Primary Sjögren's syndrome: central and peripheral nervous system involvements

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ABSTRACT

Primary Sjögren's syndrome (pSS) is a common systemic autoimmune disease characterised by exocrinopathy resulting in dryness of the mouth and eyes, unexplained fatigue and diffuse pain. Neurological involvement is uncommon in pSS, involving the central nervous system in 2–5% of cases and more frequently the peripheral nervous system in 5–15% of cases. The diagnosis of pSS is to be considered when confronted with symptoms such as mouth and eye dryness, fatigue and pain, the most frequent of pSS symptoms. Objective measures of oral and eye dryness may help assert the diagnosis of pSS, as well as ACR/EULAR criteria. Differential diagnoses have to be excluded in patients exhibiting neurological symptoms, such as cryoglobulinaemic vasculitis or multiple sclerosis, before considering a neurological involvement specific to pSS.

The treatment of these neurological manifestations takes into account different parameters, such as the presence of cryoglobulinaemic vasculitis, the severity of the symptoms, a rapidly progressing evolution and the failure of previous symptomatic treatments.

Introduction

Primary Sjögren's syndrome (pSS) is a common systemic autoimmune disease characterised by exocrinopathy resulting in dryness of the mouth and eyes, unexplained fatigue and diffuse pain (1). Sjögren's syndrome (SS) can be associated to different organ-specific auto-immune diseases, such as thyroiditis, primary biliary cirrhosis or cholangitis. It can also be associated to other systemic diseases, such as systemic lupus erythematous, rheumatoid arthritis or systemic sclerosis (in these cases mentioned as secondary SS). Systemic extraglandular manifestations can occur in 30–40% of patients with pSS, and among these central nervous system (CNS) involvement and peripheral neuropathy. Neurological involvement is uncommon in pSS, and CNS involvement concerns 2–5% of pSS while peripheral neuropathy concerns 5–15% of pSS (2). The prevalence of neurological involvement varies in the literature between 5–20%. This is due in part to selection biases, to a recent change in the criteria defining pSS and lastly to new definitions of certain CNS diseases such as neuromyelitis optica (3). Differential diagnoses have to be excluded before considering a specific neurological involvement in patients diagnosed with pSS and manifesting neurological symptoms, such as associated autoimmune diseases (*i.e.* SLE, multiple sclerosis, etc.) and cryoglobulinaemic vasculitis. The pathogenic mechanisms of nervous system impairment have not yet been elucidated. However different hypotheses have been made, such as infiltration by inflammatory cells, vascular injury mediated by autoantibodies, and ischaemia due to small vessel vasculitis (4). In this review, we will describe the PNS and CNS involvements in pSS and discuss the possible treatment strategies.

Primary Sjögren's syndrome diagnosis

pSS diagnosis should be considered when confronted with symptoms such as mouth and eye dryness, fatigue and pain, the most frequent symptoms encountered in pSS. Objective measures of oral and eye dryness may help assert the diagnosis, as well as ACR/EULAR criteria in patients exhibiting mouth and eye dryness (Supplementary Table S1) (5). However, certain patients may exhibit various systemic features, among which neurological symptoms,

while having very few symptoms of dryness. The ACR/EULAR criteria suggest considering a pSS diagnosis when confronted with symptoms defined by the ESSDAI index (Suppl. Table S2) (6). In patients with predominant extraglandular symptoms, autoantibody screening and labial salivary gland biopsy should be done.

The EULAR SS disease activity index (ESSDAI) is a systemic disease activity index whose aim is to measure disease activity in patients with pSS (Suppl. Table S2) (6). It is an important tool to better categorise the activity of each symptom. It helps define the extent of neurological involvement and its outcome after therapy. However, it is important to consider that some CNS features, such as cognitive impairment, dementia, depression and headaches are not accounted by the ESSDAI index.

