

Neurological involvement in Primary Sjögren's Syndrome

Filipa Teixeira¹, Isabel Moreira², Ana Martins Silva², Carlos Vasconcelos³, Fátima Farinha³, Ernestina Santos²

ACTA REUMATOL PORT. 2013;38:29-36

ABSTRACT

Objectives: To perform an observational retrospective cross-sectional case-control study to evaluate prevalence, clinical patterns and outcomes of neurological involvement in a cohort of Primary Sjögren Syndrome (pSS) patients followed up in a single center.

Material and Methods: From a total of 93 pSS patients, diagnosed according to the 2002 criteria proposed by the American-European Consensus Group, we reviewed the clinical data of those with neurological complaints that were referred to observation by Neuroimmunology doctors. Demographic, clinical, seroimmunological data were compared between patients with and without neurological involvement.

Results: Neurological involvement was detected in 26 (28%) of the 93 patients. Neurological symptoms preceded the diagnosis of pSS in 12 (46%) patients. They were all females. The mean age at disease onset and neurological onset were 41,2 and 47,9 years, respectively. Twelve patients (46%) had peripheral system involvement (PNS), 13 (50%) patients had central nervous involvement (CNS) disorders and one (4%) patient had both PNS and CNS involvement. In patients with PNS, pure sensory neuropathy (small fiber neuropathy confirmed by quantitative sensory testing and sural neuropathy) occurred most frequently (n=5), followed by cranial nerve involvement affecting trigeminal, facial, or trochlear nerves (n=4). Multiple mononeuropathy (n=1), sensorimotor polyneuropathy (n=1), autonomic neuropathy (n=1) and myasthenia gravis (n=1), were also observed. In patients with CNS disorders, headache (n=3) occurred most frequently, in two patients with MRI abnormalities compatible with inflammatory disease. Spinal cord involvement (n=2), seizures (n=2), motor and sensory deficit (n=2), mo-

vement disorders (n=2), neuromyelitis optica (n=2), aseptic meningitis (n=1) were others manifestations observed. Cognitive dysfunction was observed in 3 of these patients. The frequency of constitutional symptoms (such as fever and fatigue) and lung involvement was significantly higher (p<0,05) and the articular symptoms were significantly less frequent (p<0,05) in pSS with neurological involvement. The neurologic outcome was good in 77% of the patients.

Conclusion: The current study underlines the diversity of neurologic complications of pSS. The frequency of neurologic manifestations as first manifestation of pSS, especially in the event of CNS involvement, could explain why SS is frequently under diagnosed or late diagnosed. Screening for SS should be systematically performed in cases of acute or chronic myelopathy, axonal sensorimotor neuropathy, or cranial nerve involvement.

Keywords: Neurological Involvement; Primary Sjögren Syndrome.

RESUMO

Objetivos: Estudo retrospectivo, transversal caso-controlo para avaliar a prevalência, as manifestações e a evolução do compromisso neurológico numa coorte de doentes com Síndrome de Sjogren primário (SSp) de um único centro.

Material e Métodos: De um total de 93 doentes com o diagnóstico de SSp mediante os critérios propostos por o *American-European Consensus Group* de 2002, foram revistos os dados clínicos de todos os doentes com sintomas neurológicos avaliados na unidade de neuroimunologia. Os dados demográficos, clínicos e seroimunológicos foram comparados entre os dois grupos com e sem manifestações neurológicas.

