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Differences in clinical features between small fiber and sensitive large fiber neuropathies in Sjögren's syndrome

Running title: Large and small fiber neuropathies in Sjögren's syndrome

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Abstract

Background. To distinguish large (LFN) and small fiber neuropathies (SFN) in Sjögren's syndrome (SS) requires electroneuromyography (EMG) first, but this is time-consuming and has sometimes a limited accessibility, which can lead to a diagnostic delay. We aimed to identify clinical features that could distinguish SFN from sensitive LFN in SS.

Methods. The study included patients with SS who were monitored in the internal medicine and neurology departments at Angers University Hospital between 2010 and 2016, and who were tested for suspected peripheral neuropathy. Patients with clinical motor involvement were excluded. LFN diagnosis was based on EMG. SFN diagnosis was based on intraepidermal nerve fiber density on skin biopsies in patients with no abnormality on EMG.

Results. LFN and SFN were diagnosed respectively in 22 (6.9%) and 17 (5.4%) patients among 317 patients with SS. Prevalence of anti-SSA antibodies was lower in the SFN group compared to the LFN group ($p=0.002$). The types of paresthesia did not differ between the 2 groups. After adjustment for age and sex, SFN was associated with dysautonomia ($p=0.01$, OR 8.4 [CI 95%: 1.7-42.4]) and without length-dependent topography ($p=0.03$, OR 0.2 [0.04-0.8]) in comparison with the LFN group.

Conclusions. An association of non-length-dependent pattern and dysautonomia seems to predict the absence of LFN in SS and encourages the search for SFN. In contrary, patients with length-dependent involvement and without dysautonomia should be prioritized for EMG.

Keywords: Small fiber neuropathy ; Peripheral nervous system disease ; Sjögren's syndrome ; dysautonomia

Abbreviations

EMG: Electromyography; IENF: Intra-epidermal nerve fiber; LEP: Laser-evoked potentials; LFN: Large fiber neuropathy; PN: Peripheral neuropathy; QST: Quantitative sensory testing; SFN: Small fiber neuropathy; SS: Sjögren's syndrome

1. Introduction

The peripheral nervous system is affected in 10 to 20% of patients with Sjögren's syndrome (SS) [1–3]. The most commonly reported peripheral neuropathies (PN) are large fiber neuropathy (LFN), essentially pure-sensory and sensorimotor axonal polyneuropathies, and ganglionopathy [2], and small fiber neuropathy (SFN). The prevalence of SFN is estimated between 3% and 9% in SS, and would represent 25% to 55% of PN in SS [3–6].

SFN is characterized by selective damage to the A- δ small myelinated fibers and non-myelinated C fibers that affect thermo-algesic sensitivity and the autonomic nervous system [7,8]. This particular feature would lead to specific sensory disorders. However, it can be difficult clinically to distinguish sensory LFN from SNF due to the heterogeneous presentation of SFN by various clinical sensory patterns and topographies, and potentially with dysautonomia [5,9].

Even though there are various functional techniques to diagnose SFN, the gold standard is the reduction of intraepidermal nerve fiber (IENF) density on skin biopsies (grade-A recommendation) [10,11]. Nevertheless, to diagnose SFN, large fibers' impairments should first be eliminated using nerve conduction studies [9,11]. However, given the great number of requests to assess subjective neurologic symptoms in SS, the access to an electromyography (EMG) is sometimes deferred. This can lead to misdiagnosis of SFN or delay in LFN diagnosis, which may require initiation of immunosuppressive drugs [12]. Therefore, the identification of parameters allowing an early differentiation between LFN and SFN will help selecting patients who are suspected to have LFN to undergo an EMG more rapidly, and will limit SFN misdiagnosis.

In this study, we compared the clinical features of patients with SS and LFN to those with SS and SFN and aimed at identifying parameters to differentiate SFN and LFN.

2. Material and methods

2.1. Ethics

This study was approved by the ethics committee of Angers University Hospital and was conducted in compliance with the Declaration of Helsinki. Informed consent was obtained from all participants.

2.2. Diagnosis of Sjögren's syndrome and peripheral neuropathy

SS was diagnosed according to ACR/EULAR 2016 criteria [13]. The LFN diagnosis was based on the results of the EMG [14]. The SFN diagnosis was based on patients who showed no abnormality on the EMG and presented a reduction in the IENF density on skin biopsies [11], as recommended by the European Federation of Neurological Societies/Peripheral Nerve [10].