Central nervous system involvement

Demyelinating CNS involvement

Several case-series describe CNS involvement in pSS, with prevalence rates varying from 3.6 to 68%. However, the prevalence rate is most likely to be around 5% (7-11) (Table I). Various types of CNS manifestations have been described (12). In the French ASSESS cohort, the prevalence of CNS involvement was 3.6%, mainly including MS-like disorders, transverse myelitis, lymphocytic meningitis and possible cerebral vasculitis. Moreira *et al*. described 14 cases of CNS involvement in pSS (representing a prevalence of 28% in their cohort), including MS-like disorders, transverse myelitis, unusual Parkinson's syndrome, headaches and migraines with abnormal MR brain imaging and neuromyelitica optica. Delalande *et al*. described a case-series of CNS involvement encountering frequent CNS demyelinating diseases, such as neuromyelitica optica, optica neuritis, MS-like disorders and transverse myelitis (7). Demyelinating CNS diseases, such as neuromyelitica optica and disorders of the same spectrum, and pSS are frequently associated. The CNS involvement in pSS has often been found to mimic MS, with findings such as increased oligoclonal bands in CSF and non-specific T2 weighted hyperintensities on MR brain imaging (3). Early studies already raised the possibility that a subset of demyelinating CNS disorders may be specifically associated to pSS. The recent understanding of disorders of the neuromyelitica optica spectrum and MS has led to a reclassification of most of these disorders as being not specific to pSS, and rather associated diseases. Therefore, CNS demyelinating disorders fulfilling the criteria of MS or neuromyelitica optica are not to be considered specific CNS manifestations of pSS, if diagnosed concomitant to pSS, but two associated autoimmune diseases. In a series of 60 patients diagnosed with MS and routinely screened for SS, 10 (16.7%) had a confirmed SS without there being any relevant difference in the neurological features of both diseases (13).

Cerebral vasculitis

The possible cerebral vasculitis described in few cases of patients with unexplained arterial stroke, with recurrent outcome and without embolic disease or cardiovascular risk factors, need to be correlated with MR brain imaging abnormalities (14). Cerebrovascular events or white matter lesions that are likely due to atherosclerosis or cardiac embolism, arteriolosclerosis, or other autoimmune disease, which can be associated in some aged patients are not considered as specific Sjögren's CNS disease. The cerebral vasculitis associated with Sjögren's disease affects more frequently small arteries than medium or large arteries. Most of strokes reported were ischaemic, but some subarachnoid haemorrhage have been described (15, 16).

Cognitive impairment

Another diagnostic challenge is cognitive impairment, frequently encountered in patients with pSS, although usually mild. However, some cases of severe dementia have been described. A mild cognitive impairment is quite frequent and could be the most frequent neurological involvement in pSS patients. Various mechanisms have been proposed, among which depression, chronic pain and possible autoimmune encephalitis. Neuropsychological assessments of pSS patients found frequent cognitive impairment, namely a particular type described as "brain fog" (17). This feature is not considered alone in the ESSDAI index, in the absence of other defining features of CNS involvement such as a demyelinating disease or lymphocytic meningitis. No correlation with autoantibodies type, brain MRI characteristics or extra-glandular features has been shown in the majority of studies. Impaired memory and reduced verbal, attention and concentration abilities have been noted in several studies, even in patients without MRI abnormalities and normal CSF analysis (18) (19). 60% of pSS patients present cognitive impairment, including dementia, with frequencies similar to those of MS, without any correlation to age, duration of cognitive complaints or duration of pSS disease (20). However, the burden of white matter lesions seems to correlate to the severity of cognitive impairment. Among 34,660 middle-aged patients with autoimmune diseases, the prevalence of dementia was highest among SS (hazard ratio at 1.57 [1.24–1.98] for pSS and 1.64 [1.20–2.25] for secondary SS) (21). When comparing 10 pSS patients and 10 healthy controls matched on age and sex, ^{99m}Tc-ECD brain SPECT showed abnormal hypoperfusion in specific brain areas in all pSS patients, while in only 2 healthy controls. The abnormal hypoperfusion was found in the frontal, parietal and temporal cortices, suggesting an organic substratum to neurocognitive impairment in pSS (22). Data concerning the outcome of cognitive impairment is scarce, but the evolution seems stable over time (23).

