Classification and characterisation of peripheral neuropathies in 102 patients with primary Sjögren's syndrome

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Abstract

Objective

This paper aims to analyse the etiology, characterisation and outcomes of the different types of peripheral neuropathy in patients with primary Sjögren's syndrome (SS) and their association with clinical and immunological disease expression.

Methods

A total of 563 consecutive patients diagnosed with primary SS were evaluated. We retrospectively assessed the results of nerve conduction studies carried out in patients with suspected peripheral nervous system involvement. Peripheral neuropathies were classified into mononeuropathy, mononeuropathy multiplex, polyneuropathy and neuronopathy according to the patterns evidenced by electrodiagnostic studies.

Results

Nerve conduction studies were carried out in 158/563 (28%) SS patients. The results were normal in 49 and abnormal in 109 patients, in whom peripheral neuropathy was diagnosed in 102. After excluding patients with neuropathy associated with other diseases and patients with entrapment mononeuropathies, 55/563 (10%) patients were classified as having SS-related peripheral neuropathy, including axonal sensorimotor polyneuropathy (n=24), pure sensory neuronopathy (n=15), mononeuropathy multiplex (n=15) and demyelinating polyradiculoneuropathy (n=1). In spite of therapy, clinical progression measured by the MOHS scale was observed in 12% of patients with axonal polyneuropathy, 13% of those with mononeuropathy multiplex and 47% of those with neuronopathy. Survival was significantly reduced in patients with peripheral neuropathy (especially in those with mononeuropathy multiplex and axonal polyneuropathy) in comparison with the control group (log rank = 0.001).

Conclusion

We found a prevalence of SS-related peripheral neuropathy of 10%. Classification of neuropathy according to the clinical presentation and electrodiagnostic tests may be useful in determining the functional outcome, therapeutic response and survival.

Key words

primary Sjögren's syndrome, peripheral neuropathy, neuronopathy, vasculitis, focal nerve entrapment

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Received on March 10, 2012; accepted in revised form on April 19, 2012.

Funding: this work was supported by Grants La Marató de TV3 (071810) and Fondo de Investigaciones Sanitarias (080103).

Competing interests: none declared.

Introduction

Sjögren's syndrome (SS) is a systemic autoimmune disease that presents with sicca symptomatology of the main mucosal surfaces (1). The main sicca features (xerophthalmia and xerostomia) are determined by specific ocular (Rose Bengal staining, Schirmer test) and oral (salivary flow measurement, parotid scintigraphy) tests. The histological hallmark is focal lymphocytic infiltration of the exocrine glands, determined by biopsy of the minor labial salivary glands (2). The spectrum of the disease extends from sicca syndrome to systemic involvement (extraglandular manifestations) and may be complicated by the development of lymphoma. Patients with SS present a broad spectrum of analytical features (cytopenias, hypergammaglobulinaemia) and autoantibodies, of which antinuclear antibodies (ANA) are the most-frequently detected, anti-Ro/SS-A the most specific, and cryoglobulins and hypocomplementaemia the main prognostic markers (3).

Peripheral neuropathy has been reported to have a prevalence of 2–11% in large series of unselected patients with primary SS (4, 5) and is one of the most frequent extraglandular features of this disease. The diagnosis of patients with peripheral neuropathy requires exhaustive evaluation of signs and symptoms, followed by confirmation by electrodiagnostic studies, which are useful in establishing the type of neuropathy (mononeuropathy, mononeuropathy multiplex or polyneuropathy) and whether it is primarily demyelinating or axonal (6). Axonal polyneuropathy and mononeuropathy multiplex are the most frequent types of peripheral neuropathy in primary SS (7), together with pure sensory neuronopathy, which is caused by damage to the sensory neurons of the dorsal root and gasserian ganglia (8-11). There are few specific studies of peripheral neuropathy in primary SS, with limited data available on the differentiated patterns of clinical and immunological expression of the different subtypes of neuropathy and their relationship with concomitant etiologies other than SS. Two recent studies have described the characteristics of 30 and 36 French patients with primary SS and peripheral neuropathy (12, 13), respectively, although there were significant differences in the study design and classification of peripheral neuropathy, thus limiting comparison between the two studies.

