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Distinguishing fibromyalgia syndrome from small fiber neuropathy: a clinical guide

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Abstract

Introduction: Fibromyalgia syndrome (FMS) and small fiber neuropathy (SFN) are distinct pain conditions that share commonalities and may be challenging as for differential diagnosis.

Objective: To comprehensively investigate clinical characteristics of women with FMS and SFN to determine clinically applicable parameters for differentiation.

Methods: We retrospectively analyzed medical records of 158 women with FMS and 53 with SFN focusing on pain-specific medical and family history, accompanying symptoms, additional diseases, and treatment. We investigated data obtained using standardized pain, depression, and anxiety questionnaires. We further analyzed test results and findings obtained in standardized small fiber tests.

Results: FMS patients were on average ten years younger at symptom onset, described higher pain intensities requiring frequent change of pharmaceutics, and reported generalized pain compared to SFN. Pain in FMS was accompanied by irritable bowel or sleep disturbances, and in SFN by paresthesias, numbness, and impaired glucose metabolism ($P < 0.01$ each). Family history was informative for chronic pain and affective disorders in FMS ($P < 0.001$) and for neurological disorders in SFN patients ($P < 0.001$). Small fiber pathology in terms of skin denervation and/or thermal sensory threshold elevation was present in 110/158 (69.7 %) FMS patients and 39/53 (73.6 %) SFN patients. FMS patients mainly showed proximally reduced skin innervation and higher corneal nerve branch densities ($p<0.001$) whereas SFN patients were characterized by reduced cold detection and prolonged electrical A-delta conduction latencies ($P < 0.05$).

Conclusions: Our data show that FMS and SFN differ substantially. Detailed pain, drug and family history, investigating blood glucose metabolism, and applying differential small fiber tests may help to improve diagnostic differentiation and targeted therapy.

Keywords: Fibromyalgia syndrome, Small fiber neuropathy, Clinical phenotype, Pain pattern, Differential diagnosis

1. Introduction

Small fiber pathology is defined as clinical symptoms of small nerve fiber impairment accompanied by signs of small fiber damage on functional or conduction and/or morphological level.[10] Damage to the small caliber nerve fibers as a hallmark of small fiber pathology is also present in a subgroup of patients with fibromyalgia syndrome (FMS)[31,38,49] giving rise to the question, whether FMS equals small fiber neuropathy (SFN).[47] There is multilevel evidence for the distinction between FMS and SFN. The traditional clinical description of FMS is deeply located chronic widespread pain with additional symptoms such as depression and fatigue.[15,24,55] In SFN, superficial acral burning pain is predominant, accompanied by sensory disturbance and autonomic dysfunction.[2] Electrophysiologically evoked potentials investigating A-delta and C nerve fibers and microneurography have provided data supporting a distinction between FMS and SFN in some studies[10,11,38,49] while not in others.[50,52] Morphologically, loss of skin nociceptors is a confirmed finding in subgroups of FMS patients, which results in distinct innervation patterns.[7,9,11,20,46,52] However, clinical investigations so far failed to determine defined differences in FMS subgroups with and without small fiber pathology.[12] In contrast, some studies reported no small fiber pathology in FMS patients.[14,50,51] On

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a functional level, elevated thermal perception thresholds were reported in FMS.[11,32]

The question remains, if clinically applicable characteristics can be found that may help distinguishing FMS from SFN. So far, one study assessed the intergroup difference of patients with FMS with and without small fiber pathology using questionnaire data and reported minor differences.[25] We retrospectively studied an extensive data set of women with FMS and SFN who were recruited in 2 previous studies[10,11] asking for potentially distinguishing factors to be used in clinical practice.

2. Patients and methods

2.1. Patients

We retrospectively analyzed clinical data of 158 women with FMS[11] and 53 women with SFN,[10] who were monocentrically recruited during 2 individual studies at our Department of Neurology, University of Würzburg, Germany. The respective studies were approved by the Ethics Committee of the University of Würzburg (#121/14 and #135/15), and all participants gave written informed consent before study inclusion. For study inclusion, current diagnostic criteria for FMS[54,55] and SFN[8] were applied. The following inclusion criteria were further observed for both patient groups: adult patients and no hints for polyneuropathy in the neurological examination and nerve conduction studies. Exclusion criteria for both cohorts were as follows: pain of other origin, renal insufficiency, previously diagnosed diabetes mellitus, untreated thyroid dysfunction, acute infection, malignancy within the last 5 years, epilepsy, drug or alcohol abuse, eye diseases or surgery, usage of hard contact lenses, cardiac pacemaker, and pending compensation claims. In the SFN cohort, patients with B_{12} hypovitaminosis were additionally excluded.[10] In the FMS cohort, severe psychiatric disorder currently requiring treatment was another exclusion criterion.[11] All patients were interviewed in a standardized manner and neurologically investigated by a neurologist (D.E., N.Ü.). The SFN cohort consists of patients seen as regular inpatients or outpatients at our department. Patients with FMS were recruited for study participation from all over Germany.