Headaches and migraine

pSS patients frequently report headaches, mainly migraines. One case series found the prevalence of headaches to be around 47% in pSS patients (24). Migraines seem to be more prevalent in pSS when associated to anti-SSA antibodies, MR brain abnormalities and Raynaud's phenomenon (24).

MR brain imaging

MR brain imaging showed a signifi-

Table I. Prevalence and types of CNS and PNS involvements in Sjögren's syndrome from the case-series of the literature (selection criteria included studies with pSS, with sufficient data describing PNS and/or CNS Sjögren-associated involvements).

	Delalande 2004 (7) n=82	Massara 2010 (36) n=424	Jamilloux 2014 (11) n=420	Moreira 2015 (8) n=93	Carvajal Alegria 2016 (9) n=359	Ye 2018 (10) n=566
pSS	100%	100%	100%	100%	100%	73%
CNS involvement	56 (68)	25 (5.8)	38 (9)	14 (15)	14 (3.6)	63 (11)
Headaches/migraines	-	1 (0.2)	-	2 (2)	-	15 (2.6)
MS-like	33 (40)	5 (1.1)	5 (1.1)	2 (2)	2 (0.6)	5 (0.8)
Neuromyelitis optica	2 (2.4)	-	-	2 (2)	-	-
Optic neuritis	13 (16)	1 (0.2)	5 (1.1)	-	-	-
Cerebral vasculitis	- 6 (1.4)	9 (2)	-	5 (1.3)	35 (6.1)	
Encephalitis	2 (2.4)	6 (1.4)	9 (2)			
Seizures	7 (9)	1 (0.2)	1 (0.2)	2 (2)	5 (1.3)	3 (0.5)
Transverse myelitis	28 (34)	-	12 (2.8)	2 (2)	3 (0.8)	-
Lymphocytic or aseptic meningitidis	1 (1.2)	-	1 (0.2)	1 (1)	1 (0.3)	-
Movement disorders (Parkinsonian syndrome)	-	1 (0.2)	-	3 (3)	-	-
Cognitive dysfunction	9 (11)	2 (0.5)	2 (0.4)	-	-	4 (0.7)
Peripheral nervous system involvement	51 (62)	-	62 (15)	26 (28)	63 (16)	79 (14)
Pure sensory neuropathy	5 (6)	-	19 (4.5)	-	36 (9.2)	-
Sensorimotor neuropathy	19 (23)	-	25 (5.9)	-	21 (5.3)	-
Ganglionopathy	4 (4.8)	-	9 (2)	-	2 (0.6)	-
Polyneuropathy	-	-		-	5 (1.3)	-
Motoneuritis multiplex	7 (8.5)	-	3 (0.7)	-	5 (1.3)	-
Polyradiculoneuropathy	1 (1.2)	-	1 (0.2)	-	1 (0.3)	-
Cranial nerve	16 (20)	-	8 (1.9)	-	4 (1.3)	1 (0.1)
Small fibre neuropathy	-	-	-	-	-	-

cantly higher prevalence of deep white matter lesions and subcortical white matter lesions in 30 pSS patients versus 29 controls. However, after excluding patients with arterial hypertension the prevalence of these lesions was similar in both groups (25). Cranial MR examination detected small hyperintense subcortical lesions in 51.3% pSS patients *versus* 36.6% age and sex-matched controls (26). White matter lesions displayed no contrast enhancement, and were mainly multiple lesions. pSS patients with MR brain abnormalities were older than pSS patients without MR brain abnormalities. They also presented higher frequencies of diabetes and hypertension (27). Harboe *et al*. did not find any difference in total white matter abnormality scores between pSS and age and sex-matched healthy controls, however pSS patients exhibiting cognitive impairments had higher total white matter abnormality scores than those without any cognitive impairment (28). These lesions are most likely to be caused by non-specific vascular microangiopathy rather than immune-related encephalitis (3).