The aim of this case-control study was to describe the main characteristics of patients with primary SS diagnosed with peripheral neuropathy in a specialist SS unit, focusing on the etiology, characterisation and outcomes of the different types of peripheral neuropathy and their association with the clinical and immunological expression of primary SS.

Materials and methods

Patients

A total of 563 consecutive patients were evaluated by our unit between January 1990 and December 2010 and diagnosed with primary SS according to: i) fulfillment of at least four of the six 1993 European classification criteria including either positive autoantibodies (ANA, RF, anti-Ro and/or anti-La) or salivary biopsy as a mandatory criteria, and ii) exclusion of other possible causes of sicca syndrome (infiltrative processes, infections or neoplasia) and other concomitant systemic autoimmune diseases. Extraglandular involvement in primary SS was evaluated according to the 2010 EULAR Sjögren's syndrome disease activity index (14). Associated organ-specific autoimmune diseases (thyroid, liver and pancreatic diseases) and neoplasias were also collected. All patients were followed up prospectively with regular visits at 6–12 month intervals, and clinical and laboratory data were collected and computerised according to the standard protocol of the SEMI guidelines (4). The study design conformed to current Spanish ethical standards. Due to the anonymous nature of the study, informed patient consent was not required.

Neurological evaluation

We retrospectively evaluated the results of the nerve conduction studies carried out in patients with suspected peripheral nervous system involvement including paraesthesiae, distal numbness, weak-

ness and/or neuropathic pain in the upper or lower limbs. Needle electromyography (EMG) was performed in distal lower limb muscles by two experienced neurologists (J. Valls-Sole and F. Graus), and peripheral neuropathies were classified into mononeuropathy, mononeuropathy multiplex, polyneuropathy and neuronopathy, according to the patterns seen in electrodiagnostic studies detailed in previous studies (9-11, 15) and following the definitions of the American Academy of Neurology and the American Association of Electrodiagnostic Medicine (16). Cut-off values were considered from previous work done in the same laboratory in a series of healthy subjects (15). Conventional nerve conduction studies were carried out in the common peroneal, posterior tibial, sural, median, and ulnar nerves. Long latency reflex responses were studied in the legs: the H reflex was examined in the soleus muscles, the T wave in the soleus and biceps brachii muscles, and the F wave in the posterior tibial and median nerves. Somatosensory evoked cortical potentials recorded on the scalp were tested bilaterally by the stimulation of the median nerve at the wrist and the posterior tibial nerve at the ankle. The blink reflex was studied by electrical stimulation of the supraorbital nerve. Other neurological disorders (such as central nervous system, medullary, or muscular processes) were ruled out by differential diagnosis and, when necessary, by EMG, nerve or muscle biopsy, cerebrospinal fluid analysis, measurement of somatosensory evoked potentials and neuroimage techniques. Patients in whom the electrophysiological studies showed signs of peripheral neuropathy were selected as the study population and those with normal results as unmatched controls.

The evolution of neuropathy was classified as acute, subacute, chronic progressive or relapsing (17). The clinical outcome was assessed using the Modified Oxford Handicap Scale (MOHS) (18): 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. MOHS was evaluated at the diagnosis of peripheral neuropathy and at the end of follow-up. Patients were classified into 2 groups corresponding to minor-moderate disability (MOHS score ≤2) and severe disability (MOHS >2), respectively, according to previous studies (12).

Statistical analysis

The comparisons between dichotomic variables and the variable "type of neuropathy" (axonal polyneuropathy, pure sensory neuronopathy and mononeuropathy multiplex) were made using a chi-square comparison of a 2x3 table, including calculation of the Pearson chi-square (which is specified as the *p*-value in the tables), the likelihood-ratio chi-square and Yates' corrected chi-square (continuity correction). Continuous variables were analysed with the Student's *t*-test in large samples of similar variance, with results indicated as mean±standard error of the mean (SEM), and with the nonparametric Mann-Whitney U-test for small samples, with results indicated as median and interquartiles. A two-tailed value of $p<0.05$ was taken to indicate statistical significance. When several independent variables appeared to have statistical significance in the univariate analysis, a multivariate logistic regression analysis was performed using a backward conditional stepwise method allowed adjustment for age, sex and the variables that were statistically significant in the univariate analysis. The statistical analysis was performed with the SPSS programme (SPSS, Chicago, IL).

