

# Sjögren Syndrome-Associated Small Fiber Neuropathy

## Characterization From a Prospective Series of 40 Cases

Damien Sène, MD, PhD, Patrice Cacoub, MD, François-Jérôme Authier, MD, PhD, Julien Haroche, MD, PhD, Alain Créange, MD, David Saadoun, MD, PhD, Zahir Amoura, MD, Pierre-Jean Guillausseau, MD, and Jean-Pascal Lefaucheur, MD, PhD

**Abstract:** We conducted the current study to analyze the clinical, immunologic, and neurophysiologic features of primary Sjögren syndrome (pSS)-associated sensory small fiber neuropathies (SFNs). Forty consecutive pSS patients with SFN were included. SFN was defined by the presence of suggestive sensory painful symptoms with normal nerve conduction studies and abnormal neurophysiologic tests for small nerve fibers or a low intraepidermal nerve fiber density at skin biopsy. Included patients were compared to 100 pSS patients without peripheral neuropathy.

SFN patients were mainly female (92.5%). Age at pSS diagnosis was  $55.3 \pm 13.1$  years, and at SFN diagnosis,  $58.9 \pm 11.8$  years, with a median time to SFN diagnosis after symptom onset of 3.4 years. Clinical symptoms included burning pains (90%), numbness (87.5%), tingling (82.5%), pins and needles (72.5%), electric discharges (70%), and allodynia (55%). Dysautonomia included vasomotor symptoms (66%) and hyperhidrosis (47%). Abnormal neurophysiologic tests included laser evoked potentials (97.5%), thermal quantitative sensory testing (67.5%), and sympathetic skin reflex (40%). A skin biopsy revealed low intraepidermal nerve fiber density in 76% of the 17 tested patients.

Compared to the 100 pSS patients without peripheral neuropathy, the 40 pSS-SFN patients were older at pSS diagnosis ( $55.3 \pm 13.1$  vs.  $49.5 \pm 14.9$  yr;  $p = 0.03$ ), and more often had xerostomia (97.5% vs. 81%;  $p = 0.01$ ) and arthralgia (82.5% vs. 65.0%;  $p = 0.04$ ). Immunologically, they were characterized by a lower prevalence of serum B-cell activation markers, that is, antinuclear antibodies (65% vs. 85%;  $p = 0.01$ ), anti-SSA (42.5% vs. 71%;  $p = 0.002$ ), and anti-SSB (17.5% vs. 39%;  $p = 0.017$ ); rheumatoid factor (32.5% vs. 66%;  $p = 0.0005$ ); and hypergammaglobulinemia (35% vs. 62%;  $p = 0.005$ ).

In conclusion, we report the main features of SFN in patients with pSS, the first such study to our knowledge. Our results show that patients with pSS-associated SFN are characterized by an older age at pSS diagnosis and a distinctive immunologic profile hallmarked by a lower frequency of serum B-cell activation markers.

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**Abbreviations:** ANA = antinuclear antibodies, CI = confidence interval, DN4 = “Douleur Neuropathique 4” questionnaire, ENMG = electroneuromyographic examination, IENFD = intraepidermal nerve fiber density, LEP = laser evoked potential, MRI = magnetic resonance imaging, NCS = nerve conduction studies, OR = odds ratio, pSS = primary Sjögren syndrome, QST = quantitative sensory testing, SFN = small fiber neuropathy, SSR = sympathetic skin reflex.

### INTRODUCTION

Primary Sjögren Syndrome (pSS) is a systemic autoimmune disease characterized by glandular involvement and systemic extraglandular organ involvement, including skin, lung, kidney, peripheral, and central nervous system.<sup>14</sup> Peripheral neurologic involvement is reported in nearly 20% of patients (range, 5%–60%).<sup>1,15,17,20,29,54</sup> The diagnosis is usually based on clinical neurologic symptoms and signs, and confirmed by electroneuromyographic examination (ENMG). However, conventional ENMG assesses only large nerve fibers (diameter  $\geq 5$ – $7 \mu\text{m}$ ) and remains normal in patients with neuropathy selectively affecting the small nerve fibers (diameter  $< 5$ – $7 \mu\text{m}$ ), which condition is typically revealed by the occurrence of subjective sensory symptoms, mostly painful, including burning, numbness, prickling, paresthesia and dysesthesia, or signs of dysautonomia. The diagnosis of a pure small fiber neuropathy (SFN) requires specific histologic or neurophysiologic examinations. The histologic investigation is based on the evaluation of the intraepidermal nerve fiber density (IENFD) by skin biopsy after immunostaining with antineuropeptide (peptide gene product 9.5) antibodies.<sup>9,30</sup> Neurophysiologic investigations include the recording of evoked potentials to nociceptive (laser) stimulation (LEP), quantitative sensory testing (QST) to thermal stimuli, and autonomic nervous system testing, such as sympathetic skin reflex (SSR) recording.<sup>6,33,34</sup> Due to the limited availability of these procedures, SFN has scarcely been evaluated among pSS patients, and only a few series have been published to date.<sup>4,13,20</sup> We previously reported 11 cases of pSS-associated SFN from a series of 120 pSS patients, which represented 30% of the 30 pSS-associated peripheral neuropathies, and 56% of the pSS-associated nonataxic sensory peripheral neuropathies.<sup>54</sup> On the other hand, pSS might represent 9%–30% of causes of pure SFN.<sup>9,22</sup>

