RHEUMATOLOGY

Rheumatology 2010;49:1540–1549
doi:10.1093/rheumatology/keq111
Advance Access publication 5 May 2010

Original article

Central nervous system involvement in Sjögren's syndrome: unusual, but not unremarkable—clinical, serological characteristics and outcomes in a large cohort of Italian patients

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Abstract

Objectives. To perform an observational retrospective cross-sectional case–control study to evaluate prevalence, clinical patterns and outcomes of CNS involvement in a large cohort of primary SS (pSS) patients.

Methods. A total of 424 pSS patients, diagnosed according to the 2002 criteria proposed by the American–European Consensus Group, were checked for CNS involvement after exclusion of secondary causes. Demographic, clinical, seroimmunological data were compared between patients with and without CNS involvement. Neuroimaging data were also analysed.

Results. CNS involvement was detected in 25 (5.8%) patients (24 females and 1 male) both at disease onset (52%) and later (48%) with a mean latency after diagnosis of 7 years. Diffuse (40%), focal/multifocal (36%), multiple sclerosis (MS)-like disease (20%) and isolated optic neuritis (4%) were the most common CNS clinical pictures. Disease duration, lung involvement and decreased C_4 were associated with CNS involvement, while articular manifestations were more frequently observed in patients without neurological complications. Most cases had an acute, often recurrent course with spontaneous remission or only mild neurological impairment.

Conclusions. CNS involvement represents a rare but not negligible complication of pSS, which may occur with a bimodal temporal pattern, both at onset and later, prompting attention in the differential diagnosis of apparently isolated neurological syndromes. Lung involvement emerged as the strongest risk factor for CNS involvement with a relative risk of 7.9, along with disease duration and decreased C_4.

Key words: Primary Sjögren's syndrome, Neurological involvement, Central nervous system, Instrumental evaluation, Clinical findings, Extraglandular manifestations.

CLINICAL SCIENCE

Introduction

Primary SS(pSS) is a chronic autoimmune disorder, with a prevalence ranging from 0.09 to 3.5% and a reported incidence of 3.9–5.3/100 000 inhabitants [1]. The disease is characterized by a chronic lymphocytic and plasmacellular infiltration of exocrine glands (autoimmune exocrinopathy) and extraglandular features including both peripheral nervous system and CNS involvement [2]. Among neurological manifestations, peripheral nervous system involvement is well-recognized with an estimated prevalence of up to 20%. Conversely, the burden of CNS involvement still remains a debated issue with a reported frequency ranging from 0.3 to 48% [3, 4]. Previously, we have reported a frequency of CNS disease in ~8% of a small series of pSS patients, with a predominance of diffuse manifestations (Table 1) [5].

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Submitted 18 January 2010; revised version accepted 10 March 2010.

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Table 1 Spectrum of CNS involvement in pSS

Focal
Motor and/or sensory deficit
Aphasia/dysarthria
Seizure disorders
Brainstem syndrome
Cerebellar syndrome
Diffuse
Acute or subacute encephalopathy
Aseptic meningitis
Cognitive dysfunction/dementia
Psychiatric abnormalities
Spinal cord
Transverse myelitis
Chronic progressive myelitis
Neurogenic bladder
Lower motor neuron disease
Brown–Sequard syndrome
Other
Optic neuropathy
Multiple sclerosis-like disease

The aims of the present study were to assess the prevalence, seroimmunological correlations, clinical patterns and outcomes of CNS involvement in a larger cohort of Italian patients with pSS followed up in a single centre.

Patients and methods

All patients fulfilling the criteria for pSS proposed by the American–European Consensus Group [6], who consecutively attended our Rheumatology Unit in the last 10 years, were retrospectively evaluated to check the occurrence of CNS involvement. None of the patients fulfilled SLE criteria. Demographic, clinical, seroimmunological and instrumental data were retrieved from patient's clinical charts and a dedicated database. Data of patients with (CNS-pSS) and without (non-CNS-pSS) CNS involvement were compared. The subject's written consent to use clinical data in an anonymous format was obtained in accordance with the Declaration of Helsinki and ethical approval was obtained from the institutional review boards of the University Hospitals of Ferrara.

Neuropsychiatric ascertainment

All neuropsychiatric (NP) events affecting the CNS, emerging from patients' history, were recorded and confirmed by neurological (L.C.) and, if needed, psychiatric consultation. CNS involvement was deemed to be related to pSS after exclusion of secondary causes known to induce neurological manifestations. Mild and aspecific symptoms, i.e. isolated tension-type headache or minor vague complaints (anxiety, mild depression and mild cognitive dysfunction) were not taken into account. Moderate or severe cognitive dysfunctions were assessed by means of a standardized neuropsychological test battery according to 1999 ACR criteria for NP lupus [7].

