripheral neurological complications of primary Sjögren’s syndrome

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Summary

Primary Sjögren’s syndrome (pSS) is an autoimmune inflammatory disorder characterized by lymphocytic infiltration of exocrine glands, mainly the lacrimal and salivary glands leading to a chronic sicca syndrome. However, extraglandular organ systems may frequently be involved, including both central and peripheral nervous systems. Clinically significant neurologic manifestations affect approximately 20% of patients and may be the first manifestation of the disease in at least 25% of the cases. The spectrum of pSS-related neuropathies is wide including sensory neuropathies, neuronopathies, sensory-motor neuropathies, mononeuritis multiplex related to vasculitis... Central nervous system involvement is composed by multiple sclerosis-like manifestations including acute and chronic myelopathies and by more diffuse manifestations (cognitive dysfunction, subacute aseptic meningitis, encephalopathy, psychiatric symptoms, chorea, seizures...). The diagnosis and treatment of such pSS-related manifestations must be optimized in order to avoid severe disability.
and prevalence of pSS neurological complications is higher in neurological departments [3–5,11–13] in which pauci- or asymptomatic neuropathies could be systematically searched by electrophysiological studies [3–5,12,13] (table I) [1–13]. Psychiatric symptoms and carpal tunnel syndromes were also initially included in pSS neurological complications [10]. The extreme wide spectrum of central neurological involvements in pSS (cf. “Central neurological manifestations”) could also explain this discrepancy [7,10,11]. Neurologic manifestations may reveal pSS and neurological complications preceded pSS diagnosis in 25 to 65% of the cases with a mean delay of 24 months [1,10–13]. However, for others, neurologic manifestations occurred 6 to 8 years after pSS diagnosis [8,11].

### Table I

| Alexander, 1982 | 16 | 16 | 10 (0) | – | Yes | Anti-SSA positive*** |
| Hietaharju, 1992 | 27 | 6 | 21 (0) | 21 | No | Hypogammaglobulinemia* |
| Moll, 1993 | 25 | 7 | 12 (1) | 20 | No | None |
| Gemignani, 1994 | 10 | 0 | 10 (2) | 36 | Yes | Onset after 50 years |
| Grant, 1997 | 54 | 0 | 54 (10) | – | No | Anti-SSA negative*** |
| Gouoni, 1999 | 18 | 7 | 12 | 69 | Yes | Hypogammaglobulinemia |
| Barendrech, 2001 | 7 | 0 | 7 | 32 | Yes | Onset after 60 years |
| Anaya, 2002 | 3 | 3 | 0 | 117 | No | Anti-SSA positive*** |
| Delalande, 2004 | 82 | 46 | 51 (9) | – | No | Anti-SSA negative*** |
| Goransson, 2006 | 17 | 0 | 17 (8) | 45 | Yes | None |
| Gono, 2010 | 20 | 0 | 17 (8) | 12 | No | Fever |
| Pavlakis, 2010 | 9 | 0 | 9 (0) | 500 | Yes | Systemic manifestations*** |

Indeed, the clinical spectrum of peripheral neuropathies encountered in pSS is wide, and sensory neuropathies are the most commonly reported [7,8,10–16]. These pSS-related sensory neuropathies are represented by distal, length-dependent axonal sensory neuropathy and sensory ataxic neuropathy involving the dorsal root ganglia resulting in deafferentation [8,17].

Axonal sensory-motor neuropathies, mononeuritis multiplex, polyradiculoneuropathies, autonomic neuropathies and cranial neuropathies are also described [7,10–16].

### Pathogenic processes

A vasculitis pathogenesis was advanced for both pSS mononeuritis multiplex and axonal sensory-motor pSS-related neuropathies [1,13,18].

By contrast, the pathogenesis of sensory neuronopathies is related to lymphocyte infiltration into the dorsal root ganglia without any vasculitic process [1,13]. Anti-neuronal antibodies or anti-M1 or M3 muscarinic acetylcholine receptor antibodies are usually negative [8]. The research of putative neuronal immunoreactivity of pSS exhibiting neurologic manifestations was also negative [8].