Given the limited number of reported cases, and the lack of characterization of the main features of pSS-associated SFN, we designed a study to investigate systematically our pSS patients presenting with symptoms suggestive of SFN and having a normal ENMG. We report herein the clinical, laboratory, neurophysiologic, and histologic features of a consecutive series of 40 pSS patients whom we have characterized as having pure SFN, in comparison with a control group of 100 pSS patients

From the Service de Médecine Interne 2, AP-HP, Hôpital Lariboisière, Université Paris Diderot-Paris 7, Paris (D. Sène, PJG); Service de Médecine Interne 2, AP-HP, Hôpital Pitié-Salpêtrière, Paris, Université, Pierre et Marie Curie-Paris 6, Paris (PC, JH, D. Saadoun, ZA); Centre de Référence des Maladies Neuromusculaires Garches-Necker-Mondor-Hendaye, AP-HP, Hôpital Henri Mondor; INSERM U955, Equipe 10, Université Paris Est-Créteil, Créteil (FJA); and Service de Neurologie (AC) and Service de Physiologie-Explorations Fonctionnelles (JPL), APHP, Hôpital Henri Mondor, Créteil, Université Paris Est-Créteil, Créteil; France.

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Reprints: Dr Damien Sène, MD, PhD, Service de Médecine Interne 2, Hôpital Lariboisière, 2 Rue Ambroise Paré 75010 Paris, France (e-mail: damien.sene@lrp.aphp.fr).

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who did not present neurologic symptoms suggestive of SFN at the time of their last clinical evaluation.

## PATIENTS AND METHODS

Starting in March 2009, we set up the SFINESS study (Small Fiber Neuropathy in Sjögren Syndrome), based on a systematic clinical and neurophysiologic investigation of patients with suggestive neurologic symptoms of SFN and a normal ENMG. Until March 2012, we prospectively included 40 patients characterized as having pSS-associated SFN. For the control group, we collected 100 pSS patients who were followed in the Pitié-Salpêtrière (Paris, France) and Lariboisière (Paris, France) tertiary university internal medicine departments, and who did not present any suggestive clinical symptom of SFN or peripheral neuropathy. All patients fulfilled the American-European Consensus Group (AECG) criteria for pSS.<sup>58</sup> The study was approved by the Ile-de-France VI (Pitié-Salpêtrière University Hospital, Paris, France) ethical committee, and each subject gave written informed consent before SFN investigation.

### Clinical Neurologic Investigation of Patients With pSS-Associated SFN

As aforementioned, the presence of subjective sensations, mostly painful, such as burning, painful cold, electric discharge, tingling, pins and needles, numbness, or itching, was considered suggestive of SFN and recorded. Clinical examination searched for allodynia to mechanical stimuli and for objective deficit affecting any sensory modality (pain, warm, cold, touch, vibration, and proprioception), the motor system (weakness and atrophy), or the tendon reflexes (especially ankle jerks). All patients completed a questionnaire for dysautonomic signs and the “Douleur Neuropathique 4” (DN4) questionnaire for the presence of neuropathic pain.<sup>2</sup>

### Electroneuromyography (ENMG)

Conventional motor and sensory nerve conduction studies (NCS) were performed in the median, ulnar, peroneal, tibial, and sural nerve territories of all patients with sensory symptoms. In addition, electromyographic activity was studied in various muscles using a standard concentric needle.<sup>41</sup>

### Small Fiber Neurophysiologic Investigation

Neurophysiologic investigation of small fibers was performed by 1 of the authors (JPL) in all patients with suggestive symptoms of SFN and a normal ENMG. The tests included the measurements of LEP (amplitude and latency) and QST (warm and cold detection thresholds) using normal values established in our laboratory, as previously described.<sup>33,34</sup> The neurophysiologic evaluation of the autonomic system involvement was performed in all patients using the SSR (amplitude and latency) previously described.<sup>33,34</sup> In case of abnormal results, brain and spine magnetic resonance imaging (MRI) was performed to exclude a central cause of such abnormal results.

### Evaluation of IENFD by Skin Biopsy

The evaluation of IENFD by skin biopsy was not routinely available at the beginning of the study. Thus, only 17 patients were evaluated for IENFD by 1 of the authors (FJA). The skin biopsy was performed using a 3-mm punch at the distal leg (10 cm above lateral malleolus) and the proximal lateral thigh (15 cm below anterior superior iliac spine). The IENFD evaluation was performed on 50- $\mu$ m frozen sections after visualization of axons by immunofluorescence technique with polyclonal antibodies to protein gene product 9.5, as described.<sup>9</sup> The lower

limit of normal values was set at 7.6/mm at the distal leg, and 12.8/mm at the thigh, as proposed by Devigili et al.<sup>9</sup>

### Small Fiber Neuropathy Definition

SFN was diagnosed when patients had clinical signs and symptoms of small fiber impairment, with distribution consistent with peripheral neuropathy (length- or non-length-dependent neuropathy) without any ENMG abnormalities but alteration in small fiber neurophysiologic investigation and/or reduced IENFD in skin biopsy.