NP manifestations were categorized as reported in Table 1. Patients with CNS involvement were periodically re-evaluated and the outcome was assessed on the basis of clinical judgement performed by the same team (A.M., M.G., G.C., F.T. and S.B.) and graded as follows: improved, stable and worsened.

Clinical findings

In each patient, the mean age (at the time of the last observation) and mean disease duration (calculated from disease onset to the time of the last available clinical evaluation), the mean age at the time of disease onset, mean age at the time of the occurrence of NP manifestation, and the elapsing time from pSS onset and the appearance of the first NP event, were registered. Disease onset was considered as the time of the appearance of the first symptom or sign attributable to pSS, usually sicca syndrome, RP, peripheral non-erosive arthritis, cutaneous vasculitis or parotid gland enlargement. Extraglandular features of pSS were also recorded. Organ involvement was defined according to the previously proposed criteria [8]. Smoking habits were registered, and hypertension, diabetes and dyslipidaemia were checked according to formal reported definitions [9–11].

Laboratory data

In all patients, routine laboratory tests and the following seroimmunological parameters were recorded: total serum gammaglobulins; immunoglobulin classes C_3 and C_4 (g/l) detected by nephelometry (hypocomplementaemia was defined as $C_3 < 0.8$ and $C_4 < 0.11$ g/l); monoclonal gammopathy detected by immunofixation test; serum cryoglobulins, measured after centrifugation and storage at 4°C for at least 72 h; RF (IU/ml) measured by particle-enhanced nephelometry (positivity was defined as a titre >50 IU/ml); ANA tested by IIF using Hep2 cell substrate (positivity was defined as a titre $\geqslant$1/160); antibodies to ENA assayed by ELISA method; antibodies to dsDNA assayed by the *Crithidia luciliae* IIF test with cut-off titre 1:40; aPLs; and LAC detected by standardized ELISA method according to the recommendations of the 2006 revised Sydney workshop [12] and the Scientific and Standardization Committee of the International Society of Thrombosis and Hemostasis [13]. Cerebrospinal fluid (CSF) analysis was carried out in selected cases.

Instrumental evaluation

Information coming from electroencephalograms (EEG), multimodality evoked response tests, brain and spinal cord MRI and brain SPECT were retrieved. MRI and SPECT have been performed according to a local standardized previously described protocol, where criteria for definition of abnormal results were also defined [14].

Statistical analysis

The statistical analysis was performed using the software MedCalc. Student's *t*-test was applied for unpaired continuous variables, and chi-square test with Fisher's correction was applied for comparison of percentages. A multiple stepwise regression analysis, to verify correlation

between variables and CNS involvement, was performed and relative risk (RR) was calculated. Statistical significance was assumed for a $P < 0.05$, within a 95% CI.

Results

In the last 10 years, 431 consecutive pSS patients have visited our department. Seven of them, all females, were excluded from analysis because of incomplete seroimmunological data or lacking follow-up. Thus, 424 patients (390 females and 34 males) were judged eligible for the study. CNS involvement was detected in 25 (5.8%; 24 females and 1 male) of them. NP symptoms affecting the CNS represented the heralding symptom of pSS in 13 (52%) out of 25 patients; the remaining 12 patients developed neurological manifestations after a mean elapsing time of 7 years (range 1–16 years) after pSS diagnosis (Table 2).

The patient's mean age did not differ statistically between CNS-pSS and (non-CNS-pSS) [55.8 *vs* 56.9 years; P = not significant (NS)]; the mean age at disease onset was significantly lower in CNS-pSS than in (non-CNS-pSS) (42.1 *vs* 48.4 years; $P = 0.029$) accounting for a higher mean disease duration in the former (13.7 *vs* 8.4 years; $P = 0.0006$). Overall, follow-up information was available for 22 out of 25 patients. The mean elapsing time from disease onset and the occurrence of the NP picture was shorter (although not significantly) in patients with chronic/progressive or relapsing course compared with those who had an acute course [2.75 (4.19) *vs* 6.17 (6.01) years; $P = 0.145$]. Among 11 patients who presented with the NP picture earlier in their disease course, 4 deteriorated, 1 improved and 6 remained stable, whereas among those 11 patients who developed their neurological picture after the disease onset, 7 improved, 6 remained stable and none deteriorated (Table 3). Diffuse manifestations were the most frequent neurological findings [10 (40%) patients], followed by focal or multifocal pictures [9 (36%) patients] multiple sclerosis (MS)-like disorders [5 (20%) patients] and isolated optic neuritis [1 (4%) patients] (Table 3).