### Peripheral neuropathies associated with primary Sjögren’s syndrome

#### Epidemiology and subtypes

Primary SS is associated with several different types of neuropathies in approximately 2 to 20% of patients [7,8,10–12,14–16].
Clinical presentation and electrophysiological studies

Early diagnosis of pSS neuropathy and the individualization of the clinical and electromyographic subtype is key in pSS in order to improve disability and treatment. The diagnosis protocol may include the systematic analysis of pain in pSS which can be related to articular, muscular involvements, fibromyalgia and, of course, neuropathy. Indeed, none of the pSS patients spontaneously complained about neuropathic symptoms in the Barendrecht et al. study, but abnormalities in answering the questionnaire were obtained in 20% of pSS patients leading to a neuropathy diagnosis in 50% of the cases [12]. Hence, the DN4 neuropathic pain diagnostic questionnaire [19] must be systematically performed in pSS patients who exhibit chronic pain in order to early detect pSS-related neuropathies (figure 1).

Sensory neuropathies and neuronopathies

Sensory neuropathies

Primary SS patients with sensory neuropathy complain of distal, often symmetrical, paresthesias and/or neuropathic pain including burning feet sensations. Clinical examination exhibit distal (length-dependent) neurological findings affecting mostly the lower limbs including position and vibratory sensation deficits, pinprick and light touch sensory deficits [8,11]; the upper limbs can be affected in 20% of the cases [8]. Deep tendon reflexes are diminished or absent [8]. The electrophysiologic patterns are characterized by axonal dysfunction and mild to marked denervation [20,21].

Nerve biopsy usually reveals moderate changes consisting of thinly myelinated fibers, axonal degeneration associated with remyelination process without any necrotizing vasculitis lesions [13,20–22].

Neuronopathy

Neuronopathy is a highly distinctive entity related to lymphocytic infiltration of the dorsal roots ganglia. Main clinical characteristics, usually subacute or chronic, are composed by ataxia, areflexia, asymmetric loss of deep sense and pseudo-athetosis [20,22]. Electromyographic analysis usually revealed asymmetrical alteration of sensory action potentials and somato-sensory evoked potentials [13,20]. Spinal nerve biopsy, performed in 2 studies, revealed sensory neuron apoptosis and marked mononuclear cell infiltrates surrounding neurons and blood vessels, with diffuse infiltration throughout the ganglion [13,22]. T2-weighted MRI may demonstrate posterior column high intensity signals [13].

Although this neuronopathy is usually a presenting manifestation of pSS, no associated immunological pSS profile has been described [17,20,22,23]. One recent study pointed out that pSS patients with this neuronopathy are usually seronegative [9]. However, neuronopathies have been reported to be associated with an intense lymphocytic infiltration on small salivary gland biopsy [17,20,23].

Sensory-motor neuropathies


Neuropathies associated with cryoglobulinemia

Two clinical subtypes seem to be particularly characteristic of pSS; the first is a distal, grossly symmetric, predominantly sensory neuropathy with painful dysesthesias and sensory loss in a stocking distribution. The second clinical presentation is a mononeuritis multiplex of acute or subacute onset, frequently revealing a necrotizing vasculitis of the nerve [11,24–26]. Exacerbation by cold can be seen in these patients [24–26]. Sural nerve biopsy revealed necrotizing vasculitis [13,22]. Although peripheral neuropathy can present as an isolated syndrome in cryoglobulinemia, it is generally associated with or preceded by other complications of the disease [26,27].

Cranial nerve involvement

The cochlear nerve is frequently impaired, revealed by hearing loss and vestibular symptoms [11]. Sensory trigeminal nerve involvement and facial nerve involvement are also largely described [11,22]. All other cranial nerve can be involved [13].

