Neuropathic pain features suggestive of small fibre neuropathy in fibromyalgia syndrome: a clinical and ultrasonographic study on female patients

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ABSTRACT

Objective. *To evaluate the performance of two screening tools, respectively Pain Detect Questionnaire (PDQ) and Douleur Neuropathique 4 questions (DN4), and the optimal cut-off point of the sural nerve cross-sectional area (CSA), in identifying the neuropathic pain features suggestive of a small fibre neuropathy (SFN), in patients with fibromyalgia syndrome (FM).*

Methods. *Consecutive adult female FM patients fulfilling the American College of Rheumatology (ACR) 2016 criteria have been enrolled. Patients underwent a clinical assessment and ultrasound examination of the sural nerve CSA. In each patient was established the presence of neuropathic pain features suggestive of the presence of SFN. The performance of PDQ versus DN4 was compared to the clinical judgment of SFN as external criterion analysing the area under the receiver operating characteristic curve (AUC-ROC). The optimal sural nerve CSA cut-off was established with the ROC curve analysis versus the clinical judgment of SFN.*

Results. *The study involved 80 patients (mean age 49.5±10.5 years, mean disease duration 5.2±4.9 years, mean revised FIQR score 60.9±19.6). Comparing the AUC-ROCs of the screening tools with clinical judgment of SFN, a better AUC was documented, although not significantly (p=0.715), for DN4 (0.875) compared to PDQ (0.857). A sural nerve CSA of 3 mm² identifies neuropathic pain features with a sensitivity of 70% and a specificity of 90%.*

Conclusion. *Screening tools have a good concordance in identifying neuropathic pain features suggestive of SFN in FM patients, although a better performance is provided by DN4. Determining the CSA sural nerve with an ultrasound examination may provide some information about the possible presence of SFN.*

Introduction

Fibromyalgia syndrome (FM) is a condition characterised by a complex symptomatology, dominated by the presence of widespread chronic pain, fatigue, non-restorative sleep and memory deficit. These symptoms define the presence of FM in accordance with the various sets of classification criteria proposed in recent years (1). FM is a frequent cause of chronic musculoskeletal pain, third after lumbar pain and osteoarthritis (2). It is estimated that FM affects 2.3% of the European population, but studies indicate a prevalence of up to 4.7% (3-5).

Pain is a key symptom of this condition and, according to the recent review proposed by International Association for the Study of Pain (IASP), fibromyalgic pain falls under the definition of nociplastic pain, defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (6). This definition of nociplastic pain, generated in 2016 after the redefinition of neuropathic pain, implies the absence of lesions that can be demonstrated by instrumental examinations of the somatosensory system (7). However, a significant proportion of patients, estimated around 20-30%, complain of painful symptoms with neuropathic characteristics. Paresthetic symptoms such as burning pain or tingling are present in the same percentage of patients with FM and diabetic neuropathy (8). The importance of neuropathic pain features is also recognised by FM screening tools: one of five Fibromyalgia Rapid Screening Toll

(FiRST) items investigates the presence of sensations such as pinpricks, tingling and numbness (9).

Several tools are used as screening tools for neuropathic pain. There are fully patient-reported questionnaires such as the PainDetect Questionnaire (PDQ), which are widely used in chronic pain, including FM (10). Other tools, such as the Douleur Neuropathique 4 questions (DN4), are administered by the clinician and, alongside items aimed at investigating qualitative pain descriptors, include clinical evaluation (11).

The pathophysiological substrate of neuropathic pain in FM is not clarified, as is the pathophysiology of FM as a whole. However, at the basis of neuropathic pain features there may be somatosensory system alterations in small nerve fibres, which cannot be documented with the instrumental investigations used in routine clinical practice such as the electrophysiological study. Morphological alterations of the small nerve fibres are present in about half of FM patients, which can be histologically demonstrated on a skin biopsy or with confocal corneal microscopy (12).

To date, histological examination represents the gold standard for the diagnosis of small fibre neuropathy (SFN). However, given the high prevalence of FM in the general population, it is not possible nowadays to consider performing a skin biopsy or confocal corneal microscopy in all FM patients.

Some authors have shown that an increase in the cross-sectional area (CSA) of the sural nerve, assessed by ultrasonography, is an indirect sign of the presence of SFN (13). Recently, it has also been demonstrated that sural nerve CSA in FM patients is associated with BMI and the presence of neuropathic symptoms, assessed by PDQ (14). Sural nerve CSA could therefore be informative in patients with FM, indicating a clinical phenotype with peripheral nervous system involvement.