Diffuse manifestations

Ten patients developed diffuse CNS involvement. The most frequent picture [6 (60%) patients] was characterized by a recurrent, 'subacute encephalopathy' characterized by memory loss, cognitive dysfunction, visual disturbances, dizziness and reduced performance in concentration and attention. These symptoms took a mild, recurrent course, poorly affected by treatment, mainly represented by low-dose aspirin. A careful neurological examination performed at baseline and during follow-up (usually every 6–12 months) never identified neurological signs suggestive of toxic/infective/metabolic aetiology, particularly recurrent fever, ataxia, spasticity, prominent myoclonus, epilepsy, progressive dementia, etc. None of the patients had a history of chronic alcohol abuse or exposure to toxic agents. No patients presented a family history of degenerative neurological disease. Kidney and liver function were persistently normal in all cases. All patients underwent an EEG at baseline that showed mild slow-wave discharges with rare paroxysms in three cases, without abnormalities suggestive of metabolic or neurodegenerative disease. All the patients presented brain MRI abnormalities, mainly small punctate white matter hyperintensities (WMHs) in subcortical and periventricular areas; brain SPECT detected hypoperfused areas in three out of these four patients. Based on the clinical picture, a complete neuropsychological assessment was performed only in selected cases. Three patients, with diffuse pattern, underwent formal cognitive evaluation. In two patients, the cognitive dysfunction was classified as mild, with particular deficit in the areas of attention and concentration. Only one patient presented a severe cognitive impairment (Patient 7; Table 3), indicative of a subcortical type of cognitive dysfunction. In this case, the neurological examination did not reveal focal neurological deficits or signs of cortical dysfunction. Follow-up information was available for seven patients. Five out of six patients with 'subacute or acute encephalopathy' were followed for a mean 7.6 years; one patient was lost at follow-up. In four of these patients, the clinical picture took a mild, recurrent course, without significant clinical improvement; thus their course was judged stable. All patients presented small, diffuse hyperintense lesions on brain MRI that remained unchanged over time. Only one patient, with an acute onset of the encephalopathy, experienced an evident clinical improvement after 1 year of treatment with low-dose steroids, HCQ and ASA.

Table 2 Demographic data

	CNS-pSS	%	(non-CNS-pSS)	%	*P*
Number	25		399		
Female : male, *n*	24 : 1	96	366 : 33	91.7	0.698
Age, mean (S.D.), years[a]	55.8 (13.9)		56.9 (13.5)	–	0.693
Age at disease onset, mean (S.D.), years[b]	42.1 (13.5)	–	48.4 (14.0)	–	0.029
Disease duration, mean (S.D.), years[c]	13.7 (9.4)	–	8.4 (7.2)	–	0.0006
Age at first CNS-NP event, mean (S.D.), years	46.7 (13.6)	–	–	–	
Disease duration at first CNS-NP event, mean (S.D.), years[d]	3.4 (4.6)	–	–	–	

[a]At the time of the last available observation; [b]at the time of diagnosis; [c]from diagnosis to last available observation; [d]from diagnosis to the occurrence of the NP picture. CNS-pSS: patients with neurological involvement; non-CNS-pSS: patients without neurological involvement.