2.3. Inclusion and exclusion criteria

The files of patients with SS monitored from January 2010 to December 2016 in the department of internal medicine, and the department of neurology at Angers University Hospital have been extensively revised. Patients who did not present symptoms suggestive of PN, whose disorders were not investigated, who had clinical motor deficiency at diagnosis, or who did not undergo an EMG were not included. The patients were divided into two groups. The LFN group included patients with LFN involvement on EMG. The SFN group included patients without LFN involvement on EMG and with a reduction in the IENF density on skin biopsies.

2.4. Data collection

The following data were collected: demographics, extra-glandular manifestations (as defined in the ESSDAI, except for constitutional, glandular, and biological items [1]), treatments, B lymphocytes activity signs (rheumatoid factors, hypergammaglobulinemia (superior to 13.5 g/l), low complement (low C3 and/or low C4 and/or low CH50 activity), cryoglobulinemia), characteristics of symptoms such as the type of paresthesia, the presence of dysesthesia, and symptoms of dysautonomia as described by Sène [15] (cardiac symptoms: arrhythmia, sinus bradycardia or tachycardia, extrasystoles; postural hypotension; gastro-intestinal symptoms: gastroparesis, diarrhea, alternating diarrhea constipation, chronic intestinal pseudo-obstruction; genito-urinary symptoms: urinary incontinence or urine retention, dysuria, erectile dysfunction; vasomotor problems: hot flushes, erythromelalgia, dyshidrosis, hypohidrosis, hyperhidrosis; ophthalmological symptoms: accommodation reflex problems), and the results of the EMG and the IENF density evaluations.

2.5. Statistical methods

The quantitative data are presented in medians and quartiles and compared using a Mann-Whitney test. The qualitative data were presented as absolute values and as percentages and

were compared using Chi-squared or Fisher's tests. For variables with p-value ≤ 0.20 in univariate, tests were also adjusted for age and sex. The alpha risk was 5%. The odds ratio was given with a confidence interval of 95%. The analyses were carried out using SPSS software v23.0 (IBM Corp).

3. Results

3.1. Description of the population

90 (28.4%) patients presented neurological symptoms suggestive of PN among 317 patients with SS, meeting the ACR/EULAR 2016 criteria. 60 had been thoroughly investigated. Three patients were not included due to the lack of an EMG, 2 due to clinical motor deficiency at diagnosis, and 16 due to the lack of PN diagnosed after EMG and skin biopsies. Among the 39 remaining patients, 22 were in the LFN group and 17 in the SFN group (Figure 1).