Because of the rarity of CNS involvement in pSS, one should first exclude other diagnoses, such as CNS demyelinating disease, CNS features of SLE, small-vessel diseases caused by arterial hypertension, diabetes, etc., before considering a specific Sjögren's CNS involvement. Features such as chorea, psychosis or acute confusion are unusual, and in the absence of CNS infection, should be considered as a neuropsychiatric form of SLE (12). Few cases of aseptic lymphocytic meningitis have been reported, and in some cases they were associated with normal MR brain imaging (8). Lastly, other symptoms seem to be very rare, such as unusual Parkinson's syndrome.

Peripheral nervous system involvement

Peripheral neuropathies in pSS are more frequent, with a 14 to 28% prevalence (2). Symptoms can be extremely varied and comprise sensori-motor axonal polyneuropathy, sensory ataxic neuropathy (ganglionopathy), mononeuritis multiplex, trigeminal (V) neuralgia and other cranial neuropathies, radiculopathy, small-fibre neuropathy, autonomic neuropathy and inflammatory demyelinating polyneuropathy (Table I) (3). The exact prevalence of peripheral neuropathy is difficult to appreciate, due to recent changes in classification criteria with the recent individualisation of small-fibre neuropathy. In addition, peripheral neuropathies in pSS have only been evaluated in small retrospective studies that included different definitions. Different types of peripheral neuropathies can coexist in the same patient, and axonal sensory, sensorimotor and small-fibre neuropathies are the most frequent findings. When confronted with PNS symptoms it is important to first eliminate cryoglobulinemic vasculitis, as the treatment and outcome are different. Pure sensitive neuropathy is present in 4.5–9% of pSS and ganglionopathy in 0.6–4.8% of pSS. For all peripheral neuropathies (except cranial nerve neuropathy and small-fibre neuropathy), PNS involvement should be confirmed by nerve conduction studies (NCS). Other causes of peripheral neuropathy, such as diabetes, metabolic, toxic, and hereditary causes are not considered associated to pSS. The ESSDAI index allows for homogenisation of PNS activity and is a useful tool to assess PNS response (Suppl. Table S2). Sensory ataxic neuropathies charac-

terised by sensory ataxia without motor impairment can be associated with autonomic symptoms. In one study, 21 among 30 cases had abnormal pupil size, orthostatic hypotension or hypohidrosis (29). Ganglionopathies are sensory neuropathies related to dorsal root ganglia neuronal infiltration, characterised by a symmetrical pattern of paresthesia and ataxia without motor deficiency non-length dependent pattern (30). MRI findings showed hyperintensities of the spinal cord in T2 weighted images of the cervical dorsal columns (in the fasciculus cuneatus and graciis areas) (31).

Small-fibre neuropathy may be concomitant to large-fibre neuropathy, but it may also occur as an isolated event, and thus be associated with normal NCS. Patients with pure small-fibre neuropathies could be younger at the age of onset of pSS and had less frequent anti-Ro60 antibodies (32). This type of neuropathy was more frequent in males and less frequently associated to hypergammaglobulinaemia and autoantibodies (32). The diagnosis can be comforted by punch skin biopsy, showing decreased intra-epidermal nerve-fibre density (IENFD) of unmyelinated nerves (less than the fifth percentile of normal controls). Skin biopsy can also help distinguish patterns of dorsal root ganglia (DRG) and axonal degeneration. MR imaging of the lumbosacral plexus can show atrophy of dorsal root ganglia (33). In a small case-series none of the small-fibre neuropathies had evolved to axonal large fibre neuropathies (33).

Mononeuritis multiplex is usually associated to pSS cryoglobulinaemic vasculitis and to a more active systemic disease. Among pSS patients with PNS involvement, vasculitis lesions were present in 19% of those with sensory neuropathy, 63% of patients with mononeuritis multiplex and in none of those exhibiting other types of PNS involvements (29). Cryoglobulinaemia was detected in 61% of pSS patients with PNS involvement, and in 70% (14 patients) of those with sensori-motor neuropathy and multineuritis (7).