2.2. Pain characterization

Individual pain characteristics were determined by spontaneously reported descriptors of the patients covering pain phenotype (character, intensity, location, radiation, onset, relieving, and aggravating factors) and symptoms accompanying pain. Intensities were reflected on a numeric rating scale (NRS) with 0 = no pain and 10 = worst pain imaginable. To assess the potential influence of disease duration on symptoms and signs, we have performed a subgroup analysis comparing 33 patients with FMS and 32 patients with SFN with a disease duration of ≤5 years. All patients filled in the following standardized pain questionnaires: Neuropathic Pain Symptom Inventory (NPSI),[5] Graded Chronic Pain Scale (GCPS),[53] and Pain Catastrophizing Scale (PCS).[29,41] Pain chronicity was rated on the Mainz Pain Staging System (MPSS).[16] For depressive symptoms, the "Allgemeine Depressionsskala" (ADS) was used.[34] We further studied analgesic medication and nonpharmacological treatments applied.

2.3. General medical assessment

We compared data obtained on patients' comorbidities. Family history was recorded in a systematic manner asking patients about neurological diagnoses, FMS or SFN diagnosis, respectively, or similar symptoms in family members, such as parents, grandparents, siblings, own children, as well as the siblings of parents and grandparents. Laboratory data that were cross-compared comprised the oral glucose tolerance test (oGTT), glycosylated hemoglobin (HbA1c), thyroid stimulating hormone (TSH), vitamin B_{12}, and blood count (erythrocytes, leukocytes, thrombocytes, hematocrit, and hemoglobin).

2.4. Small nerve fiber assessment

We analyzed data on small nerve fiber morphology, function, and electrical conduction collected as follows: (1) intraepidermal nerve fiber density (IENFD) quantified on 6-mm skin punch biopsies taken from the lower leg and upper thigh.[45] In both studies, skin biopsies were taken according to a standardized protocol[45] and were assessed following published counting rules.[21] After fixation and immunoreaction with an antibody against protein gene product-9.5 (Ultraclone RA95101 PGP9.5 1:800; Wellow, Isle of Wight, Great Britain), imaging was performed using a fluorescence microscope (Zeiss Axiophot 2, Jena, Germany). IENFD <5.4 fibers/mm was the distal limit and <8.5 fibers/mm the proximal limit. (2) Corneal nerve fiber length (NFL), density (NFD), and branching (NFB) determined by corneal confocal microscopy (CCM).[42] (3) Individual sensory profiles established by quantitative sensory testing (QST) at the dorsal foot.[35] (4) Latencies and peak-to-peak amplitudes (PPA), when recording pain-related evoked potential (PREP) at the feet.[49] Normative values were used as detailed in Ref. 10 and listed in the respective table. Pain-related evoked potential was performed according to a standardized protocol[18,22,49] using 2 superficial and concentric stimulation electrodes on the dorsum of the feet which induce a pinprick sensation. The recording of the potentials was performed with a needle electrode at Cz and 2 reference electrodes at the earlobes (A1–A2) according to international 10 to 20 system.[19] Twenty triple pulses with an intensity twice as strong as the individual perception threshold were applied. Ten curves each were averaged and compared for the extraction of first positive peak (N1), following negative peak (P1) and peak-to-peak amplitude.

2.5. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software version 27 (IMB Deutschland GmbH, Ehningen, Germany). A significance level of $P < 0.05$ was defined. The Shapiro–Wilk test was used to test for normal distribution. Normally distributed data were analyzed with the Student *t* test, whereas nonnormally distributed data using the nonparametric Mann–Whitney *U* test. Categorical data were assessed using Fisher exact test and the χ^2 test. Krita (Version 5.1.0; Stichting Krita Foundation, Deventer, Netherlands) was used for graphical data visualization.

3. Results

3.1. Epidemiological characterization of study cohorts

Table 1 gives a synopsis of the main epidemiological characteristics of the study cohorts. At symptom onset, patients with FMS were on average 10 years younger than patients with SFN (FMS: median 35.0, 4–65 years; SFN: median 47.0, 12–67 years; $P < 0.001$). Time until diagnosis was 3 times longer in patients with FMS compared with patients with SFN (FMS: median 8.0, 0–46 years; SFN: median 2.8, 0–20 years; $P < 0.001$). We found that etiology was potentially genetic in 11 of 53 (20.8%) patients with

Table 1

Epidemiological characteristics of study cohorts.

	FMS	SFN	*P*
No. of patients	158	53	NA
Median age in years [range]	51.5 [21.6–74.8]	53.4 [22.4–73.2]	n.s.
Median age at symptom onset [range]	35.0 [4–65] (n = 158)	47.0 [12–67] (n = 52)	$P < 0.001$
Median age at diagnosis [range]	45.5 [19.6–67.3]	53.2 [20.4–73.2]	$P < 0.001$
Median disease duration in years [range]	15.8 [0.0–56.0]	4.0 [0–20.0]	$P < 0.001$
Median time in years between symptom onset and diagnosis [range]	8.0 [0–46]	2.8 [0–20]	$P < 0.001$

FMS, fibromyalgia syndrome; NA, not applicable; n.s., not significant; SFN, small fiber neuropathy.

SFN, potentially metabolic in 17 of 53 patients (32.1%), and potentially autoimmune in 6 of 53 patients (11.3%). In 19 of 53 patients with SFN (35.9%), etiology remained idiopathic.