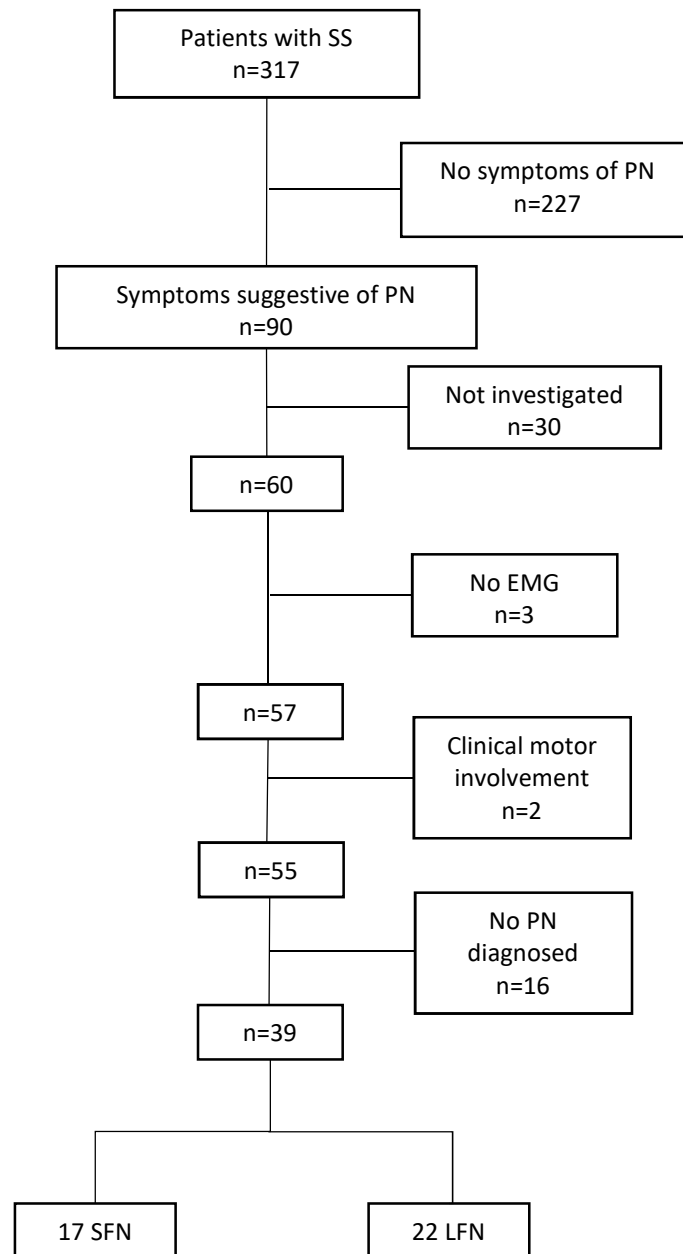


Figure 1. Flow chart

Legend:

Patients with SS according to the ACR/EULAR 2016 criteria from January 2010 to December 2016 were included. Out of them, 260 patients were not included: 227 without symptoms of PN, 30 without neurological tests, 3 with a lack of EMG, 2 patients with clinical motor deficiency and 16 with no PN diagnosed. Groups were formed according to the type of PN. EMG: electroneuromyogram; LFN: large fiber neuropathy group; NoPN: no peripheral neuropathy group; SFN: small fiber neuropathy group; SS: Sjögren's syndrome

The characteristics of the patients are summarized in Table 1. The whole population included 79.5% of females. The median age was 66 years [52-71]. Four (10.3%) patients exhibited secondary SS: two had systemic scleroderma, and one had rheumatoid arthritis in the SFN group, and one had overlap myositis in the LFN group. The presence of comorbidities that could induce peripheral neuropathy did not differ between the groups ($p>0.99$): two patients in the SFN group (one with type 2 diabetes and one with low-grade lymphoplasmacytic lymphoma), two in the LFN group (one with chronic alcoholism and one with low-grade lymphoplasmacytic lymphoma and type II cryoglobulinemia). In the LFN group, the neuropathies were ganglionopathies for 3/22 (13.6%) patients and were axonal polyneuropathies for 19/22 (86.4%), of which 11/19 (57.9%) were sensorimotor and 8/19 (42.1%) were pure sensory on the EMG. The frequency of anti-SSA antibodies varied between the two groups ($p=0.002$). No patients in the SFN group presented anti-SSA antibodies. The frequency of B-lymphocytes activity signs was more important in the LFN group: low complement and association of at least 2 B-lymphocytes activity signs was more frequent in this group (respectively $p=0.03$, and $p=0.006$). Extra-glandular manifestations were also more frequent in the LFN group ($p=0.02$).

	LFN	SFN	p-value
No. of patients (n)	22	17	
Women, n (%)	16 (72.7)	15 (88.2)	0.43
Age (years)	67.5 [57.5-74.3]	63 [50-68]	0.07
Primary SS, n (%)	21 (95.5)	14 (82.4)	0.3
SS characteristics, n (%)			
Sicca symptoms			
Ocular symptoms	22 (100)	14 (82.4)	0.07
Buccal symptoms	20 (90.9)	12 (70.6)	0.21
Schirmer's test $\leq 5\text{mm}/5\text{min}$	18 (81.8)	13 (76.5)	>0.99
Unstimulated whole saliva flow $\leq 1.5\text{ml}/15\text{min}$	13 (59.1)	10 (58.8)	>0.99
Histology			

Lymphocytic sialadenitis with focus score ≥ 1	20 (90.9)	17 (100)	0.5
Immunology			
Anti-SSA antibodies	10 (45.5)	0	0.002
Anti-SSB antibodies	5 (22.7)	0	0.06
B lymphocytes activity signs ≥ 2	8 (36.4%)	0	0.006
Rheumatoid Factors	8 (36.4)	3 (17.6)	0.29
Cryoglobulinemia	4 (18.2)	1 (5.9)	0.36
Hypergammaglobulinemia >13.5 g/L	4 (18.2)	1 (5.9)	0.36
Low complement	6 (27.3%)	0	0.03
Extra-glandular manifestations	13 (59.1)	3 (17.6)	0.02
Follow-up (months)	31 [8.5-56]	21 [7-34]	0.21

Table 1. Characteristics and symptoms of Sjögren's syndrome in the two groups

Legend:

LFN: large fiber neuropathy. SFN: small fiber neuropathy. SS: Sjögren's syndrome.