Resultados: O envolvimento neurológico foi detectado em 26 (28%) dos 93 doentes e precedeu o diagnóstico de SSp em 12 (46%) doentes, todos do sexo feminino. A idade média de início da doença e do compro-

1. Serviço de Reumatologia, Hospital de Ponte de Lima, Unidade Local de Saúde do Alto Minho

2. Serviço de Neurologia, Hospital Geral de Santo António, Centro Hospitalar do Porto

3. Unidade de Imunologia Clínica, Hospital Geral de Santo António, Centro Hospitalar do Porto

misso neurológico foi de 41.2 e 47.9 anos, respectivamente. O envolvimento do sistema nervoso periférico (SNP), do sistema nervoso central (SNC) ou ambos (SNP + SNC) foi registado em 12 (46%), 13 (50%) e 1 (4%) dos doentes, respectivamente. Nos doentes com compromisso do SNP, a neuropatia sensitiva pura (neuropatia de pequenas fibras confirmada por teste sensorial quantitativo e neuropatia sural) foi a mais frequente (n=5), seguida do compromisso de pares craneanos envolvendo o trigemio, facial ou troclear (n=4). A mononeuropatia múltipla (n=1) a polineuropatia sensitivomotora (n=1), a neuropatia autonómica (n=1) e a miastenia gravis (n=1) foram também observadas. Nos doentes com atingimento do SNC, a cefaleia foi um sintoma descrito em 2 doentes com doença inflamatória identificada por RMN. Outras manifestações registadas foram: compromisso medular (n=2), convulsões (n=2), défices motores ou sensitivos (n=2), perturbações do movimento (n=2), neuromielite óptica (n=2) e meningite asséptica (n=1). Em 3 doentes foi ainda registada disfunção cognitiva. A presença de sintomas constitucionais (como febre ou fadiga) e o envolvimento pulmonar foram mais frequentes ($p < 0.05$) e as manifestações articulares foram menos frequentes ($p < 0.05$) nos doentes com SSp com envolvimento neurológico. O *outcome* neurológico foi favorável em 77% dos doentes.

Conclusão: Este estudo enfatiza a diversidade de manifestações neurológicas no SSp. A frequência de manifestações neurológicas como primeira manifestação do SSp, particularmente no caso do envolvimento do SNC, poderá explicar o atraso no diagnóstico do SS ou a razão porque é frequentemente subdiagnosticado. O rastreio clínico de SS deveria ser preconizado de forma sistemática nos casos de mielopatia aguda ou crónica, neuropatia sensitivomotora axonal ou de pares craneanos.

Palavras-Chave: Compromisso Neurológico; Síndrome de Sjögren Primário.

INTRODUCTION

Primary Sjögren Syndrome (pSS) is an autoimmune disorder characterized by a chronic lymphocytic and plasmacellular infiltration of exocrine glands and extraglandular features including both peripheral nervous system (PNS) and central nervous system (CNS) involvement¹.

Prevalence of neurological manifestations in pSS va-

ries between 10 and 60%. The wide range is in part due to an evolving definition of Sjögren's syndrome (prior to the 2002 case definition), as well as differences in study populations, and in definition or methods of detection of neuropathy^{2,3}.

The pathogenic mechanisms responsible for most forms of neurological involvement in pSS are unknown. Several mechanisms are suggested for the development of the involvement of PNS in pSS patients. Vascular or peripheral inflammatory infiltrates with or without necrosis may be found. Vasculitis of the vasa nervorum has also been proposed as pathogenic mechanism in PNS involvement^{2,6}.

Three pathogenic factors may explain the CNS disorders. The first hypothesis is the direct infiltration of the CNS by mononuclear cells; the second hypothesis is the vascular involvement. The vascular injury may be related to the presence of antineuronal antibodies and anti-Ro antibodies. Other authors suggest that the underlying mechanism of CNS lesion in pSS is the ischemia secondary to small vessel vasculitis^{2,6-9}.

Pure or predominantly sensory polyneuropathies are the most common neurologic manifestation (e.g. sensory ataxic or small fiber sensory painful neuropathy)^{2,4}. Mononeuropathy multiplex, polyradiculopathy, symptomatic dysautonomia, cranial neuropathy, myopathy, and central nervous system involvement are less common. pSS associated sensory neuropathy is often the presenting feature of Sjögren's syndrome and, therefore, a high index of suspicion is required, particularly in female patients with nonlength-dependent, painful, or ataxic sensory neuropathy or those with trigeminal sensory and autonomic involvement⁸⁻¹⁰.