Table 3 Pattern of neurological involvement

Patient	Sex/age[a]	Neurological picture	Brain MRI	Brain SPECT	CSF analysis	Clinical course	Elapsed time between disease onset and NP picture, years	Follow-up after NP picture onset, years	Outcome	Therapy
Diffuse							Mean = 4.3	Mean = 8.2		
1	F/46	Subacute encephalopathy	+	–	ND	NA	4	NA	NA	NA
2	F/42	Psychosis	+	+	ND	NA	0	NA	NA	NA
3	F/53	Subacute encephalopathy	+	+	ND	Recurrent	13	10	S	ASA, LDGC
4	F/32	Narcolepsy	–	ND	ND	Chronic	3	7	I	Modafinil
5	F/54	Atypical, refractory headache[b]	+	+	ND	Recurrent	4	13	I—resolution	ASA, flunarizine
6	F/51	Subacute encephalopathy	+	+	ND	Recurrent	8	9	S	ASA, LDGC
7	F/60	Severe cognitive impairment	+	+	ND	NA	0	NA	NA	NA
8	F/24	Subacute encephalopathy	+	+	ND	Recurrent	1	6	S	ASA, LDGC, HCQ
9	F/40	Acute recurrent encephalopathy	+	ND	–	Recurrent	0	7	I	ASA, LDGC
10	F/42	Acute recurrent encephalopathy[b]	+	+	ND	Recurrent	10	6	S	OAC, LDGC
Focal/multifocal							Mean = 3.4	Mean = 8		
11	F/74	VII cranial nerve peripheral palsy hemiparesis and cerebellar ataxia	+	ND	IT IgG synthesis (4 OCBs)	Acute multifocal	16	7	I—resolution	i.v. pulse GC, ASA
12	F/50	Hemiparesis	–	+	ND	Acute	0	8	I—resolution	ASA, LDGC
13	F/54	Aphasia	+	+	ND	Acute	0	8	S—mild cognitive impairment	ASA, HCQ, LDGC
14	F/63	Seizure disorders (tonico-clonic generalized crisis)	+	–	ND	Recurrent	0	8	I—resolution	ASA, HCQ, LDGC, carbamazepine
15	F/49	Multifocal vascular encephalopathy[b]	+	+	ND	Acute	6	11	I—resolution	OAC, LDGC
16	F/19	Cerebellar ataxia and sensory–motor polyneuropathy	+	+	ND	Recurrent	0	6	W—recurrent neurological symptoms	i.v. pulse GC, PEX
17	F/62	Parkinson-like syndrome	ND	ND	ND	Chronic	0	8	I	Levodopa
18	M/64	Hemiparesis	+	ND	ND	Recurrent, multifocal	0	8	I	OAC LDGC
19	F/57	Hemiparesis	+	+	ND	Acute	9	NA	I	ASA
MS-like syndromes							Mean = 1.0	Mean = 7.8		
20	F/50	Brainstem involvement (Millard–Gubler syndrome) followed 4 years later by a self-limiting retrobulbar optic neuritis	ND	ND	IT IgG synthesis (<4 OCBs)	Relapsing–remitting	5	18	I—resolution	i.v. Pulse GC
21	F/35	Transient left hemiparesis followed by RON and subsequent episodes of vertigo with pyramidal signs, aPL positivity[b]	–	ND	IgG in both serum and liquor ('mirror pattern') (<4 OCBs)	Relapsing–remitting	0	8	W—recurrence of neurological symptoms	i.v. Pulse GC, anti-coagulant therapy
22	F/44	Sensory disturbances followed by cervical transverse myelitis	+	+	IT IgG synthesis (<4 OCBs)	Relapsing–remitting	0	3	I Both clinical and MRI picture	i.v. Pulse GC, ciclosporin, ASA
23	F/27	RON followed by transverse myelitis and diffuse brain involvement	+	Normal	IT IgG synthesis (>4 OCBs)	Relapsing–remitting	0	7	W—progressive worsening	i.v. Pulse GC, I.V. CTX, AZA, natalizumab
24	F/28	Right hemiparesis followed by progressive spastic paraparesis and cerebellar involvement	+	ND	IT IgG synthesis (>4 OCBs)	Secondary progressive	0	3	W—progressive worsening	i.v. Pulse GC, IFN-β-1a, AZA
Isolated optic neuritis										
25	F/48	Isolated optic neuritis	+	ND	ND	Acute	6	6	I—resolution	i.v. Pulse GC

[a]Age at onset of neurological symptoms; [b]aPL positivity. +: abnormal; –: normal; RON: Retrobulbar Optic Neuritis; ND: not done; NA: not available; IT: intrathecal; OAC: oral anti-coagulant; GC: glucocorticosteroids; LDGC: low-dose glucocorticosteroids; CTX: Cyclophosphamide; PEX: Plasma-exchange; I: improved; S: stable or unchanged; W: worsened.

The patient's MRI picture remained stable too as in the other patients except one. The treatment was conservative in all patients with low-dose aspirin and steroids.

Focal manifestations

Nine patients experienced focal or multifocal disease, with a wide range of clinical symptoms and a prevalence of focal motor deficit followed by cerebellar involvement, seizures, aphasia and parkinsonism. Five patients presented an acute, stroke-like course with neurological manifestations that remitted either with a conservative treatment (in the milder cases) or with a short cycle of glucocorticosteroid pulse therapy (in severe, multifocal disease). In three cases, the disease took a recurrent course, with several clinical bouts that remitted after institution of symptomatic drugs (anti-convulsants in patients with epilepsy) or oral anti-coagulation (in a patient with recurrent ischaemic episodes). Brain MRI was performed in eight patients showing abnormalities in seven (87.5%). MRI disclosed multiple, small areas of WMH on FLAIR sequences, mainly subcortical and periventricular, without gadolinium enhancement (Fig. 1) in six cases. Six patients underwent a SPECT evaluation, coupled with MRI, during the acute phase of the NP event. Areas of cortical hypoperfusion, mainly located in the frontal and parietal lobes, were detected in five of them. EEG was diagnostic in the patient with seizures, while diffuse abnormalities were registered in one out of three patients. CSF analysis was performed in one patient with severe multifocal disease disclosing mild pleocytosis with an elevated IgG index and several oligoclonal bands (OCBs) on agarose gel electrophoresis.