Cranial nerve involvement usually presents itself as a sensory trigeminal neuralgia, but cochlear nerve and facial nerve involvements are also possible. Radiculopathy is extremely rare, accounting for less than 3% of neurological disorders. Among pSS patients with a severe systemic phenotype, peripheral nervous system involvement was present in 12% of cases, including ganglionopathy and peripheral neuropathy in 18 of 25 cases (34).

Patients with a proven vasculitis on a neuromuscular biopsy had a more acute onset of disease, and more frequent mononeuritis multiplex and sensorimotor neuropathies than those without histologically proven vasculitis (35). Ganglionopathies were never associated with histological lesions of vasculitis. The vasculitis type (lymphocytic or necrotising vasculitis) was not associated with a particular type of pSS-associated peripheral neuropathy (35).

Table II. Therapies and their indication in Sjögren's-associated CNS involvement.

CNS active disease	
Acute or rapidly progressive CNS manifestations; multiple sclerosis-like manifestations;	Steroids (pulse methylprednisolone for 5 days and relayed by oral prednisone) combined to monthly cyclophosphamide (0.7 g/m^2) for 6 to 12 months; azathioprine and mycophenolate mofetil could also be considered; rituximab seem to be ineffective
Pure psychiatric or cognitive impairment; brain fog	Supportive care; in severe cases, after the exclusion of other potential causes, steroids and/or other immunosuppressive pies therapies could be tested

Management of pSS-associated nervous involvement

CNS involvement

It is difficult to recommend a standardised treatment for CNS involvement in the absence of any clinical trial, due to the rarity of these manifestations (Ta-

Table III. Therapies and their indication in Sjögren's-associated PNS involvement.

PNS active disease	Symptomatic therapies	Immunosuppressive or immunomodulation drugs
Pure sensory axonal neuropathy without severe ataxia, cranial V neuralgia; not severe small fibre neuropathy	Symptomatic therapies (physiotherapy, analgesic drugs)	No immunosuppressive or immunomodulation drugs for PNS involvement
Pure sensory axonal neuropathy with severe ataxia, small fibre disabling severe neuropathy	Symptomatic therapies (physiotherapy, analgesic drugs)	Intravenous immunoglobulins; rituximab or steroids seem disappointing
Cryoglobulinaemic vasculitis with neurological involvement	Symptomatic therapies (physiotherapy, analgesic drugs)	Rituximab ± steroids; rituximab and belimumab if refractory?
Axonal sensory–motor neuropathy with motor deficit ≤3/5; peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc); CIDP; severe ataxia due to ganglionopathy	Symptomatic therapies (physiotherapy, analgesic drugs)	Steroids combined to immunosuppressive therapies among rituximab, intravenous immunoglobulins, cyclophosphamide or mycophenolate mofetil; no data or not effective for other than rituximab biologics; or consider trial inclusion For CIDP consider IVIG, steroids and plasmapheresis in severe or refractory cases

ble II). We propose a treatment based on the type of CNS involvement, the presence or absence of active lesions and their severity as resumed in the Table II, even the absence of well-designed trials is lacking to give a well-defined recommendation. As of today, the treatment consists of high-dose steroids and cyclophosphamide (7-9, 11, 36). The outcome is usually poor, with a stable disease and persistent neurological sequelae, with as few as 20-30% response in patients with highly active diseases (34).

Patients with demyelinating CNS features, such as MS-like disorders, neuromyelitica optica spectrum diseases, optic neuritis and transverse myelitis, are more likely to present MS or NMO diseases than a pSS-associated CNS disease. Hence a treatment based on existing recommendations for these disorders, such as high-dose glucocorticoids, cyclophosphamide and rituximab is recommended for patients with an active inflammatory disease. A small case-series reported the benefit of monthly intravenous cyclophosphamide for 12 months in pSS-associated myelopathy with a significant neurological improvement (37). Another case series did not show significant improvement with rituximab in the treatment of pSS-associated CNS involvement (38). Some anecdotal cases reported the use of tocilizumab and plasmapheresis on myelitis and NMO spectrum disorders in pSS (39) (40) (41). Immunosuppressive therapies are an alternative in patients with severe and relapsing neurological involvements, such as acute encephalitis, cerebral vasculitis and lymphocytic meningitis. In the absence of available data, high-dose steroids and cyclophosphamide, eventually relayed by azathioprine and mycophenolate mofetil can be proposed. Neuropsychiatric features like cognitive impairment and dementia are usually managed with supportive therapies, although some cases reported a significant improvement in patients treated with steroids.