3.2. Pain in fibromyalgia syndrome is generalized and variable, while mainly focal and constant in small fiber neuropathy

Table 2 shows pain characteristics of patients with FMS and SFN. During pain interviews, the main discriminators between the 2 entities were burning (FMS: 66/158 [41.8%], SFN: 45/53 [84.9%], $P < 0.001$) or stabbing pain (FMS: 39/158 [24.7%], SFN: 35/53 [66.0%], $P < 0.001$). Patients with FMS further described pain like muscle soreness (40/158, 25.3%). Pain localization also distinguished well between FMS and SFN with widespread pain being predominant in FMS and acral pain in patients with SFN (**Fig. 1**). In FMS, physical activity, rest, and warmth alleviated pain, whereas cold and stress evoked pain (**Table 2**). In contrast, patients with SFN reported cold, warmth, and touch as both pain relieving and triggering factors (**Table 2**). Furthermore, patients with FMS reported a higher number of aggravating factors compared with patients with SFN (FMS: 2.3 [0–6], SFN: 1.6 [0–5],

Table 2

Pain characteristics of patients with fibromyalgia syndrome and small fiber neuropathy (elicitation by interview).

	FMS	SFN	*P*
Median pain intensity on NRS [range]			
During interview	5.0 [0–9] (n = 156)	4.0 [0–9] (n = 53)	<0.01
After pain medication	2.0 [0–6] (n = 126)	1.0 [0–1] (n = 40)	<0.001
Pain character			
Burning	66/158 (41.8%)	45/53 (84.9%)	<0.001
Stabbing	39/158 (24.7%)	35/53 (66.0%)	<0.001
Tearing	16/158 (10.1%)	8/53 (15.1%)	n.s.
Pain localization			
Head	91/158 (57.6%)	16/52 (30.8%)	<0.01
Neck	141/158 (89.2%)	18/52 (34.6%)	<0.001
Shoulders/upper arm	151/158 (95.6%)	18/52 (34.0%)	<0.001
Elbow/lower arm	112/158 (70.9%)	18/52 (34.0%)	<0.001
Hands/fingers	23/158 (14.6%)	34/52 (64.2%)	<0.001
Trunk	123/158 (77.8%)	7/53 (13.2%)	<0.001
Upper back	131/158 (82.9%)	17/53 (32.1%)	<0.001
Lower back	137/158 (86.7%)	22/53 (41.5%)	<0.001
Hips	124/158 (78.5%)	16/51 (31.4%)	<0.001
Thighs	130/158 (82.3%)	20/53 (37.7%)	<0.001
Knees/lower legs	102/158 (64.6%)	37/53 (69.8%)	n.s.
Feet/toes	115/158 (72.8%)	52/53 (98.1%)	<0.001
Pain triggers			
Heat	4/158 (2.5%)	18/53 (34.0%)	<0.001
Cold	106/158 (67.1%)	12/53 (22.6%)	<0.001
Stress	101/158 (63.9%)	6/53 (11.3%)	<0.001
Humidity	28/158 (17.7%)	1/53 (1.9%)	<0.01
Time of day	0/158 (0.0%)	3/53 (5.7%)	<0.05
Weather	32/158 (20.3%)	1/53 (1.9%)	<0.01
Touch	4/158 (2.5%)	20/53 (37.7%)	<0.001
Median number of pain aggravating factors [range]	2.0 [0–6]	2.0 [0–5]	<0.001
Pain relieving factors			
Physical activity	112/158 (70.9%)	12/53 (22.6%)	<0.001
Resting	73/158 (46.2%)	10/53 (18.9%)	<0.001
Cold	3/158 (1.9%)	7/53 (13.2%)	<0.01
Heat	129/158 (81.6%)	9/53 (17.0%)	<0.001
Touch	1/158 (0.6%)	5/53 (9.4%)	<0.01
Median number of pain relieving factors [range]	2.0 [0–4]	1.0 [0–3]	<0.001

FMS, fibromyalgia syndrome; NRS, numeric rating scale; n.s., not significant; SFN, small fiber neuropathy.

Table 3

Pain characteristics of patients with fibromyalgia syndrome and small fiber neuropathy (elicitation by questionnaires and Mainz Pain Staging System).

	FMS	SFN	*P*
NPSI			
Sum score: mean [range]	0.4 [0.1–0.9]	0.4 [0.0–0.7]	<0.05
Burning score: median [range]	0.5 [0–10.0]	0.4 [0.0–0.9]	n.s.
Pressure score: median [range]	0.5 [0–10.0]	0.3 [0.0–0.9]	<0.001
Attack score: median [range]	0.4 [0.0–1.4]	0.4 [0–10.0]	n.s.
Evoked pain score: median [range]	0.4 [0.0–0.9]	0.3 [0.0–0.9]	<0.001
Paresthesia/dysesthesia score: median [range]	0.4 [0.0–1.0]	0.6 [0–10.0]	n.s.
Discriminative score: mean [range]	54.3 [23.4–95.2]	51.2 [28.6–79.3]	n.s.
GCPS: median [range]			
Pain intensity	66.7 [26.7–90.0]	56.7 [13.3–86.7]	<0.001
Disability	60.0 [10.0–86.7]	50.0 [3.3–100.0]	<0.05
Grade	2.0 [1–4]	2.0 [0–4]	n.s.
ADS median [range]	23.0 [3–51]	17.0 [2–38]	<0.001
PCS median [range]	22.2 [0–49]	21.2 [3–41]	n.s.
Classification according to MPSS			
Median [range]	3.0 [2–3]	3.0 [1–3]	<0.05

ADS, allgemeine depressionsskala; FMS, fibromyalgia syndrome; GCPS, Graded Chronic Pain Scale; MPSS, Mainz Pain Staging System; NPSI, Neuropathic Pain Symptom Inventory; n.s., not significant; PCS, Pain Catastrophizing Scale; SFN, small fiber neuropathy.