Multiple sclerosis-like disease

Five patients had a MS-like CNS involvement, characterized by a relapsing–remitting course with neurological episodes disseminated in space and time. In four patients, the neurological picture represented the heralding symptom of pSS. A concomitant optic neuritis was observed in three patients, and in two this represented the first symptom of pSS. Spinal cord involvement (subacute transverse myelitis) occurred in two patients. One patient experienced a severe brain involvement with marked spastic paraparesis and sphincter dysfunction that took a secondary progressive course following the first neurological episode. In four patients, brain MRI disclosed multiple diffuse subcortical and periventricular WMH lesions, also affecting corpus callosum in one of them. CSF analysis was performed in all patients during the first acute neurological episode showing a mild lymphocyte pleocytosis in three patients; OCBs suggestive of intrathecal IgG synthesis were detected in all patients (two had >4 OCBs). All patients received high-dose i.v. methylprednisolone pulses (1g/day for 3 days during the acute attacks), followed by a short course of oral prednisone (0.5–1 mg/kg). With treatment, two patients experienced a marked improvement without developing further neurological episodes. Two patients developed a severe neurological picture despite the immunosuppressive treatment (i.v. cyclophosphamide and AZA), with dissemination of lesions on MRI (Fig. 2).

One patient, a 48-year-old woman, developed an isolated retrobulbar optic neuropathy that resolved after i.v. pulse methylprednisolone therapy. Multiple lesions in subcortical and periventricular white matter were detected by MRI scans, but no further neurological episodes were registered over the following 6 years of follow-up. Neuromyelitis optica (NMO)-IgG autoantibodies were not determined, this test being unavailable, at the time of the observation. However, due to the lack of spinal cord involvement and the presence of brain MRI abnormalities, Devic's syndrome was ruled out.

In four out of five patients with MS-like disease, the neurological picture started before the recognition of pSS. Two of them (Patients 23 and 24; Table 3) satisfied the revised diagnostic criteria for MS [15], the dissemination in space and time of both clinical events and/or MRI lesions being the more striking items to be satisfied for reaching a formal diagnosis of MS.

Fig. 1 Multifocal picture. The MRI scan shows multiple hyperintense lesions in the periventricular and sub-cortical white matter in both coronal FLAIR sequence (**A**) and axial T_2-weighted views (**B**) from the same patient.

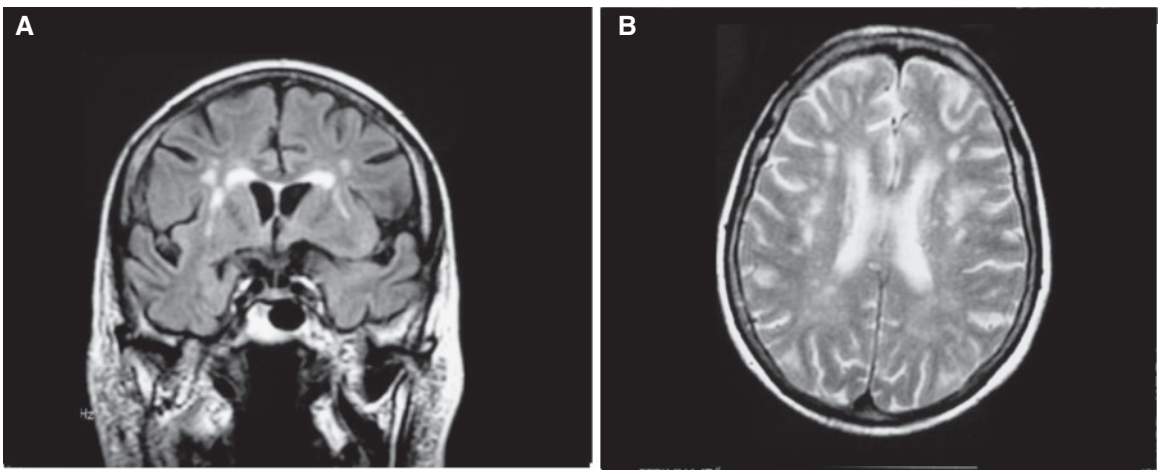

FIG. 2 Multiple sclerosis-like disease. Axial T_2-weighted image of the brain of a patient with several WMHs at disease onset (**A**), with subsequent medullary involvement 2 years later (**B**) and cerebral dissemination clearly visible in the axial FLAIR sequence (**C**) despite intensive immunosuppressive treatment.