Based on these considerations, the objectives of this study are basically twofold. First, to evaluate the performance of two screening tools, respectively PDQ and DN4, in identifying the neuropathic pain features indicative of a SFN, in relation to clinical judgment. The second, to define the cut-off for sural nerve CSA suggestive of the presence of neuropathic pain features typical of SFN, also in relation to the clinician's judgment.

Materials and methods

Setting, inclusion and exclusion criteria

This monocentric study was conducted, from May 2020 to November 2020, at the Rheumatology Clinic of the Università Politecnica delle Marche. This department represents the regional reference centre for the diagnosis and treatment of FM.

Adult female patients were consecutively included, diagnosed with FM according to the 2016 criteria of the American College of Rheumatology (ACR), regardless of the severity of the disease. Patients with diseases affecting the central or peripheral nervous system (Alzheimer's disease or other dementias, Parkinson's disease, motor neuron disease, polyneuropathy, multiple sclerosis, spinal lesions, patients with signs of large fibre involvement - *e.g.* wasting and weakness, deep-seated pain, impaired vibration perception, loss of reflexes, ataxia), with conditions potentially leading to SFN (current or past alcoholism, current or past substance abuse, current or past use of potentially neurotoxic drugs, diabetes mellitus, thyroid diseases or other uncontrolled endocrinopathies, ongoing neoplasms, chronic viral infections with HBV, HCV or HIV, connective tissue diseases, vasculitis, sarcoidosis, amyloidosis, Ehlers-Danlos syndrome or joint hypermobility syndrome), or with concomitant diseases of the musculoskeletal system (chronic inflammatory joint diseases, microcrystal arthritis, symptomatic osteoarthritis) that may interfere with clinical evaluation, were excluded. Patients which underwent previous safenectomy were also excluded due to the possibility of injuries to the sural nerve induced by stripping of the small saphenous vein (15).

All patients who participated in the study signed informed consent to undergo the assessment of the study. The study was approved by the local ethics committee (Comitato Unico Regionale - ASUR Marche, no. 1970/AV2).

Clinical and clinimetric evaluation of FM

Demographic data such as age, weight and height (in order to calculate the body mass index (BMI)) were collected from each patient.

The clinical and clinimetric evaluation of FM was conducted by FS, a rheumatologist with over thirty years' experience in the management of FM patients. In particular, the duration of the disease was recorded and the revised Fibromyalgia Impact Questionnaire (FIQR) was administered. Briefly, the FIQR consists of 21 numerical rating scales with 11 points that investigate three health domains (9 items for physical function, 10 for symptoms, 2 for overall impact) over the last seven days. The final score varies from 0 to 100, where higher values document a higher severity of symptoms (16).

During this evaluation, the rheumatologist was also asked to establish a clinical judgment on the presence or absence of neuropathic pain features suggestive of the presence of a SFN. To date, there are no defined criteria for the diagnosis of SFN. The clinical diagnosis focused in particular on the detection of characteristic neuropathic symptoms such as sock or glove distribution of sensory alterations, the presence of electric-shock pain, burning, cold-like pain, itching, pinpricks, possibly associated with the presence of autonomic symptoms. As mentioned above, patients with symptoms/signs suggestive of large fibre neuropathy such as motor deficits, proprioception deficit at toes, loss of vibratory sensitivity, areflexia, have been excluded (17).

Screening tool for neuropathic pain features

The neuropathic pain features have been evaluated through PDQ and DN4. This evaluation was conducted by PC, fellow in rheumatology.

PDQ is a completely self-administered questionnaire and does not require any objective evaluation. Also used in chronic inflammatory joint diseases, PDQ consists of four items in which

the patient has to describe the temporal pattern of pain (score -1 or +1 depending on the indicated temporal pattern), a manikin in which it is possible to represent pain irradiation (irradiated pain +2 points), and seven 5-point scales in which it is possible to report characteristic symptoms of neuropathic pain (sudden pain, allodynia, hyperalgesia, dysesthesia). The final score (range from -1 to 38) should be interpreted in terms of the probability of the presence of neuropathic pain: ≤12 low, ≥19 high, between 13 and 18 the score is defined as ambiguous (10).