Results

a) Classification of peripheral neuropathies

Nerve conduction studies were carried out in 158 (28%) of the 563 patients included in our cohort: 102 patients showed signs of peripheral neuropathy, 49 patients had results within normal limits and 7 patients had other types of neuromuscular diseases (myelopathy in 2 cases and myopathy in 5). Of the 102 patients with peripheral neuropathy, neuropathy was attributed to etiologies other than SS in 11 patients (including radiculopathy, neoplasia, chemotherapy and amyloidosis), while 36 patients had mononeuropathies due to focal entrapments.

Autoimmune neuropathies related to primary SS were diagnosed in 55/563 (10%) patients, including axonal sensorimotor polyneuropathy (n=24), pure sensory neuronopathy (n=15), mononeuropathy multiplex (n=15) and demyelinating polyradiculoneuropathy (n=1). There were 48 females and 7 males, with a mean age of 57.9 years at SS diagnosis and 60.1 years at diagnosis of polyneuropathy. With respect to the time of diagnosis of the neuropathy, which was defined as the first pathologic EMG result, 29 (53%) patients were diagnosed before diagnosis of primary SS; in the remaining SS patients (47%), peripheral neuropathy was diagnosed during the SS course.

Table I summarises the principal differences in the main clinical features and associated processes between SS patients with autoimmune peripheral neuropathies and the control group (SS patients with normal nerve conduction studies). Patients with autoimmune neuropathies were more frequently male (13% *vs*. 0%, $p=0.013$) and had a higher frequency of vasculitis (37% *vs*. 6%, $p<0.001$), cryoglobulinaemia (24% *vs*. 7%, $p=0.027$), hypocomplementaemia (41% *vs*. 12%, $p=0.002$) and monoclonal gammopathy (30% *vs*. 6%, $p=0.008$) in comparison with the control group. Multivariate analysis showed that gender ($p=0.002$) and vasculitis ($p<0.001$) were significantly associated with peripheral neuropathy.

b) Characterisation of SS-related peripheral neuropathies

– Axonal sensorimotor polyneuropathy.

There were 19 females and 5 males, with a mean age of 65.1 years at SS diagnosis and 66.5 years at diagnosis of polyneuropathy. Axonal polyneuro-

Table I. Principal differences in the main clinical features and associated processes between SS patients with autoimmune peripheral neuropathies and the control group (SS patients with normal nerve conduction studies).

	SS-related peripheral neuropathy n=54	SS with normal electromyogram n=49	Bilateral *p*-value
Gender (male)	7 (13%)	0 (0%)	**0.013***
Age at SS diagnosis (mean ± SEM)	57.80 ± 2.08	52.53 ± 2.07	0.077
Xerostomia	54 (100%)	48 (98%)	0.476
Xerophthalmia	52 (96%)	49 (100%)	0.496
Positive ocular tests	50/52 (96%)	40/44 (91%)	0.408
Severe involvement in parotid scintigraphy (grades III-IV)	25/42 (57%)	25/40 (62%)	0.824
Positive salivary gland biopsy	30/31 (97%)	25/31 (81%)	0.104
Parotid enlargement	16 (30%)	7 (14%)	0.096
Articular involvement	28 (52%)	34 (69%)	0.075
Raynaud phenomenon	9 (17%)	12 (24%)	0.341
Vasculitis	20 (37%)	3 (6%)	**<0.001***
Interstitial lung disease	5 (9%)	4 (8%)	1.000
Renal involvement	4 (7%)	1 (2%)	0.326
CNS involvement	17 (31%)	7 (14%)	0.061
Autoimmune liver disease	6 (11%)	2 (4%)	0.274
Pancreatitis	3 (6%)	0 (0%)	0.244
Thyroiditis	21/51 (41%)	17/48 (35%)	0.680
Neoplasia	9 (17%)	4 (8%)	0.243
ESR > 50 mm/h	21/53 (40%)	16/45 (36%)	0.835
Anaemia (Hb < 11 g/dL)	29 (54%)	19 (39%)	0.167
Leukopenia (<4000/mm^3)	14 (26%)	9 (18%)	0.478
Thrombocytopenia (<150000/mm^3)	12 (22%)	6 (12%)	0.205
Mean circulating gammaglobulins (%)	21.52 ± 1.17	19.53 ± 1.03	0.211
Antinuclear antibodies	43 (80%)	43 (88%)	0.300
Rheumatoid factor	27 (50%)	27 (55%)	0.694
Anti-Ro/La antibodies	28 (52%)	27 (55%)	0.844
Fulfillment of 2002 criteria	43 (80%)	41 (84%)	0.622
Monoclonal gammopathy	12/40 (30%)	2/35 (6%)	**0.008**
Cryoglobulins	12/50 (24%)	3/44 (7%)	**0.027**
Hypocomplementemia	22 (41%)	6 (12%)	**0.002**