PNS involvement

The first-line treatment of sensory and ataxic neuropathies is symptomatic with the use of tricyclic antidepressants, gabapentin, pregabalin, opioids and topical anaesthetics (Table III) (42). Just as with CNS involvement in pSS, evidence on the use of immunosuppressive and immunomodulatory therapies in PNS involvement is scarce and there are no randomised studies available. The management of these manifestations depends on the presence of a cryoglobulinaemic vasculitis, the severity of the disease, a rapidly progressing course (particularly regarding motor deficiency) and the failure of symptomatic treatments. Possible therapy strategies based on the type of PNS involvement and its severity is represented in Table III, but data are not sufficient to product strong therapeutic recommendations. Immunosuppressive therapies have been used less often in peripheral neuropathies because severe injuries are less frequent (26%) than those seen with CNS involvement (78%) (7, 11). Patients diagnosed with vasculitis in muscular biopsy presented a better neurological outcome than those without vasculitis (34). The presence of a necrotising vasculitis was the only predictive factor of a better neurological outcome (35). Vasculitis, and in particular cryoglobulinaemic vasculitis, requires a prompt immunosuppressive therapy, usually rituximab.

For sensori-motor neuropathies, immunosuppressive therapies are warranted if faced with a progressive or severe form, and in the presence of a motor deficiency. Nevertheless, data about the benefit of steroids and immunosuppressive drugs is limited, and rituximab seems to be less effective in the absence of cryoglobulinaemia (38). Intravenous immunoglobulins (IVIg) seem to be effective in a small number of steroid refractory patients (43).

In the case of failure of symptomatic treatments in small-fibre neuropathy, small case-series showed no benefit of steroids or rituximab (32). After 6 months treatment by intravenous immunoglobulins a significant improvement was noted in a case series of 11 pSS patients displaying persistent pain despite previous therapies, with similar results in a few other cases (29, 44, 45). 22 patients with sensory ataxic neuropathy presented a poor response to steroids and intravenous immunoglobulins (29).

For sensory ataxic ganglionopathy various therapies have been tested such as steroids, mycophenolate mofetil, cyclophosphamide and intravenous immunoglobulins. One small case series found a better outcome with the use of steroids and immunosuppressive drugs than intravenous immunoglobulins (30). A case series found sensory ataxic neuropathy to be the peripheral neuropathy less responsive to IVIg (43), while another case series showed a good neurological outcome in 4 cases out of 5 in patients treated with intravenous immunoglobulins. The association of intravenous immunoglobulins to mycophenolate mofetil may be useful in refractory sensory ataxic neuropathies (46, 47). Some cases presented controversial data about rituximab (38, 48). Intravenous immunoglobulins could be effective in radiculoneuropathies associated to pSS (29).

Conclusion

Central and peripheral nervous system involvements are challenging symptoms of SS. Their management is not well established and is based on immunosuppressive and immunomodulatory therapies in patients, mainly those presenting a cryoglobulinaemia or a severe and progressing course.

Take home messages

- Neurological involvement is uncommon in pSS, involving the central nervous system in 2–5% of cases and more frequently the peripheral nervous system in 5–15% of cases.
- Differential diagnoses have to be excluded in patients exhibiting neurological symptoms, such as cryoglobulinaemic vasculitis or multiple sclerosis, before considering a neurological involvement specific to pSS.
- The treatment of these neurological manifestations takes into account different parameters, such as the presence of cryoglobulinaemic vasculitis, the severity of the symptoms, a rapidly progressing evolution and the failure of previous symptomatic treatments.

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