DN4 consists of 4 questions for a total of 10 dichotomously answered items. The first 2 questions (7 items) concern typical neuropathic qualititative symptoms (burning pain, painful cold sensation, electric shocks) and the association with other paresthetic symptoms (tingling, pinprick stings, numbness, itching), the last 2 questions (3 items) represent the objective neurological evaluation of tactile hypoesthesia, pinprick hypoesthesia, and tactile allodynia. Each item with an affirmative answer is given score 1, the final score goes from 0 to 10, and the presence of a score higher than 4 indicates the presence of neuropathic pain (11).

For both PDQ and DN4 the versions available in Italian have been used (18, 19).

Ultrasound examination of the sural nerve

The ultrasound examination of the sural nerve was conducted by MDC, a rheumatologist with a decade of experience in musculoskeletal ultrasound, and also with experience in the ultrasound study of peripheral nerves (14). The sonographer conducted the examination blind with respect to clinical and clinimetric evaluation.

Sural nerve CSA was studied at calf level, at a distance of 14 cm proximal to the apex of the lateral malleolus. At this level the sural nerve is a structure identifiable on ultrasound examination, and is present as a small structure near the small saphenous vein. The ultrasound examination starts with the identification of the small saphenous vein. The measurement of CSA at this level has already been used in protocols referring to polyneuropathies in the course of vasculitis (20).

By convention, sural nerve CSA was measured unilaterally (side of the dominant hand) and was considered the final mean of three measurements. The ultrasound examination was conducted using a linear multifrequency probe (6-18 MHz) of a MyLab Class C (Esaote S.p.A, Genoa, Italy). This kind of ultrasound assessment, in the hands of experienced operators, demonstrated excellent repeatability among sonographers, with an intraclass correlation coefficient of 0.96 (14).

Statistical analysis

Data are presented descriptively as mean and standard deviation (SD) and as median and interquartile range. The correlations between the different variables studied (CSA, DN4, PDQ, FIQR, age and duration of disease) were investigated through the Spearman's rank correlation coefficient.

Based on the clinical judgment of the presence or absence of neuropathic pain features suggestive of SFN, patients were dichotomised into two groups. The differences between the two groups were investigated through the Mann-Whitney U-test.

Then, in order to verify the first objective of the study, *i.e.* to evaluate the performance of PDQ and DN4, the analysis of the area under the receiver operating characteristic curve (AUC-ROC) of the two screening tools was performed. The clinical judgment of neuropathic pain features indicative of SFN was used as external dichotomous criterion.

Finally, to carry out the second objective of the study, *i.e.* to estimate the sural nerve CSA cut-off indicative of the presence of neuropathic pain features significant for SFN, the ROC curve of the CSA in relation to the clinical judgment

Table I. Demographic and clinical data of the whole case study (80 patients).

	Mean	SD	Median	IQR
Age (years)	49.5	10.5	49.5	44.0 - 57.0
Disease duration (years)	5.2	4.9	4.0	2.0 - 6.0
BMI (Kg/m^2)	23.9	3.1	23.3	21.4 - 26.6
FIQR	60.9	19.6	64.3	44.5 - 74.8
DN4	3.9	2.2	3.0	2.0 - 6.0
PDQ	16.5	8.7	15.0	10.0 - 23.5
CSA sural nerve (mm^2)	2.7	0.8	3.0	2.0 - 3.2

SD: standard deviation; IQR: interquartile range; BMI: body mass index; FIQR: revised Fibromyalgia Impact Questionnaire; DN4: Douleur Neuropathique 4 questions; PDQ: PainDetect Questionnaire; CSA: cross-sectional area of the sural nerve.

Table II. Correlations between demographic and clinical variables.

		DN4	Disease duration	FIQR	Age	PDQ
CSA	r*	0.286	0.135	0.010	0.053	0.243
	p	0.010	0.230	0.928	0.639	0.029
DN4	r*		0.016	0.289	0.095	0.606
	p		0.888	0.009	0.403	<0.0001
Disease duration	r*			-0.040	0.051	-0.122
	p			0.726	0.656	0.280
FIQR	r*				-0.092	0.424
	p				0.418	0.0001
Age	r*					-0.159
	p					0.160

DN4: Douleur Neuropathique 4 questions; FIQR: revised Fibromyalgia Impact Questionnaire; PDQ: PainDetect Questionnaire; CSA: cross-sectional area of the sural nerve.
*Spearman's rank correlation coefficient.