### Exclusion Criteria

Particular attention was paid to exclude patients with neuropathic pain due to alternative possible causes other than SFN. Thus, patients were excluded in the presence of 1) any clinical sign of large sensory fiber impairment (light touch and/or vibratory and/or proprioceptive sensory loss and/or absent deep tendon reflexes); 2) any clinical sign of motor fiber impairment (muscle waste and/or weakness); 3) any abnormality on sensory or motor NCS; 4) any clinical or ENMG feature of painful radiculopathy; 5) any typical presentation of fibromyalgia syndrome, based on the classical tender points, although SFN can be observed in patients with fibromyalgia syndrome;<sup>57</sup> 6) any risk factor for SFN (diabetes mellitus, glucose intolerance, systemic amyloidosis, systemic vasculitis, human immunodeficiency virus (HIV) infection, alcoholism, paraneoplastic syndrome, celiac disease, B9 and B12 vitamin deficiency, and sarcoidosis).

### Immunochemistry

Antinuclear antibodies (ANA) were detected using indirect immunofluorescence on HEp-2000 cells (Immuno Concepts, San Diego, CA), with a positive result defined as  $\geq 1:80$ . Anti-extractable nuclear antigen antibodies (anti-ENA), including anti-SSA (anti-Ro 52/60) and anti-SSB (anti-La), were detected using a multiplexed microparticle-based Luminex immunoassay (AtheNA Multi-Lyte, Ingen, Antony, France). Serum cryoglobulin detection and immunochemical typing were performed with a validated immunoblotting method.<sup>45</sup> Rheumatoid factor was determined by ELISA (BMD, France), and results  $>20$  IU/mL were considered positive. Dosage of serum immunoglobulins (IgG, IgA, IgM) was performed by nephelometry (BNII, Dade-Behring). The following laboratory parameters were used as serum markers of chronic B-cell activation: ANA, anti-SSA (Ro), anti-SSB (La), rheumatoid factors, and gammaglobulin levels.<sup>54</sup>

### Statistical Analysis

Categorical variables were compared using the Fisher exact test, and continuous variables using the Mann-Whitney test. On the basis of the results of univariate analyses, variables were included in multivariate analyses using a stepwise multiple logistic regression analysis to assess independent associations. The level of significance (p value) was set at 0.05 (2-tailed). All analyses were performed using MedCalc software version 12.3.0.0 (Mariakerke, Belgium).

## RESULTS

### Clinical Features of 40 Patients With pSS-associated SFN

Clinical and laboratory features of the 40 patients with pSS-associated SFN are reported in Tables 1 and 3. SFN patients were mainly female (92.5%), and age at pSS diagnosis was  $55.3 \pm 13.1$  years. All patients had xerophthalmia, and

**TABLE 1.** Clinical and Neurophysiologic Features of p-SS Patients With Small Fiber Neuropathy (SFN)

Population (n=40)	No. (%)
Female	37 (92.5)
Age at SFN symptom onset, yr*	53.6 ± 12.9
Age at SFN diagnosis, yr*	58.9 ± 11.8
Time to SFN diagnosis, yr*	5.4 ± 6.3 (median = 3.4)
SFN revealing pSS	32 (80)
SFN-associated painful symptoms	
Burning	36 (90)
Numbness	35 (87.5)
Tingling	33 (82.5)
Pins and needles	29 (72.5)
Electric discharges	28 (70)
Allodynia	22 (55)
Painful cold	15 (37.5)
Itching	15 (37.5)
Touch hypoesthesia	12 (30)
Pricking hypoesthesia	4 (10)
Mean DN4 score*	5.7 ± 1.4
Distribution	
Lower limbs	40 (100)
Upper limbs	36 (90)
Trunk	12 (30)
Head	11 (27.5)
Neurovegetative symptoms	
Vasomotor symptoms (erythralgia, hot flash)	25/38 (65.8)
Chronic constipation	19/38 (50)
Hyperhidrosis	18/38 (47.4)
Dysuria	18/38 (47.3)
Trophic disorders (depilation)	10/38 (26.3)
Hypotension orthostatic	6/38 (15.8)

\*Mean±standard deviation.

39 patients (97.5%) had xerostomia. A positive lip biopsy, that is, showing focal lymphocytic sialadenitis with a focus score  $\geq 1$  focus/4 mm<sup>2</sup>, was present in 28 of 34 patients (82%). Four patients (10%) had parotid involvement. Extraglandular manifestations included arthralgia for 33 patients (82.5%), purpura for 3 patients (7.5%), central nervous system involvement for 3 patients (7.5%), lung involvement for 2 patients (5%), and B-cell non-Hodgkin lymphoma for 1 patient (2.5%). Immunologic abnormalities included positive ANA for 26 patients (65%), anti-SSA antibodies for 17 patients (42.5%), anti-SSB antibodies for 7 patients (17.5%), and rheumatoid factor for 13 patients (32.5%). Hypergammaglobulinemia was present in 14 patients (35%).