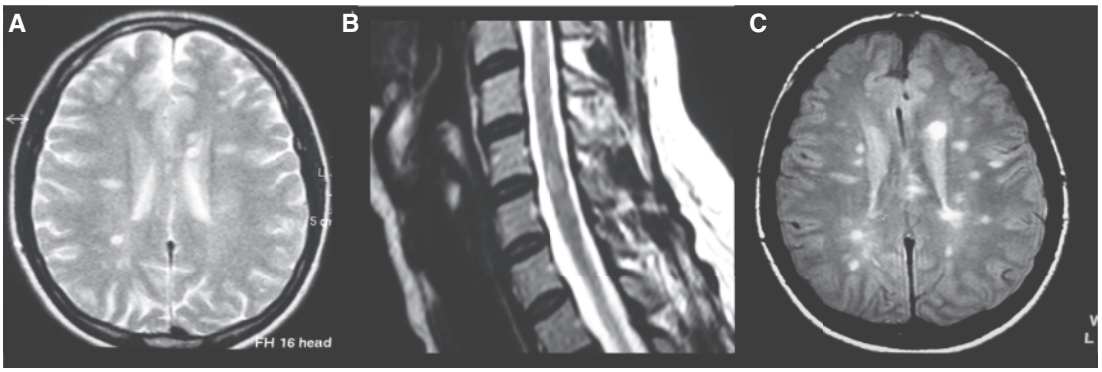

TABLE 4 Multiple stepwise regression analysis for variables independently related to CNS involvement

	Coefficient	S.E.	*t*	*P*
Independent variables				
(Constant)	0.02433			
Disease duration	0.004279	0.001386	3.088	0.0021
Lung involvement	0.2655	0.06208	4.277	<0.0001
Decreased C4	0.06956	0.0221	3.148	0.0018
Articular involvement	−0.06422	0.02129	−3.016	0.0027

Seroimmunological parameters

Compared with non-CNS-pSS, CNS-pSS patients had higher frequency of decreased C_4 (62.5 *vs* 30.5%; $P = 0.02$); low C_4 level occurred more frequently among patients with MS-like disease [four out of five patients (80%)] and those with focal/multifocal CNS involvement [seven out of nine patients (78%)] than in patients with diffuse neurological pattern [four out of 10 patients (40%)]. All patients with MS-like disease and low C_4 levels presented a worse course of the disease (i.e. recurrence or deterioration of clinical manifestations) than those with normal C_4 levels who experienced a complete resolution of their clinical picture. Similar behaviour was not observed in the remaining patients without MS-like disease (focal/multifocal or diffuse pattern), where no relationships were found between C_4 levels and outcome. A higher (but not significant) frequency of low–medium titre aPL was found among CNS-pSS compared with non-CNS-pSS patients (17.4 *vs* 6.2%, respectively; $P = 0.06$). Both IgG and IgM isotypes were detected in two patients, isolated IgG was found in others. Anti-β_2 glycoprotein-1 antibodies were never detected. LA was found in one patient with CNS involvement and in two non-CNS-pSS patients. In these patients, the classic manifestations of APS were absent. All aPL-positive patients had brain MRI abnormalities associated with multiple perfusional defects by SPECT. So far, no patients with aPL satisfied the revised ARA 1997 criteria for SLE.

The other routine lab tests and seroimmunological parameters did not significantly differ between the two groups, although hypercholesterolaemia was more frequently observed among patients with CNS involvement (56 *vs* 36.1%; $P = 0.07$; Tables 4 and 5). Anti-dsDNA was never detected among CNS-pSS patients, neither at baseline nor during follow-up.

Extraglandular manifestations

The global frequency of extraglandular manifestations was lower in CNS-pSS patients than in non-CNS-pSS (76 *vs* 88.2%; P = NS), especially arthritis (32 *vs* 63.4%; $P = 0.003$). Conversely, lung involvement occurred more frequently in CNS-pSS patients (16 *vs* 2%; $P = 0.003$); three patients with a diffuse neurological pattern and one with a focal picture presented on high-resolution CT lung signs of alveolar or interstitial involvement, i.e. ground-glass opacity and peribronchovascular interstitial thickening. One of these patients also had a history of xerotrachea and obstructive airway disease.

A multiple stepwise regression analysis was performed assuming CNS involvement as the dependent variable. The model included disease duration (years from disease onset), decreased C_4, articular and lung involvement, aPL

TABLE 5 RR for CNS involvement calculated for each variable included in the multiple stepwise regression model

	Disease duration[a]	Lung involvement	Articular involvement	aPL	Decreased C_4	Hyper-cholesterolaemia
RR	1.77	7.98	2.28	2.77	2.04	1.55
95% CI	1.37, 2.28	2.57, 24.70	0.54, 9.48	1.05, 7.30	1.45, 2.88	1.07, 2.24
Z-statistic	4.439	3.602	1.133	2.067	4.081	2.320
P	<0.0001	0.0003	0.2571	0.0388	<0.0001	0.0204

[a]Disease duration was dichotomized as >7 or ⩽7 years, the median value of this item calculated in all patients being 7 years.

and hypercholesterolaemia (all dichotomized as present/absent). Relative risk for CNS involvement was then calculated. Disease duration, lung involvement and decreased C_4 were confirmed as factors independently and directly correlated with CNS involvement, while articular involvement did prove to be inversely related to CNS disease. Hypercholesterolaemia and aPLs were not retained in this model. Lung involvement emerged as the strongest risk factor for CNS complications.