*Statistically significant in the multivariate adjusted model.

pathy was diagnosed prior to SS in 6 patients (a mean of 3.83 years before the diagnosis of SS, range 1–10 years), simultaneously with SS in 5 patients and posterior to the diagnosis of SS in the remaining 13 patients (a mean of 5.08 years later, range 1–19 years). Clinical manifestations included paraesthesiae/numbness (n=19), distal pain (n=7) and weakness (n=3); neurological symptoms involved the lower (n=24) and upper (n=5) limbs. Twelve patients were treated with oral corticosteroids (0.5–1 mg/kg/day). Immunosuppressive agents were added in 6 cases (cyclophosphamide and azathioprine, 3 cases each) and intravenous immunoglobulins in one. Seven patients were treated symptomatically (gabapentin or carbamazepine) and 5 received no treatment due to advanced age and/or mild symptoms. Patients were followed for a mean of 73 months. With respect to neuropathy, 21 patients showed neurological improvement or stabilisation (MOHS ≤ than at diagnosis) and 3 worsened (MOHS > than at diagnosis). Nerve conduction studies were repeated in 14 patients after a mean follow-up of 29 months: 10 patients showed no significant changes, 3 progression of neuropathy and one patient presented normalisation of the electrophysiological studies. The main associated processes developed during the follow-up were systemic vasculitides (n=5), cardiovascular disease (n=2), autonomic dysautonomy (n=1) and neoplasia (n=1). Five patients died due to infection (n=3), systemic cryoglobulinaemia (n=1) and myocardial infarction (n=1).

– *Mononeuropathy multiplex*. There were 14 females and one male, with a mean age of 54.1 years at SS diagnosis and 55.9 years at diagnosis of neuropathy. Mononeuropathy multiplex was diagnosed prior to SS in 4 patients (a mean of 2 years before the diagnosis of SS, range 1–3 years), simultaneously with SS in 5 patients and posterior to the diagnosis of SS in the remaining 6 patients (a mean of 5.83 years later, range 1–20 years). Clinical manifestations included paraesthesiae/numbness (n=13), weakness (n=1) and distal pain (n=2); neurological symptoms involved the lower (n=15) and upper (n=7) limbs. All patients were treated with oral corticosteroids (0.5–1 mg/kg/day) and immunosuppressive agents were added in 6 cases (cyclophosphamide in 3, mycophenolate in 2, azathioprine in 1), except one (due to advanced age and mild symptoms). Patients were followed for a mean of 84 months. With respect to neuropathy, 13 patients showed neurological improvement or stabilisation (MOHS ≤ than at diagnosis) and 2 worsened (MOHS > than at diagnosis). Nerve conduction studies were repeated in 10 patients after a mean follow-up of 24 months: 5 patients showed no significant changes, one patient evolved to polyneuropathy, one showed progression and three patients presented normalisation of results. The main associated processes developed during the follow-up were systemic vasculitides (n=6) and neoplasia (n=3). Five patients died due to infection (n=1), systemic cryoglobulinaemia (n=1), lung cancer (n=1), renal failure (n=1) and chronic pulmonary disease (n=1).