SFN symptoms preceded and revealed pSS in 32 patients (80%). The age at SFN symptom onset was 53.6 ± 12.9 years, and 58.9 ± 11.8 years at SFN diagnosis. Median time to SFN diagnosis after symptom onset was 3.4 years (95% confidence interval [CI], 2.0–4.7 yr), ranging from 0.2 to 26.8 years. SFN was clinically characterized by different types of sensory symptoms, mainly burning pains (90%), numbness (87.5%), tingling (82.5%), pins and needles (72.5%), and electric discharges (70%). Mechanical allodynia, among the most suggestive symptoms of SFN, was present in 55% of cases. The mean DN4 score was 5.7 ± 1.4 (range, 3–9). Lower limbs were involved in all patients, and upper limbs in 90% of patients. The

most frequent signs of dysautonomia were vasomotor symptoms with peripheral vasomotor manifestations, mainly erythralgia, and non-postmenopausal hot flash (66%), chronic constipation (50%), and hyperhidrosis (47%) (see Table 1).

At last evaluation, the following analgesic treatments were being taken: class I drugs (paracetamol, or nonsteroidal anti-inflammatory drugs) alone in 12 patients (30%), pregabalin in 13 patients (32.5%), clonazepam in 7 patients (17.5%), tramadol in 5 patients (12.5%), gabapentin in 3 patients (7.5%), tricyclic antidepressant drugs in 3 patients (7.5%), duloxetine in 3 patients (7.5%), and morphine sulfate in 1 patient (2.5%). The immunomodulatory or immunodepressant drugs included hydroxychloroquine in 21 patients (52.5%), oral steroids in 7 patients (17.5%), azathioprine in 1 patient (2.5%), and methotrexate in 1 patient (2.5%).

### Neurophysiologic Investigation and IENFD Measurement

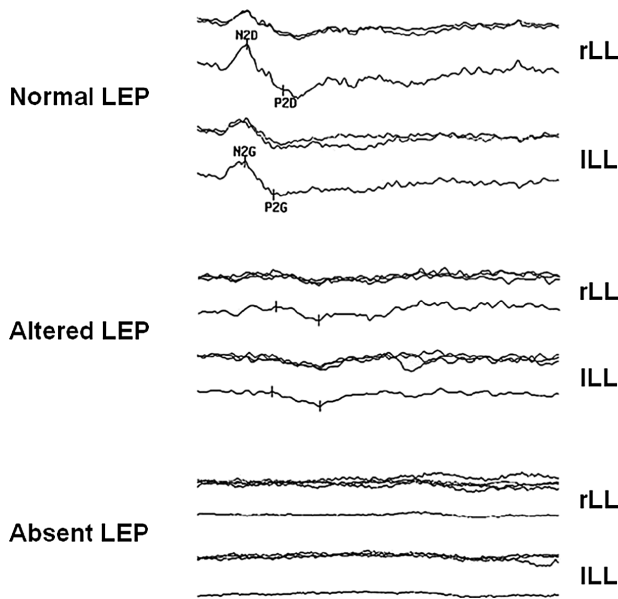
All 40 patients had at least 1 abnormal neurophysiologic test of small fibers; the results of neurophysiologic investigations are reported in Table 2 and illustrated by Figure 1. All SFN patients had either abnormal LEPs or abnormal QST. The LEPs were found altered in 97.5% of patients (39 patients): at the lower limbs in 92.5% of patients and at the upper limbs in 82.5%. Thermal QST was found abnormal in 67.5% of patients (27 patients), with abnormal thresholds for warmth in 67.5% of patients and for cold in 27.5%. The SSR was abnormal in 40% of patients (16 patients), all of them having either altered LEPs (15 patients) or abnormal QST (10 patients). Overall, the concordance analysis between these 3 neurophysiologic tests showed that 26 patients (65%) had both altered LEPs and abnormal thermal QST, 15 patients (37.5%) had both abnormal LEPs and abnormal SSR, and 10 patients (25%) had both abnormal QST and abnormal SSR. Seven patients (17.5%) had isolated abnormal LEPs, and none had isolated abnormal QST or SSR.

Thirteen of the 17 investigated patients (76%) had a reduced IENFD in skin biopsy with a mean 5.2 ± 1.2 fibers/mm IENFD at the distal leg, and 8.7 ± 1.6 fibers/mm at the proximal thigh (see Table 2 and Figure 2). Twelve of the 17 tested patients (71%) had both reduced IENFD and abnormal LEPs, 8 patients (47%) had both reduced IENFD and abnormal QST, and 7 patients (41%) had both reduced IENFD and abnormal SSR. The

**TABLE 2.** Neurophysiologic and Histologic Assessment of Small Fiber Involvement

Population Study (n=40)	No. (%)
Abnormal LEP (amplitude and/or latency)	39 (97.5)
Lower limbs	37 (92.5)
Upper limbs	33 (82.5)
Abnormal QST thresholds to warmth and/or cold	27 (67.5)
Abnormal QST thresholds to warmth	25 (62.5)
Lower limbs	25 (62.5)
Upper limbs	12 (30)
Abnormal QST thresholds to cold	11 (27.5)
Lower limbs	11 (27.5)
Upper limbs	3 (7.5)
Abnormal SSR (amplitude and/or latency)	16 (40)
Lower limbs	13 (32.5)
Upper limbs	13 (32.5)
Abnormal IENFD (n = 17)	13/17 (76)





**FIGURE 1.** Laser evoked potentials (LEPs) normal in control and altered or absent in patients with small fiber neuropathy. The main components of the LEP (N2 and P2) recorded at the vertex are presented to the stimulation of the right or left (r/l) lower limb (LL). A grand averaging is presented below 2–3 superimposed averaged traces.