Association to other systemic complications and immunological profile

Although clinical presentations of peripheral neurologic manifestations in pSS are largely described, data concerning pSS patient’s systemic and immunological profiles associated to such neurological involvements are sparse or controversial [1,3,5–8,11,14,20,22,28–30]. Indeed, previous studies that have focused specifically on systemic or immunological parameters statically associated with neurologic manifestations involved small groups of patients (< 65 pSS) and used earliest pSS criteria [3,5,7,10,12,14,20,28]. Furthermore, most of these studies concerned systematic research of asymptomatic or pauci-symptomatic neurologic manifestations [3,5,12,14,20]. First, young onset [31] and long-term evolution [32] were reported associated with pSS neuropathies. On the contrary, pSS-associated neuropathies seem to occur after the fifth decade for others [12,20].

Statistical relationships between peripheral neurologic manifestations and articular involvement, cutaneous and muscular vasculitis have been pointed out previously [6,8,10,11,27,33,34]. On the contrary, other studies didn’t find any statistical relationship between those systemic involvements and pSS neuropathies [1,7,12,20,22].

The same discrepancy has been described with neurologic manifestations associated immunological profile; neurologic manifestations have been reported associated with a higher
prevalence of both anti-SSA or anti-SSB antibodies and hyper-gammaglobulinemia in some studies [6,10,32,35]; on the opposite, neuropathies are associated with a negative immunological profile in others [3,5,11,14,22,28,29]. Complement activation was reported in 30% of patients with pSS axonal neuropathies [20]. The association between pSS neuropathies and cryoglobulinemia could have been deduced from the link previously pointed out between hypogammaglobulinemia and neurologic manifestations [5,28]. Ramos-Casals’ group has recently confirmed this pathophysiological association between neurologic manifestations and cryoglobulinemia [6,32]. In fact, immunological parameters associated with
neurologic manifestations depend of the type of neuropathy: neuronopathies seems to be seronegative, multinervitis and other cryoglobunemia-associated neuropathies associated with an active immunological profile [9].

**Treatment**

Treatment of pSS-related neuropathies are actually non-codified. Treatment of mild forms of sensory neuropathies is usually limited to antalgics. Severe forms of sensory-motor neuropathies and neuronopathies could respond to prednisone, azathioprine, cyclophosphamide and intravenous immunoglobulins [11,20,36,37]. Rituximab seems to be effective in severe pSS neuropathies related to cryoglobulinemia [38,39].

**Small fiber neuropathy and primary Sjögren’s syndrome**

The prevalence of small fiber neuropathy in pSS is actually unknown; however, the systematic DN4 screening of neuropathic pain in pSS is positive at least in 10 to 15% of the cases [8,40], with abnormal electromyographic studies in 45% of the cases only. Hence, a small fiber involvement could be suspected in 5 to 8% of pSS patients [8,16,41]. pSS patients with SFN exhibited chronic neuropathic pain (i.e. burning sensation, prickling, dysesthesia, alldynia). Neuropathic pain involved mostly hands and feet, with a distal predominant distribution. Neurological examination confirmed both reflexes normality and absence of motor weakness [42]. Small fiber neuropathy may be confirmed by skin biopsy with epidermal nerve fiber density study (figure 1) [42]. Prevalence, physiopathology and neurological evolution of such small fiber neuropathy remain unknown.

**Central neurological manifestations**

**Epidemiology and subtypes**

CNS involvement in pSS was initially controversial and seems to occur in 1 to 60% of patients depending on heterogeneous inclusion criteria [1,3–6,29]. However, more recent reports emphasize the involvement of the CNS, often mimicking the clinical symptoms of primary progressive or relapsing-remitting multiple sclerosis although the association of pSS and multiple sclerosis is possible. Hence, pSS appears to be a great imitator of multiple sclerosis, involving the CNS more often than previously recognized [6]. CNS involvement is also associated with pSS-related neuropathies in 30 to 50% of the cases [10,11,29]. Clinical manifestations can be focal (acute transverse or progressive myelopathy, multiple sclerosis-like symptoms, sensory deficits, optic neuropathy) or diffuse (cognitive dysfunction, subacute aseptic meningitis, encephalopathy, psychiatric symptoms, chorea, seizures... ) (box 1). CNS involvement can be severe, with severe disability despite pSS treatment in 40% of the cases [11].