Discussion

CNS involvement in pSS still represents a controversial issue. In the largest series of pSS published so far, not more than 1% of CNS disease has been detected [16]. Since 1985, the reported prevalence appears widely heterogeneous and a definitive conclusion about the real burden of this complication has not yet been reached [17–19]. Overall, the lack of formal classification criteria for CNS involvement in pSS seems the most relevant explanation for these discrepancies [3, 4, 20]. In our cohort, we found a prevalence of CNS involvement of 5.8%, similar to what we have already reported in a smaller series [5].

According to previous observations [17, 21–23], our findings confirm that CNS involvement can frequently (52%) represent the initial manifestation of pSS, when mild complaints of sicca symptoms can be overlooked. This information has practical implications emphasizing the need to consider pSS in the differential diagnosis when dealing with any apparently idiopathic, multifocal, recurrent neurological pictures affecting CNS. We have found a slight predominance of diffuse neurological pictures, especially a subacute encephalopathy, often occurring as acute episodes and, less frequently, with a recurrent–relapsing modality.

The role of brain MRI in the assessment of CNS-pSS has not yet been fully defined. Diffuse, small and punctate WMHs represent a frequent but aspecific finding with increasing prevalence with ageing, diabetes, atherosclerosis and hypertension [24–26]. Multiple WMHs have been detected in up to 80% of patients with pSS and focal progressive neurological dysfunctions and also in 50% of patients with a diffuse pattern [4]. These abnormalities have been more frequently reported in asymptomatic pSS patients than in age- and sex-matched healthy subjects [27, 28]. However, MRI has usually been performed in patients with a mean age of >60 years [29, 30], whereas in our patients with subacute encephalopathy, the mean age at onset of neurological symptoms was 42.6 years, and only two of them had a history of stable and well-controlled hypertension.

The significance of these findings remains uncertain, being compatible with small infarction, ischaemia, gliosis, oedema or demyelination. Their occurrence has been related to subtle psychiatric or cognitive disorders [28, 31, 32] providing some support for an organic aetiology.

MS-like syndromes (20% of the patients) could represent a particular subset of neuro-Sjögren, which may heavily affect outcome [33]. Delalande *et al.* [21] reported in his series, a high frequency of this picture (41%). Since our institution represents a tertiary referral centre, a selection bias could have led to an overestimation of this pattern of neurological involvement as reported in other studies [34–36]. In a recent population-based study, patients with MS-like disease were not found [37]. This observation suggests that the association of MS with pSS may be no greater than that expected if the two diseases occur by chance.

The differential diagnosis between pSS with MS-like features and classical MS may be very difficult, since a sicca syndrome and a number of autoantibodies may also be found in the latter condition [34, 38, 39]. The presence of extraglandular manifestations [40, 41], antibodies against α-fodrin more frequently detectable in pSS [42, 43] and some MRI features [27, 33, 44] may be useful for the differential diagnosis. CSF examination may be relevant in such cases, since immunoglobulin intratechal synthesis and OCBs represent a common finding in MS, even if a similar CSF pattern has been reported in previous case series of pSS patients with established, progressive and active CNS disorders mimicking MS [33, 40]. A lower number (fewer than four) of OCBs in CSF has been advocated as more common in pSS than MS [45, 46]. In our series, we found OCBs in all patients with MS-like involvement, both in low (fewer than four) and high (more than four) numbers. Although difficult, correct diagnosis is relevant because of therapeutic implications, since IFN-β has been reported to be ineffective in neuro-Sjogren [47] and even favouring the activity of Th2-mediated autoimmune diseases [48].

Anti-Ro/SSA antibodies have been detected in 40–60% of pSS patients, and they have been found to be associated with more severe CNS disease and small vessel vasculopathy [3, 33, 49]. Recently, intrathecal anti-Ro/SSA antibody synthesis has been demonstrated in three

pSS patients with CNS involvement [50]. In our patients, as in other series, the frequency of serum anti-Ro/SSA antibodies did not differ between patients with and without neurological manifestations [5, 21].