4 patients with a normal IENFD had either altered LEPs (3 patients) or abnormal thermal QST (1 patient).

**Clinical and Immunologic Features in pSS Patients With SFN and pSS Patients With No Symptoms of Peripheral Neuropathy**

Table 3 includes the clinical and immunologic features of the study population and the results of comparisons between patients with SFN (n = 40) and patients without peripheral neuropathy (n = 100). Briefly, the pSS patients with SFN were older at pSS diagnosis than the pSS patients without neuropathy (aged 55.3 ± 13.1 vs. 49.5 ± 14.9 yr, respectively; p = 0.03), and more frequently had xerostomia (97.5% vs. 81.0%; p = 0.01) and arthralgia (82.5% vs. 65.0%; p = 0.04). Regarding pSS treatment, patients with SFN less frequently received oral steroids (17.5% vs. 40%; p = 0.01) and an immunosuppressant drug (5% vs. 18%; p = 0.06) compared to patients without neuropathy, but there was no difference regarding the use of hydroxychloroquine (40% vs. 48%; p = 0.7).

Comparing immunologic features, pSS patients with SFN presented with a lower prevalence of serum markers of B-cell chronic activation, that is, ANA (65% vs. 85%; p = 0.01), anti-SSA (42.5% vs. 71%; p = 0.002), and anti-SSB antibodies (17.5% vs. 39%; p = 0.017); rheumatoid factor (32.5% vs. 66%; p = 0.0005); and hypergammaglobulinemia (35% vs. 62%; p = 0.005), with lower median serum levels of total gammaglobulins (11.4 vs. 14.8 g/L; p = 0.01) compared to pSS patients without neuropathy. They also had low serum C4 levels less frequently (14.7% vs. 44.4%; p = 0.007).

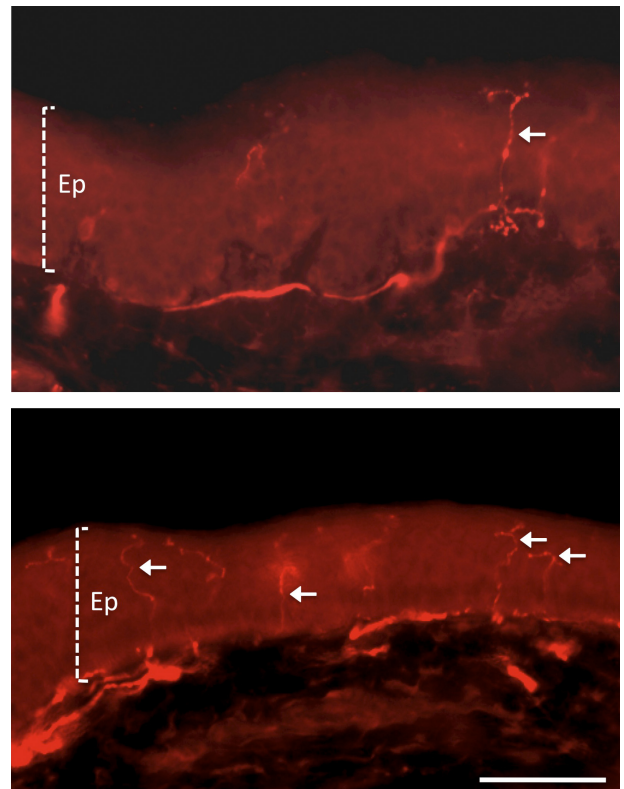
For the multivariate analysis, low C4 was excluded among retained variables because of the high number of missing data in the control group. Finally, after a stepwise multivariate logistic regression, 2 variables remained negatively associated with the presence of SFN: anti-SSA antibodies (odds ratio [OR], 0.4;

95% CI, 0.16–0.80; p = 0.018), and rheumatoid factor (OR, 0.3; 95% CI, 0.1–0.7; p = 0.007).

**DISCUSSION**

In the current study, we report the first comprehensive analysis of a large series of pSS patients with associated SFN. As expected, pSS-related SFN was clinically characterized by painful sensory symptoms affecting the lower limbs in all cases, and the upper limbs in up to 90% of patients. The most frequent neurophysiologic abnormalities were altered LEPs (97.5%), and abnormal QST thresholds (67.5%). Pathologic analysis of skin biopsies was frequently informative, with up to 76% of the 17 tested patients having a reduced IENFD. Beyond the clinical, neurophysiologic, and pathologic description of pSS-associated SFN, our objective was to characterize pSS patients with SFN in comparison to pSS patients without any symptom of peripheral neuropathy. We found that SFN was associated with an older age and more frequent xerostomia and arthralgia. Considering laboratory parameters, we found that SFN was associated with a low prevalence of markers of polyclonal B-cell chronic activation, including ANA, anti-SSA, anti-SSB, rheumatoid factor, and hypergammaglobulinemia, and with low C4 serum levels.