– *Pure sensory neuronopathy*. There were 14 females and one male with a mean age of 49.7 years at SS diagnosis and 50 years at diagnosis of neuronopathy. Pure sensory neuronopathy was diagnosed prior to SS in 4 patients (a mean of 3.25 years before the diagnosis of SS, range 1–6 years), simultaneously with SS in 6 patients and posterior to the diagnosis of SS in the remaining 5 patients (a mean of 3.4 years later, range 1–8 years). Clinical manifestations included numbness and paresthesias (15 patients), trigeminal neuropathy (6 patients), ataxia (4 patients) and Adie's pupil (3 patients). Severe involvement of the upper extremities was associated with pseudoathetosis and

Table II. Principal differences in the main clinical features and associated processes between patients with axonal polyneuropathy (PN), pure sensory neuronopathy (PSN) and mononeuropathy multiplex (MM); *p*-values indicate significant differences with respect to the other two types of neuropathies.

	PN n=24	PSN n=15	MM n=15
Gender (male)	5 (21%)	1 (7%)	1 (7%)
Age at SS diagnosis (mean±SEM)	65.12±2.31	**49.73±3.53**$^{0.003}$	54.13±4.53
Xerostomia	24 (100%)	15 (100%)	15 (100%)
Xerophthalmia	22 (92%)	15 (100%)	15 (100%)
Positive ocular tests	23/24 (96%)	14/15 (93%)	13/13 (100%)
Severe involvement in parotid scintigraphy (grades III-IV)	9/20 (45%)	7/12 (58%)	**9/10 (90%)**$^{0.031}$
Positive salivary gland biopsy	12/13 (92%)	11/11 (100%)	7/7 (100%)
Parotid enlargement	5 (21%)	5 (33%)	6 (40%)
Articular involvement	14 (58%)	5 (33%)	9 (60%)
Arthritis	4 (17%)	2 (13%)	4 (27%)
Raynaud phenomenon	**1 (4%)**$^{0.033}$	4 (27%)	4 (27%)
Vasculitis	6 (25%)	5 (33%)	**9 (60%)**$^{0.03}$
Interstitial lung disease	2 (8%)	0 (0%)	3 (20%)
Renal involvement	1 (4%)	1 (7%)	2 (13%)
CNS involvement	5 (21%)	**8 (53%)**$^{0.049}$	4 (27%)
Autoimmune liver disease	1 (4%)	2 (13%)	3 (20%)
Pancreatitis	1 (4%)	1 (7%)	1 (7%)
Thyroiditis	9 (38%)	7 (47%)	5 (33%)
Neoplasia	4 (17%)	3 (20%)	2 (13%)
ESR > 50 mm/h	8 (33%)	**2 (14%)**$^{0.017}$	11 (73%)
Anaemia (Hb < 11 g/dL)	13 (54%)	**4 (27%)**$^{0.013}$	12 (80%)
Leukopenia (<4000/mm3)	4 (17%)	4 (27%)	6 (40%)
Thrombocytopenia (<150000/mm3)	7 (29%)	2 (13%)	3 (20%)
Mean circulating gammaglobulins (%)	19.87±1.75	19.30±1.89	**26.12±2.17**$^{0.04}$
Antinuclear antibodies	20 (83%)	**9 (60%)**$^{0.036}$	14 (93%)
Rheumatoid factor	**7 (29%)**$^{0.014}$	10 (67%)	10 (67%)
Anti-Ro/La	10 (42%)	8 (53%)	10 (67%)
2002 criteria	**16 (67%)**$^{0.046}$	15 (100%)	12 (80%)
Monoclonal gammopathy	7/19 (37%)	1/10 (10%)	4/11 (36%)
Cryoglobulins	5/22 (23%)	1/14 (7%)	6/14 (43%)
Hypocomplementemia	10 (42%)	**3 (20%)**$^{0.05}$	9 (60%)