**Box 1**

**Central nervous system (CNS) manifestations in patients with primary Sjögren’s syndrome.**

- **Focal symptoms:**
  - stroke with motor or sensory deficits, associated with CNS vasculitis (cryoglobulinemia related or not) [11,45];

- **Movement disorders and cerebellar syndromes:**
  - Parkinsonism [55];
  - chorea [70];
  - central pontine myelinolysis [71];
  - cerebellar ataxia [72].

- **Diffuse non-focal symptoms:**
  - acute or subacute encephalopathy [11];
  - aseptic meningoencephalitis and recurrent Molaret meningitis [11];
  - cognitive dysfunction or dementia [11].

- **Spinal cord involvement:**
  - transverse myelitis [11];

- **Multiple sclerosis-like syndromes:**
  - optic neuropathy [11];
  - myelopathy [11];
  - neuromyelitis optica (anti-aquaporin positive) [63];

**Clinical and paraclinical presentation**

**Multiple sclerosis-like manifestations**

Alexander et al. first reported the frequent occurrence of a syndrome resembling multiple sclerosis associated with cutaneous vasculitis in pSS patients [43]. Multiple sclerosis-like manifestations involved the brain in 60% of the cases [43] whereas 40% of pSS patients presented with a spinal cord involvement [11,43]. Both could be associated and the realization of a brain RMI must be systematic in cases of pSS-related myelopathy [10,11,44]. Some cases presented a combination of optic neuropathy and chronic myelopathy that could be confused with Devic disease or spinal forms of multiple sclerosis [29]. Magnetic resonance imaging (MRI) showed usually multiple sclerosis-like white matter lesions and CSF analysis revealed oligoclonal bands synthesis [11,29,45–47].

The occurrence of pSS in patients with confirmed multiple sclerosis ranges from no case [48] to about 5% [49,50]. Hence, systematic research of anti-SSA and SSb antibodies must be performed in multiple sclerosis patients complaining with sicca
syndrome; however, these multiple sclerosis-like manifestations are often seronegative and the sicca syndrome very mild [49,51]. Anti-alpha fodrin antibodies could be associated with pSS neurologic manifestations but they definitively lack of specificity [52]. The realization of flow cytometry in order to detect B-cell subpopulations characteristic to pSS may help the clinician to make early diagnosis of seronegative pSS neurologic presenting forms [53].

**Focal encephalitic manifestations**

Focal manifestations mostly presented with stroke-like features such as aphasia, hemiplegia, hypoesthesia, cerebellar ataxia consistent with a focal vasculitis [11,29,54]. Intracerebral or subarachnoid hemorrhage may signal the presence of vasculitis. Several other focal neurologic manifestations have been described in pSS including internuclear ophthalmoplegia [29], nystagmus, dystonia, athetosis, intention tremor, chorea, L-dopa resistant Parkinsonism, focal and generalized seizures [28,29], cerebellar involvement [5,11], and spastic tetraparesis [11,44,55].

**Meningoencephalitis**

Meningoencephalitis is a relatively common neurologic complication of pSS [11,28]. It begins with headache, flu-like arthromyalgias, confusion, and meningeal signs with or without fever [11]. Focal neurologic signs may be present as cranial nerve palsy, cerebellar involvement or seizures [11]. Brain MRI can be normal or shows hyperintense inflammatory changes in the cerebral white mater and cortex or cerebral vasculitis [5,11,45]. The CSF profile is consistent with an aseptic lymphocytic meningitis, with up to 900 cells/mm³ [5,11,29].

**Optic neuropathy**

Bilateral visual loss secondary to retrobulbar optic neuropathy has been largely described in pSS [11,43]. In some cases, blindness secondary to bilateral optic neuropathy is the first manifestation of Sjögren’s syndrome. In about 12% to 15% of patients, the diagnosis was revealed by abnormal visual evoked potentials [11]. The pathogenesis of optic nerve involvement in Sjögren’s syndrome is postulated to result from a combination of ischemic vasculitis and demyelination [11].