$P < 0.001$). When using pain questionnaires, the NPSI pressure score (FMS: median 0.5 [0.0–1.0], SFN: median 0.3 [0–0.9], $P < 0.001$), evoked pain score (FMS: median 0.4 [0–0.9], SFN: median 0.3 [0–0.9], $P < 0.001$), and GCPS pain intensity (FMS: median 66.7 [26.7–90.0], SFN: median 56.7 [13.3–86.7], $P < 0.001$) discriminated best between FMS and SFN (**Table 3**). Interview data are summarized in **Figure 2**.

3.3. Patients with fibromyalgia syndrome report sleep disturbance and depressed mood, whereas patients with small fiber neuropathy mainly suffer from sensoalgesic symptoms

We evaluated patients' comorbidities and further symptoms, an overview is given in **Table 4**. The average number of additional symptoms spontaneously reported by the patients was higher in patients with FMS than in patients with SFN (FMS: median 8.0 [0–28], SFN: median 4.0 [0–14], $P < 0.001$). Patients with FMS rarely reported paresthesias, whereas patients with SFN often described tingling (FMS: 26/158 [16.5%], SFN: 36/53 [67.9%], $P < 0.001$), numbness (FMS: 19/158 [12.0%], SFN: 15/53 [28.3%], $P < 0.01$), or hypersensitivity to touch (FMS: 1/158 [0.6%], SFN: 7/53 [13.2%], $P < 0.001$). Patients with FMS more frequently suffered from gastrointestinal and urogenital symptoms than patients with SFN (**Table 4**). Patients with FMS also more frequently described sleep problems (**Table 4**), fatigue (FMS: 139/158 [88.0%], SFN: 3/53 [5.7%], $P < 0.001$), or apathy (FMS: 24/158 [15.2%], SFN: 2/53 [3.8%], $P < 0.01$). They reported cognitive impairment (FMS: 62/158 [39.2%], SFN: 0/53 [0%], $P < 0.001$) or problems of attention (FMS: 114/158 [72.2%], SFN: 1/53 [1.9%], $P < 0.001$). Furthermore, patients with FMS more prevalently reported depressed mood (FMS: 29/158 [18.4%], SFN: 1/53 [1.9%], $P < 0.01$) than patients with SFN.

3.4. Family history is indicative of chronic pain in fibromyalgia syndrome while of neurological disorders in small fiber neuropathy

Mental disorders (FMS: 30/158 [19.0%], SFN: 3/53 [5.7%], $P < 0.05$) and chronic pain (FMS: 78/158 [49.4%], SFN: 17/53 [32.1%], $P < 0.05$) were mostly present in the family history of patients with FMS. In contrast, patients with FMS had fewer relatives suffering from neurological diseases than patients with SFN (FMS: 26/158 [16.5%], SFN: 22/53 [41.5%], $P < 0.001$). Detailed data and reported diseases are listed in **Table 5**.

3.5. Glucose metabolism is often impaired in small fiber neuropathy but mostly normal in patients with fibromyalgia syndrome

Table 6 shows the results of the blood tests performed. Patients with FMS had lower HbA1c levels compared with patients with SFN (FMS: median 5.4% [4.7–6.4], SFN: median 5.5% [3.6–7.7], $P < 0.05$). However, data may be biased because diagnosed diabetes mellitus before study inclusion was an exclusion criterion. HbA1c was ≤6.4% in all patients with FMS. In contrast, 3 of 51 (5.9%) patients with SFN had an HbA1c >6.4%,indicating diabetes mellitus ($P < 0.05$). Although fasting blood glucose levels revealed no difference between the 2 cohorts, abnormalities were evident in the oGTT: after 1 hour (FMS: median 138.0 [68–246] mg/dL, SFN: median 172.0 [89–333] mg/dL, $P < 0.01$) and 2 hours (FMS: median 120.0 [65–217] mg/dL, SFN: median 123.0 [79–284] mg/dL, $P < 0.05$), patients with FMS were characterized by lower blood glucose levels than patients with SFN and less frequently had pathological results (2h oGTT >140 mg/dL: FMS: 23/157 [14.6%], SFN: 14/47 [29.8%]). As for TSH and vitamin B_{12} levels, patients in both cohorts showed normal values.

3.6. Analgesic treatment attempts are more frequent in patients with fibromyalgia syndrome history than in small fiber neuropathy

We further recorded the pharmacological and nonpharmacological therapeutic approaches that patients had undertaken to treat FMS and SFN symptoms (**Table 7**). Patients with FMS reported more frequent therapy attempts than patients with SFN. This was reflected by the number of different pharmacological therapies (FMS: median 4.0 [0–19], SFN: median 3.0 [0–10], $P < 0.001$), medical interventions such as injections or surgery (FMS: median 0.0 [0–6], SFN: median 0.0 [0–1], $P < 0.01$), as well as nonpharmacological therapies (FMS: median 2.0 [0–17], SFN: median 0.0 [0–7], $P < 0.001$). Frequently used medication is listed in **Table 7**.