One of the largest cohorts of SFN patients was reported in 2008 by Devigili et al<sup>9</sup> with 67 patients, including 6 cases of pSS-related SFN. Although the overall neurologic presentation



**FIGURE 2.** Immunofluorescence quantification of intraepidermal nerve fiber density (IENFD). The skin biopsy samples show a decreased IENFD in a pSS patient with SFN (top) in comparison with a patient with normal IENFD (bottom). Arrows indicate intraepidermal axons. Abbreviation: Ep = epidermis. Bar represents 50 μm (frozen sections [5 μm], immunofluorescence (Cy3) for PGP9.5, × 25).

**TABLE 3.** Main Features of Patients With pSS-Associated SFN Compared to pSS Patients Without Peripheral Neuropathy (Control Group)

Feature	pSS-SFN Patients (n=40)	pSS Patients Without PN (n=100)	Univariate Analysis		Multivariate Analysis	
			P	OR (95% CI)	P	
Age at pSS diagnosis, yr*	55.3 ± 13.1	49.5 ± 14.9	0.027			
Female, n (%)	37 (93)	87 (87)	0.56			
White, n (%)	30 (75)	62 (62)	0.17			
Black, n (%)	4 (10)	15 (15)	0.59			
Xerostomia, n (%)	39 (97.5)	81 (81)	0.01			
Xerophthalmia, n (%)	40 (100)	92 (92)	0.10			
Positive labial biopsy (focal lymphocytic sialadenitis with a focus score ≥1 focus/4 mm <sup>2</sup> ), n (%)	28/34 (82)	69/84 (82)	1.00			
Immunologic Features						
ANA+, n (%)	26 (65)	85 (85)	0.01			
Anti-SSA (Ro)+, n (%)	17 (42.5)	71 (71)	0.002	0.4 (0.16–0.8)		0.018
Anti-SSB (La)+, n (%)	7 (17.5)	39 (39)	0.017			
Gammaglobulin level, g/L†	11.4 (10–14)	14.8 (14–16)	0.011			
IgG, g/L†	11 (10–12)	14.9 (14–17)	0.001			
IgA, g/L†	2.3 (1.9–2.5)	2.6 (2.3–2.9)	0.049			
IgM, g/L†	0.93 (0.8–1.4)	1.4 (1.3–1.5)	0.037			
Hypergammaglobulinemia, n (%)	14 (35)	62 (62)	0.005			
Rheumatoid factor+, n (%)	13 (32.5)	57/86 (66)	0.0005	0.3 (0.1–0.7)		0.007
Low C4 level, n (%)	5/34 (14.7)	20/45 (44.4)	0.007			
Cryoglobulin, n (%)	1 (2.5)	10 (10)	0.18			
Monoclonal gammopathy, n (%)	3 (7.5)	15 (15)	0.28			
Extraglandular Manifestations						
Arthralgia, n (%)	33 (82.5)	65 (65)	0.04			
Purpura, n (%)	3 (7.5)	13 (13)	0.56			
Parotiditis, n (%)	4 (10)	14 (14)	0.78			
Lung involvement, n (%)	2 (5)	13 (13)	0.23			
B-NHL, n (%)	1 (2.5)	3 (3)	1.00			
CNS involvement, n (%)	3 (7.5)	4 (4.0)	0.41			
pSS Treatment						
Hydroxychloroquine, n (%)	21 (40)	48 (48)	0.7			
Oral steroids, n (%)	7 (17.5)	40 (40)	0.01			
Immunosuppressant drug, n (%)‡	2 (5)	18 (18)	0.06			

Abbreviations: B-NHL = B-cell non-Hodgkin lymphoma, CNS = central nervous system, PN = peripheral neuropathy.

\*Mean±standard deviation.

†Median (95% CI).

‡Methotrexate, azathioprine, cyclophosphamide, mycophenolate mofetil, rituximab.

was similar, the current series differed from that previously published series by having a higher prevalence of painful symptoms and signs: burning sensations (90% in the current series vs. 54% in the series of Devigili et al), electric discharges (70% vs. 4.5%), painful cold (37.5% vs. 3%), itching (37.5% vs. 6%), and allodynia (55% vs. 27%). The higher prevalence of pain features reported in our cohort might be explained by the prospective design of our study, and the systematic use of the DN4 questionnaire to determine the presence of neuropathic pain. Our results are close to those reported by Gorson et al<sup>21</sup> in a series of 23 patients with definite SFN; they reported burning sensations in 22 patients (96%), prickling in 13 (57%), electric discharges in 13 (57%), and allodynia in 11 (47.8%). Another study, comparing 63 patients with non-length-dependent SFN to 175 patients with length-dependent SFN,<sup>27</sup> reported that 81% of patients with non-length-dependent SFN had painful symptoms.