The aim of the study was to describe the prevalence, clinical patterns and outcomes of neurological involvement in a cohort of pSS patients followed up in a single center.

MATERIALS AND METHODS

PATIENTS AND CONTROLS

This observational retrospective cross-sectional case-control study included all patients with pSS diagnosis followed up in Neurology Department and Clinical Immunology Unit of our center.

These patients were diagnosed as having pSS on the basis of the revised version of the European criteria proposed by the American-European Consensus Group³. Patients with an overlapping syndrome such as rheumatoid arthritis, systemic lupus erythematosus, or sys-

TABLE I. SPECTRUM OF CNS AND PNS INVOLVEMENT IN PSS

CNS	PNS
Focal Motor and/or sensory deficit Aphasia/dysarthria Seizure disorders Brainstem syndrome Cerebellar syndrome	Sensory neuropathy Small fiber neuropathy Sensory ataxic neuropathy Sensorimotor polyneuropathy Polyradiculopathy Multiple mononeuropathy Autonomic neuropathy Cranial neuropathies Myasthenia gravis
Diffuse Acute or subacute encephalopathy Aseptic meningitis Cognitive dysfunction/dementia Movement disorders	
Spinal Cord Dysfunction Transverse myelitis Chronic progressive myelitis Lower motor neuron disease	
Other Neuromyelitis optica Multiple sclerosis-like disease	

temic sclerosis were excluded. Clinical data were obtained from medical records. The duration of data collection was 3 months.

Demographic, clinical, immunological data were compared between patients with and without neurological involvement.

Fever was defined as higher than 38.0°C, and the positivity of antinuclear antibody (ANA) was defined as a titer superior to 1/160 by the indirect immunofluorescence method or ELISA method.

CLASSIFICATION OF NEUROLOGICAL INVOLVEMENT

Neurological involvement, and classification of the two subsets PNS an CNS, was assessed by neurological examination, peripheral nerve conduction study (NCS) with quantitative sensory testing (QST), magnetic resonance imaging (MRI), electroencephalogram (EEG), and cerebrospinal fluid (CSF). Manifestations were categorized as reported in Table I.

NEUROLOGIC OUTCOME

Clinical outcome was assessed using the Modified Oxford Handicap Scale (MOHS)^{4,5}:

- 0 = No symptoms.
- 1 = Minor symptoms not interfering with lifestyle.
- 2 = Minor handicap with symptoms leading to some

restriction in lifestyle but not interfering with the patient’s capacity to look after himself or herself.

- 3 = Moderate handicap with symptoms that significantly restrict lifestyle and prevent totally independent existence.
- 4 = Moderately severe handicap with symptoms that clearly prevent independent existence though not needing constant attention.
- 5 = Severe handicap leading to total dependence and requiring constant attention during night and day.
- 6 = Death.

STATISTICAL ANALYSIS

Statistical analyses were performed using the Fisher exact test and student T test for categorical and continuous variables, respectively. The data were analyzed with SPSS 17.1 software. A value of P<0.05 was considered to indicate statistical significant

RESULTS

COMPARISON OF CLINICAL MANIFESTATIONS BETWEEN PATIENTS WITH AND WITHOUT NEUROLOGICAL INVOLVEMENT IN PSS

As shown in Table II, 93 patients with pSS were en-

TABLE II. COMPARISON OF CLINICAL FEATURES BETWEEN PNS/CNS GROUP AND NON-PNS/CNS GROUP

	All	PNS/CNS	Non-PNS/CNS	P value
Ratio ♀:♂	90♀:3♂	26♀	64♀:3♂	–
Number	93	26	67	
Age at onset symptoms	44,2	41,8	45,8	p = 0,698
Age at diagnosis	47,6	45,1	48,7	p = 0,767
Duration (years)	11,4	11,7	11,15	p = 0,934