Table 4

Additional symptoms and comorbidities in patients with fibromyalgia syndrome and small fiber neuropathy.

	FMS	SFN	*P*
Comorbidities			
Bronchial asthma	20/158 (12.7%)	1/53 (1.9%)	<0.05
Migraine with aura	12/158 (7.6%)	3/53 (5.7%)	n.s.
Migraine without aura	27/158 (17.1%)	1/53 (1.9%)	<0.01
Tinnitus	18/158 (11.4%)	1/53 (1.9%)	<0.05
Depression	74/158 (46.8%)	6/53 (11.3%)	<0.001
Diabetes type 2	0/158 (0.0%)	3/53 (5.7%)	<0.05
Sicca syndrome	8/158 (5.1%)	3/53 (5.7%)	n.s.
Borreliosis	9/158 (5.7%)	3/53 (5.7%)	n.s.
Hypothyreosis	20/158 (12.7%)	7/53 (13.2%)	n.s.
Hyperthyreosis	1/158 (0.6%)	1/53 (1.9%)	n.s.
Hashimoto disease	13/158 (8.2%)	7/53 (13.2%)	n.s.
Neurological symptoms			
Numbness	19/158 (12.0%)	15/53 (28.3%)	<0.01
Tingling	26/158 (16.5%)	36/53 (67.9%)	<0.001
Paresthesias	24/158 (15.2%)	6/53 (11.3%)	n.s.
Hypersensitivity to touch	1/158 (0.6%)	7/53 (13.2%)	<0.001
Hypohidrosis	8/158 (5.1%)	6/53 (11.3%)	n.s.
Hyperhidrosis	59/158 (37.3%)	28/53 (52.8%)	n.s.
Conspicuous sweating (hypohidrosis or hyperhidrosis)	66/158 (41.8%)	34/53 (64.2%)	<0.01
GI and urogenital symptoms			
Irritable bladder	25/158 (15.8%)	1/53 (1.9%)	<0.01
Obstipation	25/158 (15.8%)	1/53 (1.9%)	<0.01
Diarrhea	24/158 (15.2%)	5/53 (9.4%)	n.s.
Irritable bowel	69/158 (43.7%)	1/53 (1.9%)	<0.001
Nausea	1/158 (4.4%)	5/53 (9.4%)	n.s.
Sleep problems			
Unrefreshed sleep	81/158 (51.3%)	0/52 (0.0%)	<0.001
Sleep disturbance	100/158 (63.3%)	11/53 (20.8%)	<0.001
Difficulties in falling asleep	29/158 (18.4%)	2/53 (3.8%)	<0.01
Mental symptoms			
Fatigue	139/158 (88.0%)	3/53 (5.7%)	<0.001
Apathy	24/158 (15.2%)	2/53 (3.8%)	<0.01
Asthenia	30/158 (19.0%)	6/53 (11.3%)	n.s.
Agitation	16/158 (10.1%)	1/53 (1.9%)	n.s.
Irritability	13/158 (8.2%)	1/53 (1.9%)	n.s.
Depressed mood	29/158 (18.4%)	1/53 (1.9%)	<0.01
Cognitive symptoms	62/158 (39.2%)	0/53 (0.0%)	<0.001
Concentration problems	114/158 (72.2%)	1/53 (1.9%)	<0.001
Other symptoms			
Limb stiffness	95/158 (60.1%)	3/53 (5.7%)	<0.001
Joint swelling	8/158 (5.1%)	9/53 (17.0%)	<0.05
Vertigo	19/158 (12.0%)	8/53 (15.1%)	n.s.
Circulatory problems	12/158 (7.6%)	11/53 (20.8%)	<0.05
Palpitations	14/158 (8.9%)	3/53 (5.7%)	n.s.
Respiratory distress	13/158 (8.2%)	0/53 (0.0%)	<0.05
Restless legs	12/158 (7.6%)	2/53 (3.8%)	n.s.
Total number of additional and spontaneously reported symptoms: median [range]	8.0 [0–28]	4.0 [0–14]	<0.001

FMS, fibromyalgia syndrome; GI, gastrointestinal; n.s., not significant; SFN, small fiber neuropathy.

Table 5

Family history of patients with fibromyalgia syndrome and small fiber neuropathy.

	FMS	SFN	*P*
Chronic pain (eg, migraine, joint/back pain, FMS, and rheumatoid arthritis)	78/158 (49.4%)	17/53 (32.1%)	<0.05
Neurological diseases (eg, multiple sclerosis, epilepsy, Parkinson disease, polyneuropathy, and dementia)	26/158 (16.5%)	22/53 (41.5%)	<0.001
Mental disorders (eg, depression, bipolar disorder, schizophrenia, drug or alcohol abuse, and psychosis)	30/158 (19.0%)	3/53 (5.7%)	<0.05

FMS, fibromyalgia syndrome; SFN, small fiber neuropathy.

Table 6

Blood tests in patients with fibromyalgia syndrome and small fiber neuropathy.