**Spinal cord involvement**

At least 60 cases of spinal cord involvements in pSS have been reported, indicating that this neurologic complication is not uncommon [47,51,56–62]. Acute myelitis is the most frequent form of spinal cord involvement in pSS [51,56]. The spectrum of acute myelitis is wide in pSS including severe transverse myelitis resulting in tetraparesis or paraparesis and sphincter dysfunction, moderate subacute transverse myelitis, lateral cervical myelitis resulting in hemiplegia, posterior myelopathy with a predominance of sensory symptoms and a recurrent course and Brown-Sequard syndrome [47,51,56–62]. Spinal cord MRI revealed extended T2- weighted hyperintensities with a predominant cervical involvement [11]. Spinal cord involvement may present also as a subacute progressive myelitis, with sensory symptoms, sphincter incontinence, and difficulty walking progressing to spastic paraplegia. Lower motor neuron disease forms are also described [51]. Acute myelitis could be associated with optic neuritis in pSS resulting as a Devic disease presentation, with positive aquaporin autoantibodies in 80% of the cases [63].

**Cognitive disorders**

Also common in pSS, and independently of depressive disorders, are cognitive changes with poor concentration and memory and abnormalities in neuropsychometric testing, including executive dysfunction, visuospatial disorders and long- or short-term memory deficits [5,64]. Brain MRI is usually normal (80% of the cases) or can revealed white matter lesions of the fronto-parietal subcortical regions [5,64]. SPECT can show cortical hypoperfusion localized predominantly in the frontal and temporal regions [5,64].

**Figure 2**

Brain magnetic resonance imaging (MRI) of a cerebral cryoglobulinemia associated vasculitis in a 42-year-old Primary Sjögren’s syndrome patient complaining of rapid and severe memory impairment.
Association to other systemic complications and immunological profile

Only two studies have specifically focused on pSS profile associated with central neurologic manifestations [29,65]; in both, pSS patients with central neurologic manifestations tented to have anti-SSA antibodies [29,65]. However, the absence of a control group [65] or the small sample of central neurologic manifestations in the other [29] could explain the opposite results obtained in others studies in which anti-SSa and anti-SSb antibodies are found in less than 50% of patients with pSS central neurological manifestations [5,49,66]. Alexander et al. pointed out the association of CNS involvement, systemic vasculitis and presence of cryoglobulinemia [65]; this association concerned mostly stroke-like form; by contrast, systemic sclerosis-like form is not usually associated with vasculitis and cryoglobulinemia. Indeed, Anaya et al. pointed out that pSS patients with central neurological manifestations exhibit no other systemic involvement or immunological characteristics [29].

Furthermore, there is no statistical relationship between antiphospholipid antibodies and CNS involvement in pSS [29,67,68].

Treatment

Acute and chronic myelopathies are frequently severe, leading to permanent disability, and respond poorly to corticosteroids alone [10,11,43]. Cyclophosphamide infusions combined with 1 g methylprednisolone are now considered as a first-line therapy if a severe deficit is observed [51,56].

The treatment of multiple sclerosis-like forms, cerebral vasculitis and cognitive involvement is actually un-codified. Methylprednisolone infusions combined or not with cyclophosphamide are reported to be effective at least in 50% of patients [11]. Rituximab has been recently reported as ineffective in a small retrospective uncontrolled study [69].

Conclusion

Neurological complications affect 20% of pSS patients and may be inaugural. Both peripheral and central involvement could be related to a vasculitis process. Hence, systematic research of complement activation and cryoglobulinemia must be systematic in pSS patients suspect from neurologic manifestations. However, no characteristic immunological profile has been associated with pSS neurologic manifestations. The DN4 questionnaire may improve early detection of pSS-related neuropathies. Axonal neuropathies subtypes are evaluated by electrophysiological examination. Skin biopsy is helpful to diagnosed small fiber neuropathies, which are responsible of chronic neuropathic pain with normal electrophysiological analysis.

CNS involvement often mimics the clinical symptoms of multiple sclerosis with the same MRI and CF analysis abnormalities. SPECT must be performed in pSS patients with isolated cognitive impairment unrelated to depressive disorders.

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References


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