loss of spatial discrimination in 5 patients. All patients suffered loss of proprioceptive and kinesthetic sensitivity. Twelve patients were treated with oral corticosteroids (0.5–1 mg/kg/day) and immunosuppressive agents were added in 4 cases (cyclophosphamide in 2, azathioprine in 2). Four patients were treated with intravenous immunoglobulins and 2 with rituximab. In spite of therapy, the neuropathy remained insidious and chronically progressive in most patients, although minor improvement or stabilisation was observed in patients treated with intravenous immunoglobulins and rituximab. Patients were followed for a mean of 106 months. With respect to neuropathy, 8 patients showed neurological improvement or stabilisation (MOHS ≤ than at diagnosis) and 7 worsened (MOHS > than at diagnosis). Nerve conduction studies were repeated in 9 patients after a mean follow-up of 77 months: 3 patients showed no significant changes and 6 progression of neuropathy. The main associated processes developed during the follow-up were cardiovascular disease (n=2) and autonomic dysautonomy (n=2). Two patients died due to infection (n=1) and myocardial infarction (n=1).

c) Comparison between the main types of SS-related peripheral neuropathy.

Table II summarises the principal differences in the main clinical features and associated processes between patients with axonal polyneuropathy, mononeuropathy multiplex and pure sensory neuronopathy. In comparison with the other two types of neuropathy, patients with mononeuropathy multiplex had a higher prevalence of severe scintigraphic involvement (p=0.031) and vasculitis (p=0.03), those with axonal polyneuropathy a lower prevalence of Raynaud phenomenon (p=0.033), RF (p=0.036) and fulfillment of the 2002 criteria (p=0.046) and a higher prevalence of cardiovascular risk factors (p=0.006) and hypertension (p=0.007), and patients with pure sensory neuronopathy a higher frequency of CNS involvement (p=0.049) and a lower prevalence of high ESR (p=0.017), anaemia (p=0.013), ANA (p=0.036) and hypocomplementaemia (p=0.05).

Survival was significantly reduced in patients with peripheral neuropathy (especially in those with mononeuropathy multiplex and axonal polyneuropathy) in comparison with the control group (Fig. 1, log rank =0.001).

Discussion

Peripheral neuropathy is a common neurological disease with an overall prevalence of around 2%, rising to 8% in people aged >55 years (19). A combination of clinical findings, electrodiagnostic tests and personalised laboratory investigations allows most neuropathies to be categorised by subtype and etiology, which permits rational assessment of the prognosis and a tailored therapeutic approach. In primary SS, one of the systemic autoimmune diseases most often associated with peripheral neuropathy, the wide range of peripheral nerve diseases makes clear definitions of the different subtypes of neuropathy essential. Electrodiagnostic tests show the predominant pathophysiology (demyelinating or axonal) and the anatomical distribution (mononeuropathy, mononeuropathy multiplex or polyneuropathy) (6). We found a prevalence of peripheral neuropathy of 10% in our primary SS patients, using the same classification stated by Delalande *et al*. (12) into four electrodiagnostic patterns. In contrast, a recent study (13) has classified neuropathies according to clinical patterns (ataxic neuropathy, nonataxic sensory neuropathy and sensorimotor neuropathy), thus limiting comparison between the studies. However, classification of peripheral neuropathies according to electrodiagnostic patterns provides a more accurate profile of the type of neuropathy and the possible causes, and may suggest more specific treatment options (6). The clearly-differentiated patterns of