	FMS	SFN	*P*
Median [range]			
HbA1c (%)	5.4 [4.7–6.4]	5.5 [3.6–7.7]	<0.05
Fasting blood sugar levels (mg/dL)	95.5 [56–128]	97.0 [74–144]	n.s.
oGTT 1 h (mg/dL)	138.0 [68–246]	172.0 [89–333]	<0.01
oGTT 2 h (mg/dL)	120.0 [65–217]	123.0 [79–284]	<0.05
TSH (mU/L)	1.8 [0.0–10.8]	1.6 [0.0–9.2]	n.s.
Vitamin B_{12} (pg/mL)	449.5 [183–2000]	470.5 [215–2000]	n.s.
Pathological test results			
HbA1c indicating prediabetes (5.7–6.4%)	32/157 (20.4%)	16/50 (32.0%)	n.s.
HbA1c indicating diabetes (>6.4%)	0/157 (0.0%)	3/51 (5.9%)	<0.05
Pathological oGTT (>140 mg/dL after 2 h)	23/157 (14.6%)	14/47 (29.8%)	<0.05
Pathological TSH (<0.4/> 4.0 mU/L)	20/157 (12.7%)	8/50 (16.0%)	n.s.
Reduced vitamin B_{12} (<200 pg/mL)	2/142 (1.4%)	0/50 (0%)	n.s.

FMS, fibromyalgia syndrome; HbA1c, glycated hemoglobin A1c; n.s., not significant; oGTT, oral glucose tolerance test; SFN, small fiber neuropathy; TSH, thyroid-stimulating hormone.

Nonpharmacological therapies were predominantly applied by patients with FMS, whereas patients with SFN rather used food supplements in addition to pharmaceuticals. Psychotherapy was more frequently applied in patients with FMS than in patients with SFN (FMS: 21/158 [13.3%], SFN: 1/53 [1.9%], $P < 0.05$).

3.7. Small fiber pathology mainly manifests as proximal skin denervation in fibromyalgia syndrome and prolonged electrical A-delta conductance in small fiber neuropathy

Table 8 lists the results of small fiber tests. **Table 9** compares the frequency of pathological test results. **Table 10** summarizes the main differences in small fiber tests. Neurological examination revealed sensory abnormalities in thermal hypoesthesia or allodynia in 31 of 53 (58.5%) patients with SFN. The most striking result was that mere reduction of proximal IENFD was a phenomenon twice frequently observed in patients with FMS (48/157, 31%) than in patients with SFN (8/53, 15%, $P < 0.05$). In contrast, distal IENFD did not differ between groups. When comparing individual IENFD with our laboratory normative values, 18 of 158 (11%) patients with FMS had reduced distal IENFD compared with 10 of 53 (19%) patients with SFN ($P > 0.05$).

In QST, we first assessed patients' individual data comparing results with published normative values.[27] QST showed small fiber impairment in 24 of 157 (15.3%) patients with FMS compared with 19 of 53 (35.8%) patients with SFN ($P < 0.01$). Direct comparison of the 2 cohorts revealed diversity for the cold detection threshold (CDT), cold pain threshold (CPT), mechanical

Table 7

Therapy approaches in fibromyalgia syndrome and small fiber neuropathy.

	FMS	SFN	*P*
Median number of medications [range]	4.0 [0–19]	3.0 [0–10]	<0.001
Median number of medical interventions [range]	0.0 [0–6]	0.0 [0–1]	<0.01
Median number of nonpharmaceutical therapies [range]	2.0 [0–17]	0.0 [0–7]	<0.001
Median number of rehabilitations [range]	0.0 [0–7]	0.0 [0–2]	<0.01
Multimodal treatment	29/157 (18.5%)	2/53 (3.8%)	<0.01
Medication: median [range]			
Nonopioids (NSAID/metamizole dipyrone/acetaminophen)	2.0 [0–5]	0.0 [0–3]	<0.001
Opioids	0.0 [0–3]	0.0 [0–2]	n.s.
Anticonvulsants	0.0 [0–3]	1.0 [0–4]	<0.001
SSRI	0.0 [0–2]	0.0 [0–1]	<0.01
SSNRI	0.0 [0–2]	0.0 [0–1]	n.s.
Tricyclic antidepressants	1.0 [0–3]	0.0 [0–3]	<0.01
Muscle relaxer	0.0 [0–2]	0.0 [0–1]	<0.05
Topical agents	0.0 [0–1]	0.0 [0–2]	n.s.
Nonpharmaceutical approaches: median [range]			
Food supplements	0.0 [0–5]	0.0 [0–4]	<0.05
Active methods	0.0 [0–3]	0.0 [0–1]	<0.001
Passive methods	0.0 [0–4]	0.0 [0–1]	<0.001
Acupuncture	0.0 [0–2]	0.0 [0–1]	<0.05
Temperature methods	0.0 [0–2]	0.0 [0–1]	<0.001
Electricity methods	0.0 [0–2]	0.0 [0–1]	<0.05
Relaxation methods	0.0 [0–3]	0.0 [0–1]	<0.001
Asian relaxation methods (ie, Tai Chi, Yoga, Qigong)	0.0 [0–2]	0.0 [0–1]	<0.05
Psychotherapy			
In past	38/158 (24.1%)	2/53 (3.8%)	<0.01
Currently	21/158 (13.3%)	1/53 (1.9%)	<0.05

FMS, fibromyalgia syndrome; n.s., not significant; NSAID, nonsteroidal anti-inflammatory drugs; SFN, small fiber neuropathy; SSNRI, selective serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Table 8

Small fiber examinations.