TABLE III. NEUROLOGICAL FINDINGS IN PSS PATIENTS WITH PNS INVOLVEMENT

	N
Sensorial neuropathy	5
– small fiber neuropathy	3
– sural neuropathy	2
Cranial neuropathy	4
– facial nerve palsy	2
– trigeminal neuralgia	1
– abducens nerve palsy	1
Multiple mononeuropathy	1
Sensorimotor polyneuropathy	1
Autonomic neuropathy	1
<i>Myasthenia gravis</i>	1
Total	13

TABLE IV. NEUROLOGICAL FINDINGS IN PSS PATIENTS WITH CNS INVOLVEMENT

	N
Headache with MRI abnormalities compatible with inflammatory disease	2
– migraine with visual aura	2
Tension-type headache	1
Spinal cord involvement	2
Seizures	2
Motor and sensory deficits	2
Movement disorders	2
Neuromyelitis optica	2
Aseptic meningitis	1
Total	14

rolled in this study, including 26 patients with neurological involvement that were all female. The age at diagnosis with pSS was $41,2 \pm 18,4$ years (mean \pm SD) and $45,8 \pm 13,3$ years (mean \pm SD) in patients with and without neurological involvement, respectively.

The disease duration was defined as years between onset of sicca symptoms and the time of data collection from medical records. The median duration was 11,7 years and 11, 15 years in the PNS/ CNS and non-PNS/CNS groups, respectively.

Neurologic involvement frequently preceded the diagnosis of pSS in 12 (46%) patients. Twelve patients (46%) had peripheral system involvement PNS, 13 (50%) patients had CNS disorders and one (4%) patients had both PNS and CNS involvement.

The frequency of constitutional symptoms (such as fever and fatigue), lung involvement and articular symptoms was 19 (20%), 8 (9%) and 11 (12%) in the PNS/CNS group and 10 (11%), 2 (2,1%) and 46 (49%) in the non-PNS/CNS group, respectively.

The frequency of constitutional symptoms and lung

involvement was significantly higher ($p < 0,05$) and the articular symptoms were significantly less frequent ($p < 0,05$) in pSS with neurological involvement. There was no statistical significant difference between the two groups in involvement of other organs or systems, including cardiovascular, endocrine, gastrointestinal, renal and skin involvement.

NEUROLOGICAL FINDINGS IN PSS PATIENTS WITH PNS INVOLVEMENT

PNS findings included five patients with sensorial neuropathy and four patients with cranial neuropathy. Multiple mononeuropathy, sensorimotor polyneuropathy and autonomic neuropathy were observed each in one patient (Table III). There was also one patient with myasthenia gravis (generalized with positive anti-acetylcholine receptors antibodies) that was considered to have this disease associated with pSS.

Five patients with sensorial neuropathy included three with small fiber neuropathy and two with sural neuropathy. Four patients with cranial neuropathy included two with facial nerve palsy, one with trigemi-

nal neuralgia, one with abducens nerve palsy.

The nerve conduction velocity studies showed absence of the sensory action potential in two patients with sural neuropathy, increase of the threshold of sensitivity to cold in two patients with small fiber neuropathy. The others findings were reduction in amplitude of sural and peroneal nerves in patients with mononeuritis multiplex and axonal sensory polyneuropathy asymmetric in patients with sensorimotor polyneuropathy.

NEUROLOGICAL FINDINGS IN PSS PATIENTS WITH CNS INVOLVEMENT

As shown in Table IV, CNS findings included three with headache, two patients with migraine with visual aura, which have MRI abnormalities compatible with inflammatory disease; and one patient with tension-type headache.

Two patients presented optic neuritis with a tetraparal syndrome and a posterior columns syndrome. Both were positive for anti- Aquaporin4 (AQ4) antibodies. Spinal cord MRI showed an extensive centro-medular lesion from C2 to C5 in one patient and from C2 to C7 in another patient. Brain MRIs were normal. These patients were diagnosed as having neuromyelitis optica associated with pSS.