Table III. Differences between demographic and clinical variables grouping the patients according to the clinical judgment of the absence or presence of neuropathic pain features suggestive of small fibre neuropathy.

	Neuropatic pain features – absence (50 patients)				Neuropatic pain features – presence (30 patients)				*p**
	Mean	Median	SD	IQR	Mean	Median	SD	IQR	
Age (years)	48.88	49.00	10.64	43.00 - 55.00	50.63	50.00	10.35	44.00 - 58.00	n.s.
Disease duration (years)	4.78	4.00	4.10	2.00 - 5.00	5.96	4.00	6.07	2.00 - 7.00	n.s.
BMI (Kg/m^2)	23.16	22.58	3.15	21.09 - 24.60	25.36	25.21	2.77	23.43 - 27.55	0.002
CSA (mm^2)	2.42	2.11	0.59	2.00 - 3.00	3.34	3.22	0.99	3.00 - 4.00	<0.0001
DN4	2.88	2.00	1.75	2.00 - 3.00	5.80	6.00	1.62	5.00 - 7.00	<0.0001
PDQ	12.36	13.00	7.29	7.00 - 17.00	23.40	24.00	6.26	21.00 - 28.00	<0.0001
FIQR	55.80	58.50	17.79	42.80 - 72.00	69.44	73.30	19.77	59.50 - 84.50	0.002

SD: standard deviation; IQR: interquartile range; BMI: body mass index; CSA: cross-sectional area of the sural nerve; DN4: Douleur Neuropathique 4 questions; PDQ: PainDetect Questionnaire; FIQR: revised Fibromyalgia Impact Questionnaire. *Mann-Whitney U test.

(also in this case used as external dichotomous criterion) was analysed in terms of sensitivity, specificity, positive likelihood ratio (LR+), and Youden index.

The *p*-values of were considered statistically significative if <0.05, and the statistical analysis was conducted with MedCalc version 18.0.0.

Results

The study was conducted on a total of 80 female FM patients, with a mean age of 49.5±10.5 years and a mean disease duration of 5.2±4.9 years. On average, the disease was found to be of moderate severity, with a mean FIQR score of 60.9±19.6. The descriptive data of the entire population studied are described in Table I.

Correlation analysis documented a moderate correlation between the two screening tools studied (r=0.606; $p<0.0001$). Poor but significant correlations were found between CSA and DN4 (r=0.286; $p=0.01$) and between CSA and PDQ (r=0.243; $p=0.029$). Significant correlations also emerged between the severity of disease, measured by FIQR, and neuropathic pain features, respectively evaluated with DN4 (r=0.289; $p=0.009$) and PDQ (r=0.424; $p=0.0001$) (Table II).

Based on clinical judgment, in 30 (37.5%) of 80 patients the presence of neuropathic pain features suggestive of SFN was established. Comparing the characteristics of the two groups (Table III), patients with neuropathic pain features showed a statistically significant larger CSA ($p<0.0001$), showed higher scores of DN4, PDQ ($p<0.0001$ for both) and FIQR ($p=0.002$), and showed higher BMI ($p<0.002$). No significant differences in age and duration of disease were found.

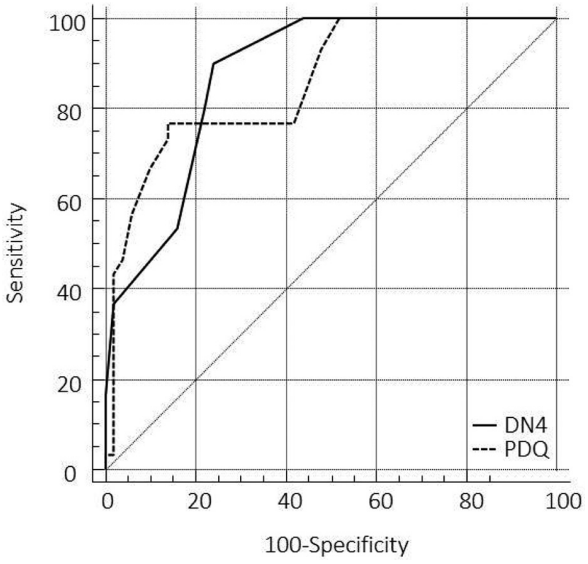

Fig. 1. Receiver operating characteristic curve of the Douleur Neuropathique 4 questions (DN4) (continuous line) and of PainDetect Questionnaire (PDQ) (dotted line) in indentifying the presence of neuropathic pain features suggestive of small fibre neuropathy, applying the clinical judgment as external criterion.