	FMS	SFN	*P*
Skin biopsy			
Median IENFD lower leg (fibers/mm) [range]	6.3 [0.0 to 14.4]	5.4 [0.0 to 16.3]	n.s.
Median IENFD upper thigh (fibers/mm) [range]	8.4 [1.2 to 20.0]	8.8 [1.5 to 16.5]	n.s.
QST: median [range]			
CDT (°C)	−2.2 [−22.0 to −0.9]	−3.9 [-22.0 to −0.8]	<0.001
WDT (°C)	6.7 [1.8 to 18.0]	5.4 [1.0 to 17.6]	n.s.
TSL (°C)	10.5 [1.5 to 40.0]	11.1 [4.0 to 40.0]	n.s.
PHS (x/3)	0.0 [0 to 3]	0.0 [0 to 3]	n.s.
CPT (°C)	16.1 [10.0 to 30.6]	11.1 [10.0 to 29.4]	<0.05
HPT (°C)	45.2 [35.8 to 50.0]	46.0 [37.2 to 50.0]	n.s.
MDT (mN)	2.1 [0.2 to 724.1]	4.9 [0.2 to 207.9]	<0.001
MPT (mN)	59.7 [5.7 to 724.1]	27.9 [5.7 to 724.1]	<0.01
MPS (rating)	1.8 [0.0 to 72.7]	1.3 [0.0 to 20.3]	n.s.
DMA (rating)	0.0 [0.0 to 70.6]	0.0 [0.0 to 5.3]	n.s.
WUR (ratio)	2.0 [0.0 to 42.0]	2.0 [1.0 to 5.0]	n.s.
VDT (x/8)	7.0 [3 to 8]	6.5 [5 to 8]	n.s.
PPT (kPa)	368.0 [196 to 1030]	441.0 [235 to 840]	<0.01
CCM			
Median NFD (fibers/mm^2) [range]	23.0 [5.2 to 38.5]	23.0 [6.3 to 36.5]	n.s.
Median NBD (fibers/mm^2) [range]	66.6 [9.7 to 181.5]	46.4 [10.4 to 102.1]	<0.001
Median NFL (mm/mm^2) [range]	13.3 [5.7 to 21.8]	13.1 [7.2 to 19.9]	n.s.
PREP (average left/right side): median [range]			
Foot N1 latency (ms)	168.2 [97.7 to 232.3]	206.7 [0.0 to 285.3]	<0.001
Foot P1 latency (ms)	211.5 [118.9 to 310.6]	272.8 [0.0 to 332.8]	<0.001
Foot PPA (μV)	11.7 [1.2 to 39.8]	13.5 [0.0 to 26.9]	<0.05

CCM, corneal confocal microscopy; CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; FMS, fibromyalgia syndrome; HPT, heat pain threshold; IENFD, intraepidermal nerve fiber density; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; N1, first negative peak latency; NBD, nerve branch density; NFD, nerve fiber density; NFL, nerve fiber length; NRS, numeric rating scale; n.s., not significant; P1, subsequent positive peak latency; PHS, paradoxical heat sensations; PPA, peak-to-peak amplitudes; PPT, pressure pain threshold; PREP, pain-related evoked potentials; QST, quantitative sensory testing; SFN, small fiber neuropathy; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

detection threshold (MDT), mechanical pain threshold (MPT), and pressure pain threshold (PPT).

The evaluation of CCM showed no differences in corneal NFD and NFL between the 2 cohorts, also in comparison with our laboratory normative values (NFD <19.3 fibers/mm^2: FMS 34/133 [25%], SFN 11/50 [20%]; NFL <11.1 mm/mm^2: FMS 33/133 [25%], SFN 14/50 [28%]). However, NBD was pathologically reduced in 15 of 133 (11%) patients with FMS and in 18 of 50 (36%) patients with SFN ($P < 0.001$).

When recording PREP, 52 of 123 (42%) patients with FMS and 21 of 39 (54%) patients with SFN had pathological findings. Comparing data with our laboratory normative values, N1 latencies were prolonged in 14 of 39 (36%) patients with SFN (FMS: 3/123 [2%], $P < 0.001$). In 15 of 39 (39%) patients with SFN, the P1 latency was longer than normal (FMS: 2/123 [2%], $P < 0.001$). Peak-to-peak amplitude was pathologically reduced more in patients with FMS than in patients with SFN (FMS: 51/123 [41.5%], SFN: 7/38 [18.4%], $P < 0.05$).

3.8. Influence of disease duration

In contrast to data analysis of the entire study groups, pain intensity without analgesic treatment and the number of analgesics used were comparable in both patient groups when assessed for ≤5 years of disease duration (**Table 11**). Also, distal skin innervation was higher in patients with FMS than in patients with SFN with a short disease duration ($P < 0.05$).

4. Discussion

Since the description of small fiber pathology in FMS patient subgroups,[11,49] there is an ongoing controversy weather FMS equals SFN.[47] The distinction is crucial because prognosis and treatment options differ substantially between both entities. We pioneer a direct comparative approach and report clinical characteristics that may be useful in differential diagnosis.