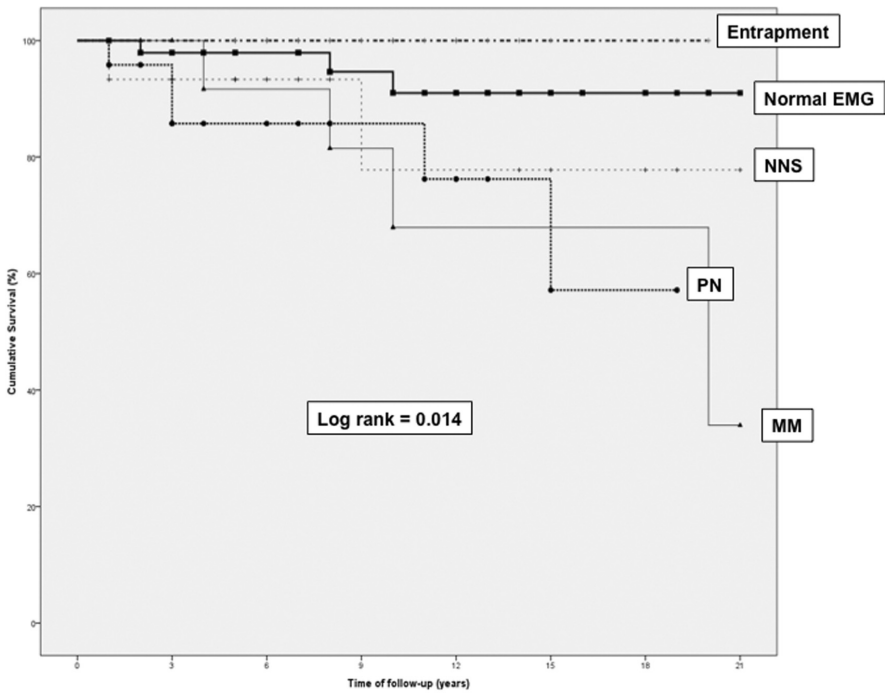

Fig. 1. Kaplan-Meier survival curves according to the results of the electrodiagnostic tests at diagnosis of neuropathy.

expression of the three main peripheral neuropathies identified in our cohort (axonal polyneuropathy, pure sensory neuronopathy and mononeuropathy multiplex) suggests the utility of classifying peripheral neuropathies according to the electrodiagnostic findings.

As in the general population, the most common type of polyneuropathy in our patients with primary SS was axonal symmetrical polyneuropathy, whose differential diagnosis is broad. The classification of polyneuropathy as demyelinating or axonal provides a more accurate etiological approach. Demyelinating polyneuropathy may be inherited (Charcot-Marie-Tooth disease) or acquired (CIDP or paraproteinaemic polyneuropathy), while symmetrical axonal sensorimotor polyneuropathy is mainly related to autoimmune, endocrine or metabolic diseases, or external causes (drugs, toxins). Chronic polyneuropathy is classified as idiopathic in 20–25% of patients (6). Our study reports the largest number of patients with SS-related axonal polyneuropathy from a single centre: of the 27 patients, polyneuropathy clearly attributed to etiologies other than primary SS in only 3 cases. The remaining 24 patients had a characteristic profile consisting of older age, a low frequency of systemic/immunological SS-related features and fulfilment of the 2002 criteria, and a high frequency of monoclonal gammopathy and cardiovascular risk factors. Some of these features (age >55 years, monoclonal gammopathy, metabolic disease) are associated with a higher risk of peripheral neuropathy in the general population (6). This suggests that the etiology of axonal polyneuropathy in primary SS may extend beyond the autoimmune disease itself. Therefore, specific evaluation of possible underlying haematological disease, combined with monitoring and control of cardiovascular risk factors, should be recommended in SS patients with axonal polyneuropathy.

In this study, axonal polyneuropathy was the type of neuropathy with the lowest frequency of SS-related immunological markers (Ro/La, RF), as reported in previous studies (12, 13, 20, 21). This may influence the diagnostic approach, especially because neuropathy was diagnosed before or simultaneously with SS diagnosis in nearly half these patients. Because the fulfilment of SS criteria requires positive anti-Ro/La or a salivary biopsy, a biopsy would therefore be mandatory to confirm SS in patients presenting with axonal polyneuropathy, sicca features and negative Ro/La antibodies. Taking into account the predominantly good evolution found in our patients with SS-related axonal polyneuropathy (only 12% progressed during the followup), a conservative approach may be recommended at diagnosis, centring on controlling neuropathic symptoms and associated cardiovascular risk factors. Treatment with prednisone 60 mg daily may be initiated especially in patients with an acute/severe presentation, although the aim should be to withdraw treatment as soon as possible. If the response is inadequate or adverse effects are not tolerated, the next step may be IVIG or rituximab, combined with a renewed search for associated medical conditions unrelated to primary SS.