The spinal cord involvement was observed in two patients, one with transverse myelitis with CFS with increased protein level and cell count, and other with chronic progressive myelopathy with progressive spastic paraparesis and urinary disorders. This patient had progressive worsening, developed a dementia syndrome and died nine years later. Brain MRIs showed multiple, some confluent, small hiperintense lesions in the supratentorial white matter, mainly subcortical and posterior. The one that developed a dementia syndrome also had a cortico-subcortical diffuse atrophy. Spinal cord MRIs were normal.

There were two cases of epilepsy with complex partial seizures, which started at 23 and 66 years old. Neurological examinations were normal. MRIs showed on the first a gliotic focus of unspecific nature in right frontal subcortical white matter and on the second multiple T2 hyperintense lesions in the periventricular white matter, semioval centers, left thalamus and right cerebellar hemisphere. EEGs showed paroxistic activity anterior and lateral bilaterally, with generalized paroxysmal activity with spikes and waves during the seizures. CSF analysis was normal and NMDA-antibodies were negative

Two patients had motor and sensory deficits. One at 40 years suddenly had left hemiparesis and dysesthesia that disappeared gradually in 2 months. Brain MRI was normal. The other was referred to neurology by generalized weakness since 64 years old and presented with a slight tetraparesis with brisk reflexes and episodes of dizziness. Brain MRI showed multiple hyperintense lesions on the basal ganglia, corpus callosum and pons.

In two patients was observed movement disorders secondary to pSS, one with clinical features of atypical Parkinsonism with a symmetric akinetic/rigid syndrome, gait disorder, and postural instability, without prominent tremor. In this patints brain MRIs showed multiple focal lesions scattered in the subcortical and deep white matter of nonspecific nature, probably gliotic/ischemic. Another patient has a clinical picture more closely resembling idiopathic Parkinson's disease (PD), with asymmetric tremor and bradykinesia. CSF exams were normal. A lack of response to L-dopa was observed in the two cases, arguing against the diagnosis of idiopathic PD.

One patient had a clinical picture of subacute afebrile aseptic meningitis (AM) as neurological manifestation of pSS, as initial manifestation of disease. The neurological symptomatology presented gradual onset and progression of mild headache, neck rigidity and diplopia. CSF analysis showed moderate lymphocytosis and increased protein level but no evidence of immunoglobulin intrathecal synthesis. Three bolus of intravenous steroid therapy led to a complete disappearance of the neurological symptomatology and to normalization of the CSF inflammatory pattern.

Spinal Cord or brain MRI was not performed in three patients: the patient with aseptic meningitis, the one with tension-type headache and the other patient with movement disorder.

During the follow-up, one patient with spinal cord involvement and others two with movement disorder and the headache (tension-type headache) developed cognitive dysfunction with criteria for dementia. One patient whose initial manifestation was the cranial neuropathy during the follow-up had CNS involvement (migraine with visual aura with brain MRI abnormalities compatible with inflammatory disease). The remaining 21 patients had no other neurological manifestations secondary to SS.

According to Modified Oxford Handicap Scale^{4,5}, the neurologic outcome was good in all patients with PNS involvement. The patient with transverse myelitis had a severe handicap leading to total dependence

and the patient with chronic progressive myelopathy died. The patients with movement disorder and headache that developed cognitive dysfunction also had an unfavorable evolution of disease with moderate handicap.

Fifteen patients were treated with corticosteroids, resulting in a durable neurologic amelioration or stabilization in 12 cases. This treatment was totally ineffective in three patients, those with spinal cord involvement and in other patient with multiple mononeuropathy. Eight patients received immunosuppressive therapy, including cyclophosphamide in three patients. It resulted in a partial recovery or stabilization in two of the four treated patients. In one patient with spinal cord involvement and other with multiple mononeuropathy, cyclophosphamide was ineffective. Nine patients received only symptomatic treatment, including antiepileptic, antiparkinsonian drugs and pyridostigmine for myasthenia gravis.