Histopathological data coming from brain tissue specimens have suggested that the main pathogenetic mechanism in CNS-pSS may be related to an immunologically mediated small vessel vasculopathy, while true vasculitis is a less-frequent finding [33]. Indirect evidence of an immunologically mediated mechanism in neuro-Sjogren lies on the demonstration of both intrathecal activation of the terminal complement pathway and the evidence of intrathecal synthesis of IgG in patients with active CNS involvement [51–53]. Our findings are in keeping with this hypothesis, since low serum C_4 was more frequently found among CNS-pSS patients than in controls (62.5 *vs* 30.5%; $P < 0.002$) and it has been found to be associated with systemic manifestations (peripheral neuropathy and vasculitis) and worse outcome [54–56]. In all patients who underwent brain SPECT, multiple focal perfusional defects, associated with diffuse white matter abnormalities on MRI scanning, have been detected, further supporting the role of a diffuse brain small vessel vasculopathy.

An issue that deserves some comment is the finding of aPL among some CNS-pSS patients. Although aPLs have been reported in low–moderate titres in pSS in about 5–56% of the patients [57–59], their pathogenetic relevance in neuro-Sjogren has not been emphasized. In our series, aPLs were detected at medium–high titre only in two patients (one patient with MS-like disease and the other with atypical, refractory headache), while the remaining had low titre and transient positivity. None of these patients had other clinical manifestations typical of the APS.

Both hypercholesterolaemia and hypertension have been more frequently found in CNS-pSS patients than in controls, although the differences were not statistically significant. Recently, a higher frequency of metabolic abnormalities in patients with pSS compared with age- and sex-matched healthy controls has been reported [60]. Both hypertriglyceridaemia and diabetes mellitus have also been associated with a higher occurrence of extraglandular manifestations. Since these abnormalities are well-known modifiable risk factors for cerebrovascular disease, their management should be included in the global therapeutic strategy when approaching CNS-pSS.

In our series, no significant differences have been found about extraglandular manifestations between CNS-pSS and non-CNS-pSS patients, with the exception of lung involvement (more frequently detected in the former) and musculoskeletal symptoms (in the latter). The meaning of these associations is unclear. To the best of our knowledge, a more frequent lung involvement in CNS-pSS has never been reported so far. It could simply be related to the very low prevalence of lung involvement in non-CNS-pSS patients, as we did not perform lung function test routinely in the absence of overt clinical manifestations. However, in the multiple stepwise regression model, lung involvement, along with disease duration and decreased C_4, were retained as independently and significantly correlated with CNS involvement, the lung involvement being the strongest factor related to CNS complications (RR = 7.98).

Our study has some limitations. First of all, its retrospective design. Secondly, our institution is a tertiary referral centre for neurological complications in systemic autoimmune diseases, therefore a potential 'bias' in the observed frequencies of CNS disease should be taken into account. Thirdly, assessment for cognitive dysfunctions has not been routinely performed in all patients, yielding a probable underestimation of this complication. Finally, we have considered only major CNS pictures, excluding from analysis mild symptoms such as isolated headache or minor vague complaints (i.e. anxiety and mild depression).

About outcomes, the emerging profile of CNS-pSS included in our cohort suggests that most cases take an acute, often recurrent course with spontaneous remission or only mild neurological impairment. Such pictures usually need a conservative approach. Adding an antiaggregation treatment, in our opinion, may be useful in order to improve brain microcirculation, in aPL-positive patients. In the presence of persistent disease activity or rapid progression, as may occur in MS-like pictures, a course with moderate to high doses of glucocorticosteroids and eventually immunosuppressive treatment is warranted in order to prevent serious and sometimes irreversible damage.

In conclusion, our findings remark the great heterogeneity of CNS involvement in pSS, which represents a rare but not negligible complication of the disease. The occurrence of CNS involvement has a bimodal temporal distribution, both at onset and later during the course of the disease. In the first case, CNS involvement represents a diagnostic challenge for the clinician and should prompt consideration of pSS in the differential diagnosis of any orphan, multifocal, recurrent neurological picture. The association between lung involvement and CNS complications deserves attention but needs further confirmations in prospective studies. As it has happened for lupus, where the availability of a normative classification of NP syndromes boosted the research in this field. We strongly advise, in the near future, a similar multidisciplinary and international multicentre effort for pSS.

Rheumatology key messages

- CNS involvement in pSS represents a rare (5.8%) but not negligible complication.
- NP involvement occurred with a bimodal temporal distribution, both at disease onset and later.
- Patients with appearance of NP involvement at onset had a worse course.

Acknowledgements

Funding: Supported by grants from the Fondo Regione Emilia Romagna (PG 08 23943/2008/P18A) and Fondazione Cassa di Risparmio di Ferrara, Italy.

Disclosure statement: The authors have declared no conflicts of interest.

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