3.2. Expressing neuropathic pain

The characteristics of the neurological symptoms are summarized in Table 2. The distribution of expressed paresthesia did not differ between the 2 groups. After adjustment for age and sex, symptoms of dysautonomia (64.7% vs 18.2%) ($p=0.01$, OR 8.4 [CI 95%: 1.7-42.4]), non-length-dependent topography (77.3% vs 35.3%) ($p=0.03$, OR 0.2 [0.04-0.8], and thighs localization of paresthesias (58.8% vs 18.2%) ($p=0.02$, OR 5.9 [1.3-27.5]) remained associated with the SFN group in comparison with the LFN group.

	LFN	SFN	p-value	p-value after adjustment for age and sex
No. of patients (n)	22	17		
Paresthesia, n (%)	22 (100)	17 (100)		

Type of paresthesia, n (%)				
Burning	6 (27.3)	8 (47.1)	0.2	0.31
Painful coldness	1 (4.5)	0	>0.99	
Electric shocks	4 (18.2)	5 (29.4)	0.66	
Pins and needles	9 (40.9)	6 (35.3)	0.72	
Tingling sensations	3 (13.6)	0	0.24	
Numbness	8 (36.4)	2 (11.8)	0.14	0.10
Allodynia, n (%)	3 (13.6)	1 (5.9)	0.62	
Dysesthesia, n (%)	10 (45.5)	3 (17.6)	0.09	0.06
Dysautonomia, n (%)	4 (18.2)	11 (64.7)	0.009	0.01
Cardiac	1 (25)	1 (9.1)	0.48	
Postural hypotension	0	2 (18.2)	>0.99	
Digestive	1 (25)	3 (27.3)	>0.99	
Genito-urinary	1 (25)	2 (18.2)	>0.99	
Vasomotor problems	1 (25)	6 (54.5)	0.57	
Dyshidrosis	0	0	>0.99	
Ophthalmologic	1 (25)	1 (9.1)	0.48	
Topography, n (%)				
Lower limbs	21 (95.5)	16 (94.1)	>0.99	
Feet	21 (95.5)	16 (94.1)	>0.99	
Legs	16 (72.7)	14 (82.4)	0.7	
Thighs	4 (18.2)	10 (58.8)	0.02	0.02
Upper limbs	6 (27.3)	7 (41.2)	0.36	

Hands	6 (27.3)	7 (41.2)	0.36	
Arms + forearms	1 (4.5)	5 (23.5)	0.07	0.11
Trunk	2 (9.1)	0	0.5	
Face	1 (4.5)	0	>0.99	
Length-dependent	17 (77.3)	6 (35.3)	0.008	0.03
Symmetrical	11 (50)	14 (82.4)	0.049	0.06

Table 2. Neuropathic features of the 2 groups

Legend:

LFN: large fiber neuropathy. SFN: small fiber neuropathy.

4. Discussion

Currently, SFN diagnosis requires excluding large fiber involvement with EMG before starting specific tests for small fibers [11]. This process is time-consuming and sometimes limited by the accessibility of the EMG, resulting in diagnostic uncertainty. The identification of parameters that can early guide the diagnosis towards large or small fiber involvement will help prioritizing LFN exploration, for which immunosuppressive treatments may be considered.

Our SS population with neurological disorders presented the typical characteristics of SS, in line with the literature [16], except for the low frequency of anti-SSA antibodies, particularly in the SFN group. Three studies about SS also reported a low frequency of anti-SSA antibodies in SFN: 23.1% in patients with SFN diagnosed by skin biopsies [17], 33.3% for SFN diagnosed by skin biopsies compared to 79.9% in the absence of SFN [18], and 42.5% for SFN diagnosed by electrophysiological tests compared to 71% in the absence of PN [19]. Two teams also observed lower frequencies of anti-SSA antibodies for patients with SS in SFN compared to LFN with, 43% versus 55% for Chai et al. [4], and 39% versus 64% for Mori et al. [6], respectively. Our findings support these results even if the absence of anti-SSA antibodies in the SFN group remains unusual. Nevertheless, these results were consistent with the low frequency of B-lymphocytes activity signs in the SFN group, as previously described in two studies comparing SS with and without SFN [18,19].