Pure sensory neuropathy (PSN) affected less than 3% of our primary SS patients. Both the presentation and the patient profile were clearly different from those of patients with axonal polyneuropathy. Clinically, PSN was characterised by asymmetrical sensory involvement, usually starting in the upper limbs and predominantly affecting kinesthesic and vibratory sensations, with some patients also having associated Adie's pupil or trigeminal sensory involvement. We described the outcome of 15 patients with primary SS and PSN and found similar results to previous studies (12, 22, 23). PNS preceded or coincided with the diagnosis of SS in two thirds of cases, therefore, SS should be discarded in all patients presenting with PNS, including both a salivary biopsy and anti-Ro/La antibody testing for the reason described above. At the onset of neuropathy, sensory involvement may be unilateral and may mimic lesions in the spinal cord or thalamus, in which case magnetic resonance studies may be required. SS patients with PNS were overwhelmingly female, had a younger age at diagnosis of SS and a lower frequency of analytical markers often associated with chronic inflammatory processes (high ESR, anaemia) and immunological markers (hypergammaglobulinaaemia, ANA and hypocomplementaaemia). PSN was chronic and insidious

in most patients, with a poor response to treatment with corticosteroids or immunosuppressive agents, although stabilisation of symptomatology (spontaneously or after treatment with intravenous immunoglobulins or rituximab) was observed (24-26). The importance of the diagnosis of PSN lies in the fact that it may precede the diagnosis of primary SS, it is not associated with systemic vasculitis, and treatment with standard immunosuppression is often ineffective (27).

As recommended in the general guidelines to manage peripheral neuropathies (6), the diagnosis of patients with suspected multiplex mononeuropathy is also urgent in primary SS, since many of these patients have vasculitis (in our series, nearly two thirds of cases, mainly associated with cryoglobulinaaemia). The main symptoms at presentation included distal paresthesiae, with painful and/or burning sensations in the lower limbs, which often worsens at night. The profile of the SS patient with multiplex mononeuropathy is clearly different from that of patients with other types of peripheral neuropathy, not only due to the strong association with underlying vasculitis, but also to the high prevalence of severe parotid involvement, extraglandular features, cytopenias and immunological markers. This is consistent with a patient profile of "high systemic activity". In contrast to polyneuropathies, the therapeutic response of patients with multiplex mononeuropathy to corticosteroids and immunosuppressive agents was excellent (28). However, this was not associated with a better prognosis, but rather the contrary. SS patients with multiplex mononeuropathy had the lowest survival rate, due not to neuropathic involvement, but to the underlying systemic vasculitis. This emphasises the need for early identification of neurological symptoms suggestive of multiplex mononeuropathy and initiation of therapy.

Possible concerns in observational retrospective studies include that objective studies are not available for all patients during the follow-up and selection bias (in our study, only symptomatic patients with altered EMG results were included). This patient profile excluded patients with small fiber neuropathy (in whom EMG is normal and diagnosis is carried out by cutaneous biopsy) and makes it impossible to extrapolate our results to the whole population of primary SS patients. In addition, application of subjective scores to evaluate neurological outcomes has the limitation of the possible influence of other processes associated with SS such as fibromyalgia, a diagnosis that was excluded in our patients with SS-related peripheral neuropathy. The retrospective design and the wide variety of therapies used also limits an adequate evaluation of the neurological response to the treatment. Nevertheless, in spite of these limitations, we believe that the recruitment of 55 patients with SS-related peripheral neuropathy is significant and permits useful information on the characteristics and outcomes to be obtained.

Peripheral neuropathy is one of the most frequent extraglandular manifestations of primary SS and was found in 10% of our patients. Electrodiagnostic tests confirmed peripheral neuropathy in two out of three patients in whom there was clinical suspicion of peripheral neuropathy. Axonal sensorimotor neuropathy was the most frequent type of neuropathy, pure sensory neuropathy the most disabling in the long-term and multiplex mononeuropathy having the poorest survival. Although therapeutic management may be often discouraging (especially in pure sensory neuronopathy), early identification of the type of neuropathy and the associated processes (vasculitis, cardiovascular disease) is essential in order to improve the prognosis and outcomes of SS patients affected by peripheral neuropathy.

Acknowledgements

We wish to thank David Buss for his editorial assistance.

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