DISCUSSION

Our results showed that neurological complications were present in 26 (28%) patients, all females. This study underlines the diversity of neurologic manifestations of pSS and suggests that the frequency of CNS involvement is similar to that of PNS involvement. This result is quite different from previous studies, where PNS involvement was mainly described^{2,6,11}.

With regard to clinical features, the frequency of constitutional symptoms and pulmonary involvement was significantly higher in patients with pSS with neurological complications.

The current study agrees with those of Deland et al, Mellgren et al and Lafitte et al, who described many cases (between 47-53%), of pSS with neurologic manifestations as presenting symptoms¹¹⁻¹³. The absence of sicca symptoms in 46% of our patients at the onset of neurologic signs, especially in cases of CNS involvement, emphasizes the difficulty of the diagnosis and the utility of systematically screening for SS in patients with neurologic symptoms such as sensory motor axonal polyneuropathy, pure sensory neuropathy, cranial nerve involvement (especially cochlear and trigeminal nerves), acute or chronic myelopathy, or multifocal CNS involvement with onset after 50 years of age^{2,9}.

Our study confirms that peripheral neuropathy is the commonest PNS complication in pSS, mainly the sensorial neuropathy. Our series include the main ty-

pes of neuropathy already described in pSS. Small fiber neuropathy (SFN) is a neurological manifestation of pSS recently describe and the most published series there is no reference to this manifestation^{12,13}.

SFN is a polyneuropathy selectively involving small-diameter myelinated (A-delta) and non-myelinated (C) nerve fibers and leaving large myelinated fibers relatively unaffected. Clinical manifestations were mainly distal burning sensation, dysesthesia, prickling, and allodynia, localized in both hands and feet without muscle weakness and decreasing of the deep tendon reflex^{6,16-17}.

A peripheral nerve conduction study (NCS) usually reveals normal findings in SFN; however, SFN is occasionally complicated with autonomic nervous failure¹³. In our study SFN was confirmed by quantitative sensory testing in two patients.

Whereas the trigeminal nerve seems to have been more frequently involved in previous studies, we found a more frequent involvement of the facial nerve palsy^{14,18}.

In our cohort, as in other series, the CNS involvement was most frequently focal. Only one series (Masara et al) have found a slight predominance of diffuse neurological pictures, especially a subacute encephalopathy¹⁹.

Unlike other series, in which no cases of NMO is reported (there are only reports of isolated clinical cases), in our series we had two cases of this clinical picture. This can be explained by the fact that NMO previously had been considered as one component of the spectrum of complications associated with MS. However, NMO recently has been considered a different entity from MS, after the discovery of the antibody anti-AQP4. NMO was classically described as optic neuritis and longitudinal extensive transverse myelitis, and is frequently associated to autoimmune disorders such as thyroiditis, systemic lupus erythematosus (SLE), or pSS in 10-40% of patients^{6,20-21}.

With the recent discovery of an antibody anti-AQP4 (NMO-IgG), which is considered to be specific for neuromyelitis optica, an overlap between patients with primary SS and neuromyelitis optica spectrum diseases (NMOSD) is being noted, but there are few studies that have attempted to address the relationship between SS and NMOSD^{4,19}.

In the present study, anti-AQ4 antibody was detected in two patients with optic neuritis and myelitis and the diagnosis of NMO was made. If optic neuritis or multiple lesions in the spinal cord and white matter are found in pSS patients, anti-AQ4 antibody should

be screened²⁰⁻²².

Movement disorders such as tremor, dystonia, and pseudoathetosis have rarely been reported such neurologic manifestation of pSS. Eleven cases of parkinsonism associated with pSS have been published to date. In our series we describe two cases of a movement disorder associated with pSS^{23,24}.