Comparing the AUC-ROCs of the two screening tools with clinical judgment, a better AUC was documented, although not significantly ($p=0.715$), for DN4 (0.875, 95% confidence interval [CI] 0.783-0.939) compared to PDQ (0.857, 95% CI 0.761-0.925) (Fig. 1).

Finally, in determining the optimal cut-off of sural nerve CSA in the identification of neuropathic pain features suggestive of SFN, it was found that a 3 mm^2 CSA identifies neuropathic pain features with a sensitivity of 70%, a specificity of 90%, a LR+ of 7, and a Youden index of 0.600 (Table IV).

Discussion

In this study we compared two screening tools to detect the presence of neuropathic pain features suggestive of SFN in FM patients, demonstrating a better performance of DN4 compared to PDQ with respect to clinical judgment. We also identified an ultrasound cut-off, *i.e.* the presence of a 3 mm^2 CSA sural nerve, as indicative of neuropathic pain features suggestive of SFN. To the best of our knowledge, this is the first work that compares two screening tools and provides an ultrasound definition of sural nerve alterations suggestive of SFN in FM patients.

FM is a complex chronic pain condition (21), and the use of screening tools to investigate neuropathic components can help in patient profiling. Despite the wide availability of examinations to diagnose nerve damage, SFN still remains a difficult condition to diagnose and is underdiagnosed (22).

Subjective reporting of neuropathic pain features can provide useful information about the pathophysiological

Table IV. Receiver operating characteristic curve analysis for the determination of the optimal cut-off point of the sural nerve cross-sectional area in identifying the presence of neuropathic pain features suggestive of small fibre neuropathy, applying the clinical judgment as external criterion.

Criterion*	Sensitivity	95% CI	Specificity	95% CI	LR+	LR-
>1	100.00	88.4 - 100.0	4.00	0.5 - 13.7	1.04	0.00
>1.09	96.67	82.8 - 99.9	4.00	0.5 - 13.7	1.01	0.83
>1.6	96.67	82.8 - 99.9	6.00	1.3 - 16.5	1.03	0.56
>1.98	90.00	73.5 - 97.9	6.00	1.3 - 16.5	0.96	1.67
>2	90.00	73.5 - 97.9	46.00	31.8 - 60.7	1.67	0.22
>2.02	86.67	69.3 - 96.2	46.00	31.8 - 60.7	1.60	0.29
>2.1	86.67	69.3 - 96.2	48.00	33.7 - 62.6	1.67	0.28
>2.11	83.33	65.3 - 94.4	50.00	35.5 - 64.5	1.67	0.33
>2.2	83.33	65.3 - 94.4	54.00	39.3 - 68.2	1.81	0.31
>2.4	80.00	61.4 - 92.3	54.00	39.3 - 68.2	1.74	0.37
>2.88	80.00	61.4 - 92.3	62.00	47.2 - 75.3	2.11	0.32
>3**	70.00	50.6 - 85.3	90.00	78.2 - 96.7	7.00	0.33
>3.1	66.67	47.2 - 82.7	90.00	78.2 - 96.7	6.67	0.37
>3.11	63.33	43.9 - 80.1	94.00	83.5 - 98.7	10.56	0.39
>3.21	53.33	34.3 - 71.7	94.00	83.5 - 98.7	8.89	0.50
>3.22	46.67	28.3 - 65.7	96.00	86.3 - 99.5	11.67	0.56
>3.3	46.67	28.3 - 65.7	98.00	89.4 - 99.9	23.33	0.54
>3.4	43.33	25.5 - 62.6	98.00	89.4 - 99.9	21.67	0.58

CI: confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio.
*sural nerve cross sectional area expressed in mm^2. **optimal cut-off point.

mechanisms of pain. DN4 and PDQ are recommended questionnaires for neuropathic pain screening in patients with mixed pain conditions, although the performance of these screening tools is reduced in patients with chronic widespread pain (23).