With regard to the expression of neuropathy, we did not observe a difference in the types of paresthesia expressed between the groups. Only trends were noted concerning less frequent numbness and dysesthesia in the SFN group. Ng Wing Tin et al. recently reported an increased sensation of squeezing, pressure sensations, and allodynia in case of SFN among 30 patients with SS [20]. The description of neuropathic pain is difficult to interpret due to its subjectivity, and there is significant variation according to the studies in the literature [17–19]: burning sensations (47.1% in our study compared to 90% in the study of Sène et al., 100% in the study of Fauchais et al. and Birnbaum et al.), electric shocks (29.4%, 70%, 38%, and 53.8%, respectively), numbness (11.8%, 87.5%, not evaluated in the studies by Fauchais et al. and Birnbaum et al.), and allodynia (5.9%, 55%, 92% and 53.8%). We consider that the type of paresthesia is not a relevant marker for differentiating LFN and SFN.

In our study, the topography appears to be an interesting indicator for LFN. The univariate analyses adjusted for age and sex showed a strong association of a length-dependent involvement with the LFN group (77.3%) compared with the SFN (35.3%). This result seems to be in agreement with the 75% of non-length-dependent involvement observed in a previous study about SS patients with SFN [17].

Presence of dysautonomia symptoms was also strongly associated with the SFN group (64.7%) in our study. However, the frequency of dysautonomia in SFN appears to vary, notably depending on the diagnostic technique used in these studies: 95% in a study using LEP (97.5%) [19], 14% and 88.4% in two studies using skin biopsy [7,17] and 48% in a study using QST (46.9%) [7]. In the series of Sène et al. [19], 17/40 patients with SS and SFN had a skin biopsy and only 13/17 (76%) had a reduction in IENF density, while 17/17 patients had either an abnormal LEP or QST. One limitation of our study is that the SFN diagnosis was based solely on the skin biopsy. Actually, in the present study, 16 patients with SS and who expressed neurological symptoms were not included due to the lack of PN diagnosis. Those patients, who were only explored with skin biopsy for the SFN diagnosis could be false negative for it, due to the lack of sensitivity of this method. Other techniques include electrophysiological methods, such as Laser-Evoked Potentials (LEP) or Quantitative Sensory Testing (QST) [21]. These techniques explore the autonomic nervous system using sweat tests [21] and corneal confocal microscopy [22]. Although the IENF density measurement is the gold standard [11], it seems to be less sensitive than these functional techniques [20]. Adding functional tests to explore autonomic nervous system appears to be essential in the presence of neurological disorders suggestive of PN with symptoms of dysautonomia. This will avoid

to misdiagnose the pain of patients with SS as somatoform disorder while the SFN was not identified by only one technique.

In our SS population, the association between length-dependent involvement and the absence of dysautonomia appears to be a predictor of LFN, with a percentage of well-ranked patients of 86.3%. These results need to be confirmed in a large cohort, but we think that associating these two simple clinical parameters (length-dependent involvement and absence of dysautonomia) in view of a sensory PN in SS would allow prioritizing diagnostic tests. In SS patients presenting symptoms of PN with motor, or sensory involvement of length-dependent pattern and without dysautonomia signs access to electrophysiological tests should be prioritized to search for LFN diagnosis and enable rapid introduction of immunosuppressive treatment if necessary [12]. In other cases where sensory symptoms are present with a non-length-dependent pattern, and with dysautonomia, exploring small fibers can be carried out to identify the neurological involvement and to eliminate a somatoform disorder. Then, a non-urgent EMG can be realized. We think that a strategy based on these simple clinical elements would enable to stratify investigations according to the potential therapeutic impact and to optimize accessibility to EMG.

5. Conclusion

Patients with SS have a considerable prevalence of symptoms suggestive of PN. We have demonstrated that, after excluding patients with clinical motor disorders, the association of non-length-dependent involvement and dysautonomia seems to be a predictor of the absence of LFN and enhances SFN exploration. These elements enable to prioritize access to an EMG for patients who are likely to have LFN. For patients with high probability of SFN, investigations should be extensive with two different techniques (anatomical and functional) to avoid misdiagnosis of SS patients with neurological manifestations as having a somatoform disorder.

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