Lafitte et al found a high frequency of cognitive dysfunction during pSS. We cannot confirm this finding because we did not systematically screen patients for cognitive impairment. However, in 3 patients we confirmed cognitive profile with subcortical dysfunction^{11,13}.

MS-like syndromes could represent a particular subset of neurological involvement, which may heavily affect outcome. Other series reported high frequency this picture. In our series we didn't find any event MS-like^{2,19}.

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. The presence of extraglandular manifestations, antibodies against alfa-fodrin more frequently detectable in pSS and some MRI features may be useful for the differential diagnosis¹⁹.

The role of brain MRI in the assessment of CNS-pSS has not yet been fully defined. Diffuse, small and punctuate white matter hyperintensities (WMHs) represent a frequent but a unspecific finding with increasing prevalence with ageing, diabetes, atherosclerosis and hypertension. 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^{19,25}. These abnormalities have been more frequently reported in asymptomatic pSS patients than in age- and sex-matched healthy subjects²⁵⁻²⁷.

In our series, the main differences regarding extraglandular manifestations between PNS/CNS-pSS and non-PNS/CNS-pSS patients were related to constitutional symptoms, lung and articular involvement. The frequency of constitutional symptoms and lung involvement was significantly higher in pSS with neurological involvement than in pSS without neurological involvement and the articular symptoms were significantly less frequent in pSS with neurological involvement. The meaning of these associations is unclear. However, the fact that the articular symptoms were less frequent in patients with neurological involvement, may explain the low prevalence of neurological involvement in series of patients from rheumatology departments²⁸.

In our study, severe disability was more frequent in cases of CNS involvement than in cases of PNS involvement, suggesting the need for intensive and early treatment in cases of CNS involvement.

CONCLUSION

In conclusion, our findings remark the great heterogeneity of neurological involvement in pSS, which represents a not negligible complication of the disease.

A lower prevalence of neurological complications was reported in other series. Maybe it was due to missed diagnosis or different methodologies. In our cohort, the CNS involvement had similar frequency to PNS involvement. This result is quite different from that of previous studies where PNS involvement was mainly described.

The association between lung involvement, constitutional symptoms and neurological complications deserves attention but needs further confirmations in prospective studies. As it happened with lupus patients in which the availability of a normative classification of neuropsychiatric syndromes boosted the research in this field, we strongly advise, in the near future, a similar multidisciplinary and international multicentre effort for pSS.

CORRESPONDENCE TO

Filipa Daniela Dias Teixeira
Serviço de Reumatologia, Hospital de Ponte de Lima,
Unidade Local de Saúde do Alto Minho, Portugal
E-mail: filipadteixeira@gmail.com

REFERENCES

1. Tzioufas, A.G., D.I. Mitsias, and H.M. Moutsopoulos, Sjögren's Syndrome, in Rheumatology, M.C. Hochberg, et al., Editors. 2008, Elsevier: Philadelphia.
2. Chai J, Logigian E. Neurological manifestations of primary Sjogren's syndrome. *Current Opinion in Neurology* 2010, 23:509-511.
3. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61:554-558.
4. Bamford J, Sandercock P, Dennis M, Warlow C, Jones L, McPherson K, Vessey M, Fowler G, Molyneux A, Hughes T. A prospective study of acute cerebrovascular disease in the community. *J Neurol Neurosurg Psychiatry*. 1988;51:1373-1380
5. Bamford JM Sandercock PAG et al. Letter to the Editor: Interobserver agreement for the assessment of handicap in stroke patients. *Stroke* 1989; 20: 828.
6. Gono T, Kawaguchi Y, Katsumata Y et al. Clinical manifestations of neurological involvement in primary Sjögren's syndrome.