From a classification point of view, according to the recent revision provided by the IASP, chronic widespread pain of fibromyalgic nature should be identified as nociplastic pain (7). However, a significant proportion of FM patients report neuropathic symptoms and 49% of patients have histologically documented SFN. The proportion rises to 59% considering alterations detectable with corneal confocal microscopy (12). This area of research is relatively recent, considering the fact that the first study involving skin biopsy in FM patients dates back to 2013 (24). In this percentage of patients, the histological demonstration of alterations to the somatosensory system is to all intents and purposes part of the domain of neuropathic pain. The identification of this kind of involvement could lead to SFN targeted treatment.

From the findings of this study, there was no significant difference between the two screening tools, although the performance of DN4 was slightly better. It is likely that the addition of some items involving clinical examination of the patient gives DN4 a better sensitivity and specificity. While examination in patients with SFN is poor in clinical findings, signs such as pinprick hypoesthesia are detectable in patients with SFN (17) and are included in DN4. Some researchers have also criticised the use of PDQ in FM patients, stressing the importance of accurate clinical evaluation as it would seem that central pain sensitisation causes excessive background noise in order to correctly interpret the results of the questionnaire (25). The evaluation of neuropathic pain features through screening questionnaires as PDQ is however becoming more and more relevant in rheumatology: it has been demonstrated that neuropathic pain features are present in 13% of patients with early rheumatoid arthritis and how these symptoms negatively condition the achievement of remission after one year of treatment (26), while in psoriatic arthritis high PDQ scores are associated with the presence of coexisting FM (19).

In order to correctly classify pain in FM patients, alongside the patient-reported evaluation, which is emphasised in the diagnostic criteria of the ACR under the definition of widespread pain index (27), the objective assessment of the patient remains of paramount importance.

Some useful information can also be provided by the measurement of sural nerve CSA in FM patients. In a previous study conducted at our centre we demonstrated the correlation of sural nerve CSA with the presence of neuropathic pain features and BMI in FM patients, assuming a potential clinical use of sural nerve ultrasound to identify a category of FM patients with peripheral nervous system involvement, particularly in terms of SFN (14). The current work has shown that sural CSA is significantly higher in patients with SFN than in patients without SFN. The optimal cut-off, which distinguishes the presence of SFN with a LR+ of 7, is a 3 mm^2 sural CSA.

Thus, in patients with the presence of symptoms suggestive of SFN, an enlarged sural nerve can effectively be documented. The sural nerve is a purely sensory nerve. Its role as an imaging biomarker in SFN was hypothesised in a work dating back to 2015, where Ebadi and collaborators demonstrated that an enlarged sural nerve CSA can be detected in SFN in a similar way to large fibre polyneuropathy (13). The mean value of CSA indicative of SFN detected in that work (3.2±0.8 mm^2) is very similar to the mean value obtained in the present study (3.34±0.99 mm^2). Little is known about the pathophysiological mechanisms underlying this magnification of sural nerve CSA in patients with SFN, but it is assumed that it is a sign of an altered axoplasmic flow secondary to the damage to small-calibre nerve fibres (A delta and C) (13).

The data from this study also show that in the group of patients with SFN the FIQR scores are higher, indicating an even more severe clinical phenotype of disease, and a higher BMI emerges. Conditions linked to high BMI such as increased waist circumference have been shown to be associated with neuropathy, even in normoglycemic subjects (28).

Obviously, the sural nerve CSA represents a continuum, however, the application of a cut-off is necessary to provide a clinical interpretability of the data.

Mentioning the limits of the study, it can be said that the main one is represented by the absence of the histological examination performed on skin biopsy. Although there are no universally accepted criteria for the diagnosis of SFN, histological examination is the gold standard. The use of an external clinical criterion for the presence of SFN has led to a certain circularity in the assessment of neuropathic pain features. A second limit is the absence of data concerning nerve conduction studies. However, in patients with symptoms suggestive of SFN, nerve conduction studies typically show up as normal. A third limit is that only female subjects have been included, and a fourth limit is the monocentric enrolment.

In conclusion, in this study, two screening tools for the identification of neuropathic pain features indicative of SFN in patients with SFN were compared and, from the results obtained, DN4 provides a better performance (although not statistically significant) than PDQ, comparing them with clinical judgment. The presence of a 3 mm^2 sural nerve CSA is the optimal cut-off that identifies the presence of neuropathic pain features indicative of SFN, when compared to clinical judgement.

It is desirable that physicians caring of FM patients are increasingly aware of the potential presence of concomitant SFN.

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