Concerning the involvement of the autonomic nervous system, 66% of patients in the current study had vasomotor symptoms, and about 50% had constipation or hyperhidrosis. This was consistent with the results provided by neurophysiologic investigation, showing abnormal SSR in 40% of patients, and might reflect the co-involvement of C small fibers in addition to the sensory Aδ small fibers. In the study by Devigili et al,<sup>9</sup> clinical signs of dysautonomia were present in 48% of patients, including hypo- or anhidrosis (28%) and hyperhidrosis (18%). Functional autonomic tests showed a higher prevalence of abnormalities, with abnormal laser Doppler flowmetry in 76% of patients. A similar prevalence of clinical dysautonomia (48% of patients) was reported by Gorson et al,<sup>21</sup> mainly consisting of sicca complex and hyperhidrosis. Although sicca syndrome is herein associated with pSS as a cornerstone criterion, it may also reflect in part the involvement of the autonomic nervous system. This might explain

the higher prevalence of xerostomia in SFN patients (97.5%) and keratoconjunctivitis sicca (100%) compared to control patients (81% and 92%, respectively). Of note, as most SFN patients presented with signs of SFN and were receiving neuropathic pain treatments, the higher prevalence of sicca symptoms in SFN patients may reflect the potential anticholinergic side effects of these psychotropic treatments.

Regarding the association between pSS and SFN, only a small amount of data are available in the literature.<sup>53</sup> Gøransson et al<sup>20</sup> found a significant reduction of IENFD in 2 patients from a series of 62 patients (3%) with definite pSS, representing 25% of the cases of pSS-associated sensory neuropathy. Overall, Gøransson et al reported a significant decrease of the IENFD in pSS patients compared to healthy controls.<sup>19</sup> From a series of 20 patients with pSS-associated peripheral neuropathy, Chai et al<sup>4</sup> identified 7 patients (35%) who presented with pure SFN with reduced IENFD or morphologic abnormalities on skin biopsy. Fauchais et al<sup>13</sup> reported a series of 14 pSS patients with SFN proven on skin biopsy. They showed clinical and immunologic features close to our results, including female prevalence (100%), the presence of burning pain (100%) or electric discharge (71%), involving both lower and upper limbs (93%). Allodynia was more frequent (71%). Only 4 patients (29%) had anti-SSA antibodies, and 3 patients (21%) had anti-SSB antibodies. We previously reported 11 cases of pSS-associated SFN from a series of 120 pSS patients, a prevalence of 9% of the entire series of patients.<sup>54</sup> We showed that SFN was the most frequent pSS-associated neuropathy, representing 30% of the 30 pSS-associated peripheral neuropathies, and 56% of the pSS-associated nonataxic sensory peripheral neuropathies.<sup>54</sup> Gono et al<sup>18</sup> reported 8 cases of pSS-associated SFN out of 17 pSS patients with peripheral neuropathy, with SFN representing again the most frequent type of pSS-associated peripheral neuropathy (47%). In the study by Devigili et al,<sup>9</sup> 6 patients might have pSS, without any more detailed information. Khan et al<sup>27</sup> reported 2 cases of pSS-associated SFN in their large series of SFN (238 patients). Finally, Lopate et al<sup>36</sup> assumed the presence of SFN in 45% of a series of 22 pSS patients with normal NCS, using clinical questionnaires on pain and dysautonomia, but without any neurophysiologic investigation or skin biopsy to confirm the diagnosis of SFN. Other published data concerned anecdotal isolated cases.<sup>8,60</sup> Taken together, these data suggest that pSS might represent 0.8%–30% of causes of pure SFN.<sup>9,16,22,27</sup> On the other hand, SFN might account for 5%–22% of all types of pSS-associated peripheral neuropathies.<sup>17,42,61</sup>

The diagnosis of pSS-related SFN is probably overlooked in pSS patients because neurologic examination and NCS are usually normal. However, there is a high prevalence of clinical symptoms suggestive of small nerve fiber impairment in pSS patients, and the development of diagnostic tools (skin biopsy and neurophysiologic tests) is needed to confirm the presence of SFN in this context.<sup>40</sup> Some assessment tools, such as IEFND measurement, can show only small nerve fiber degeneration and loss, which is not the only pathophysiologic mechanism of SFN. In fact, these processes are more heterogeneous and remain largely unknown. For example, recent studies showed that idiopathic SFN may be associated with functional variants of the sodium channel Na(v)1.7 that impair slow-inactivation, leading to dorsal root ganglion neuron hyperexcitability.<sup>11,24</sup> Such a finding has not yet been evaluated in pSS-associated SFN. Kawagashira et al<sup>26</sup> recently showed, from autopsy data of 2 patients with pSS-related SFN and ganglionopathy, a decreased density of myelinated fibers and neurons in the dorsal spinal roots and ganglions, mainly affecting the small neurons. The reduction

of the small neurons was associated with a prominent CD8+ T-lymphocyte infiltration in the dorsal root ganglion, sympathetic ganglion, and epineurial and perineurial space throughout the peripheral nerve trunks, suggesting the role of cytotoxic autoimmunity against ganglion neurons. More data are lacking concerning the pathophysiology of SFN during pSS; better understanding of the mechanisms underlying the appearance of pSS-associated SFN is one of the most important issues to be investigated.