- Clin Rheumatol 2011; 30:485–490.
7. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. *Brain* 2005; 128:2518–2534.
 8. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in Sjögren's syndrome-associated neuropathy. *Brain* 2005; 128:2518–2534.
 9. Font J, Valls J, Cervera R, et al. Pure sensory neuropathy in patients with primary Sjögren's syndrome: clinical, immunological, and electromyographic findings. *Ann Rheum Dis* 1990; 49:775–778.
 10. Grant IA, Hunder GG, Homburger HA, Dyck PJ. Peripheral neuropathy associated with sicca complex. *Neurology* 1997; 48:855–862.
 11. Delande S, et al. Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. *Medicine (Baltimore)* 2004;83:280–291.
 12. Mellgren SI, Conn DL, Stevens JC, Dyck PJ. Peripheral neuropathy in primary Sjögren's syndrome. *Neurology* 1989;39:390–394.
 13. Lafitte C, Amoura Z, Cacoub P, Pradat-Diehl P, Picq C, Salachas F, Leger JM, Piette JC, Delattre JY. Neurological complications of primary Sjögren's syndrome. *J Neurol*. 2001;248:577–584.
 14. Pavlakis PP, et al. Peripheral neuropathies in Sjögren syndrome: a new reappraisal. *J Neurol Neurosurg Psychiatry* 2011;82:798–802.
 15. Sène D, et al. Peripheral neuropathies associated with primary Sjögren syndrome: immunologic profiles of nonataxic sensory neuropathy and sensorimotor neuropathy. *Medicine (Baltimore)*. 2011 Mar;90(2):133-138.
 16. Hoitsma E, Reulen J, de Baets M, Drent M, Spaans F, Faber C. Small fiber neuropathy: a common and important clinical disorder. *J Neurol Sci* 2004; 227:119–130.
 17. Al-Shehlee A, Chelmsky T, Preston D Review: small fiber neuropathy. *Neurologist* 2002; 8:237–253.
 18. Lecky B, Hughes R, Murray N Trigeminal sensory neuropathy. A study of 22 cases. *Brain* 1987;110(Pt 6):1463–1485.
 19. Massara A, Bonazza S, Castellino G, et al. Central nervous system involvement in Sjögren's syndrome: unusual, but not unremarkable—clinical, serological characteristics and outcomes in a large cohort of Italian patients. *Rheumatology* 2010;49:1540–1549.
 20. Takahashi T, Fujihara K, Nakashima I, Misu T, Miyazawa I, Nakamura M et al. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain* 2007; 130 :1235–1243.
 21. Wingerchuk D, Lennon V, Lucchinetti C, Pittock S, Weinshenker B. The spectrum of neuromyelitis optica. *Lancet Neurol* 2007; 6:805–881.
 22. Kahlenberg J.M. Neuromyelitis Optica Spectrum Disorder as an Initial Presentation of Primary Sjögren's Syndrome. *Semin Arthritis Rheum* 2011; 40:343-348.
 23. Walker R, Spiera H, Brin H, Olanow C. Parkinsonism Associated With Sjögren's Syndrome: Three Cases and a Review of the Literature. *Mov Disord* 1999; 14: 262–268.
 24. Creange A, Sedel F, Brugieres P, Voisin M-C, Degos JD. Primary Sjögren's syndrome presenting as progressive parkinsonian syndrome. *Mov Disord* 1997;12:121–123.
 25. Ioannidis JP, Moutsopoulos HM. Sjögren's syndrome: too many associations, too limited evidence. The enigmatic example of CNS involvement. *Semin Arthritis Rheu* 1999;29:1–3.
 26. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. I. Correlation with age and cerebrovascular risk factors. *Stroke* 1986;17:1084–1089.
 27. Ovbiagele B, Saver JL. Cerebral white matter hyperintensities on MRI: current concepts and therapeutic implications. *Cerebrovasc Dis* 2006;22:83–90.
 28. Malladi AS, Sack K, Shiboski S et al. Primary Sjögren's syndrome as a systemic disease: A study of participants enrolled in an International Sjögren's syndrome registry. *Arthritis Care Res* 2012;64:911-918.

II CURSO DE CIRURGIA PERCUTÂNEA DA MÃO

Faro, Portugal
20 Abril 2013