Another objective of the current study was the characterization of the immunologic profile of pSS patients with SFN in comparison to pSS patients with no sign of peripheral neuropathy. The main result we found is the low prevalence of serum markers of B-cell chronic activation in pSS patients with SFN compared to the pSS patients without neuropathy, as demonstrated by the negative association of SFN with ANA, anti-SSA antibodies, anti-SSB antibodies, rheumatoid factor, and hypergammaglobulinemia. This result is consistent with our previous report in which SFN was analyzed together with other types of peripheral sensory neuropathies.<sup>54</sup> Various immunologic profiles of pSS-associated sensory neuropathies have been reported. Grant et al<sup>23</sup> found ANA in 10% of patients with pSS-associated peripheral neuropathy. Anti-SSA (Ro) antibodies were observed in 39% of pSS patients with painful sensory neuropathy<sup>42</sup> and in 46% of pSS patients with suspected SFN.<sup>4</sup> Other studies have shown that the subset of pSS patients with negative anti-SSA (Ro) antibodies was older and less often had serologic markers of chronic B-cell activation and systemic complications, including peripheral neuropathies.<sup>7,12,44,51</sup> Concerning immunologic data, we found a higher prevalence of low C4 in pSS patients without neuropathy (44%) compared to pSS-SFN patients (15%). This result was not expected, as fewer than 10%–20% of pSS patients presented with low C4 in the largest cohorts, except in the presence of symptomatic cryoglobulin or B-cell non-Hodgkin lymphoma.<sup>25,51</sup> It might be explained by the high rate of missing data in the group of pSS patients without peripheral neuropathy (55% of patients) and the fact that all patients were recruited in tertiary university hospitals, with more severe patients, as suggested by the more frequent use of steroids and immunosuppressant drugs.

Treatment of SFN is not well defined, particularly when it is related to dysimmune mechanisms. Therapy is mainly symptomatic, based on drugs that are administered to relieve neuropathic pain, but with no effect on the underlying immunologic process. Steroids or immunosuppressive drugs were found to be ineffective in painful inflammatory neuropathies.<sup>42</sup> In contrast, the use of B cell-depleting drugs such as rituximab has not been evaluated in pSS-associated sensory neuropathies. Cases of rapid and frank, but transitory, improvement of pain scores have been reported after intravenous immunoglobulin infusion in pSS patients.<sup>28,42,43,60</sup> These results are encouraging, but remain to be confirmed in larger prospective studies, including objective assessment by IENFD measurement and/or specific neurophysiologic methods to test small nerve fibers, in addition to visual analogue scores of pain and clinical questionnaires.

We must acknowledge some limitations to the current study, including the fact that patients were recruited in only 2 centers and were assessed for the presence of SFN only in case of suggestive clinical symptoms of SFN. Another limitation is the methods used for the diagnosis of SFN. In various papers, skin biopsy with measurement of IENFD has been presented as the “gold standard” technique for the diagnosis of SFN,<sup>9,31</sup> and this test was available in only 17 of our 40 SFN patients. However, there is no formal evidence, based on well-conducted

multicenter controlled studies, that IENFD is the best technique, required for the diagnosis of SFN. Some consensus papers are considering IENFD among other techniques, without giving the highest level of evidence for any of the various techniques used for this purpose.<sup>10,56</sup> In fact, compared to QST, IENFD was found to be more sensitive,<sup>9,38,48,52</sup> equally sensitive,<sup>39,55,59</sup> or even less sensitive for the diagnosis of SFN in various series of patients,<sup>37,47,50</sup> including a large cohort of 210 patients with symptoms and signs of SFN of different causes.<sup>46</sup> Compared to LEP, IENFD was found to be either slightly more sensitive<sup>3,5</sup> or frankly less sensitive.<sup>50</sup> In particular, assessing skin biopsies by PGP9.5 immunostaining alone, as is usually done in clinical practice, may miss regenerating small nerve fibers, reducing the diagnostic and prognostic value of IENFD compared to neurophysiologic tests, such as LEPs.<sup>35,49</sup> In contrast, IENFD was found to be clearly more sensitive than any autonomic test to date, such as QSART,<sup>48</sup> SSR, or RRIV,<sup>59</sup> although SFN can affect autonomic fibers as well. In addition, all previous studies have compared 1 single type of neurophysiologic test to IENFD, and not a battery of neurophysiologic tests as performed herein. Such a battery is likely to be more efficient than IENFD for the diagnosis and follow-up of SFN, because a larger skin surface can be explored, with different types of methods that are strictly noninvasive and are easy to repeat. However, the respective sensitivity of these approaches for the diagnosis of SFN remains debatable. Our opinion is that no technique is superior to another, and their diagnostic value is a matter of practice and experience. We have a particularly long experience in the neurophysiologic assessment of SFN,<sup>32–35</sup> which justifies the specificity of this approach in the present study. Finally, the “single-center” design of our study in tertiary university hospitals may be associated with more severe clinical and laboratory features in SFN patients than in the control group.

In conclusion, we report the main clinical, neurophysiologic, and histologic features of patients with pSS-associated SFN, which are immunologically characterized by a low prevalence of serum markers of B-cell chronic activation. pSS-associated SFN is probably overlooked and should be appraised using neurophysiologic tests and/or IENFD measurement in any patient with painful neuropathic symptoms associated with normal NCS. The main issues that remain to be addressed are the pathophysiology of pSS-associated SFN and the evaluation of treatment efficacy, possibly based on B cell-depleting drugs and intravenous immunoglobulins.

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