We confirm that also patients with FMS may have small nerve fiber impairment as reported before.[17,38,49] However, it is the patients with SFN who rather suffer from a neuropathic pain phenotype with mainly acral pain accompanied by additional sensory symptoms together with a family history of neurological diseases. Thirty-one of 53 (58.5%) women with SFN showed sensory abnormalities indicating peripheral deafferentiation. A similar distribution was reported previously[8] and emphasizes the importance to equally consider the results of neurological examination when making the diagnosis of SFN. Patients with FMS were characterized by generalized musculoskeletal pain regularly accompanied by sleep disturbance, fatigue, and concentration problems along with a family history of chronic pain syndromes. Depression and depressed mood occurred more frequently in patients with FMS than in patients with SFN (**Table 4**).

While nonpharmacological treatment is recommended first line in FMS in national[39] and international guidelines,[26,44] tricyclic antidepressants, anticonvulsants, and serotonin norepinephrine reuptake inhibitors are used first line against pain in idiopathic SFN treatment.[13] Although patients with SFN and FMS received analgesic medication mostly in accordance with national and international guidelines, it was the patients with FMS who reported numerous insufficient analgesic treatment attempts, whereas patients with SFN mostly experienced pain relief upon antineuropathic pain treatment. Patients with FMS reported a higher number of analgesics used than patients with SFN. However, the number of drug therapy attempts was comparable between groups in patients with short disease duration, ie, ≤5 years. It is of note that standardized pain questionnaires such as the NPSI and the GCPS were of minor use in distinguishing FMS from SFN. A

Table 9

Data of pathological small fiber tests.

	FMS	SFN	*P*
Skin biopsy			
IENFD distally reduced (ie, <5.4 fibers/mm)	18/158 (11.4%)	10/53 (18.9%)	n.s.
IENFD proximally reduced (ie, <8.5 fibers/mm)	48/157 (30.6%)	8/53 (15.1%)	<0.05
IENFD generally reduced (ie, distal <5.4 fibers/mm AND proximal <8.5 fibers/mm)	38/158 (24.1%)	13/53 (24.5%)	n.s.
Pathological IENFD in at least one localization	104/157 (66.2%)	31/53 (58.5%)	n.s.
QST pathological[16]			
CDT	6/157 (3.8%)	10/53 (18.9%)	<0.01
WDT	13/157 (8.3%)	10/53 (18.9%)	<0.05
TSL	18/157 (11.5%)	15/53 (28.3%)	<0.01
QST (ie, CDT, WDT, or TSL pathological)	24/157 (15.3%)	19/53 (35.8%)	<0.01
PHS	32/157 (20.4%)	18/53 (34.0%)	n.s.
CPT	0/157 (0%)	2/53 (3.8%)	n.s.
HPT	16/156 (10.3%)	7/53 (13.2%)	n.s.
MDT	13/157 (8.3%)	10/53 (18.9%)	<0.05
MPT	25/157 (15.9%)	16/53 (30.2%)	<0.05
MPS	34/156 (21.8%)	12/52 (23.1%)	n.s.
DMA	14/157 (8.9%)	2/52 (3.8%)	n.s.
WUR	6/157 (3.8%)	4/52 (7.7%)	n.s.
VDT	18/157 (11.5%)	3/53 (5.7%)	n.s.
PPT	23/157 (14.6%)	4/53 (7.5%)	n.s.
CCM			
Pathological NFD (ie, <19.3/mm^2)	34/133 (25.6%)	11/50 (22.0%)	n.s.
Pathological NBD (ie, <36.3/mm^2)	15/133 (11.3%)	18/50 (36.0%)	<0.001
Pathological NFL (ie, <11.1 mm/mm^2)	33/133 (24.8%)	14/50 (28.0%)	n.s.
At least one pathological CCM parameter	47/133 (35.3%)	22/51 (43.1%)	n.s.
PREP			
Pathological N1 (ie, >224.89 ms)	3/123 (2.4%)	14/39 (35.9%)	<0.001
Pathological P1 (ie, >285.46 ms)	2/123 (1.6%)	15/39 (38.5%)	<0.001
Pathological PPA (ie, <10.0 μV)	51/123 (41.5%)	7/38 (18.4%)	<0.05
At least one pathological PREP parameter	52/123 (42.3%)	21/39 (53.8%)	n.s.

CCM, corneal confocal microscopy; CDT, cold detection threshold; CPT, cold pain threshold; DMA, dynamic mechanical allodynia; FMS, fibromyalgia syndrome; HbA1c, glycated hemoglobin A1c; HPT, heat pain threshold; IENFD, intraepidermal nerve fiber density; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; N1, first negative peak latency; NBD, nerve branch density; NFD, nerve fiber density; NFL, nerve fiber length; n.s., not significant; oGTT, oral glucose tolerance test; P1, subsequent positive peak latency; NRS, numeric rating scale; PHS, paradoxical heat sensations; PPA, peak-to-peak amplitudes; PPT, pressure pain threshold; PREP, pain-related evoked potentials; QST, quantitative sensory testing; SFN, small fiber neuropathy; TSH, thyroid-stimulating hormone; TSL, thermal sensory limen; VDT, vibration detection threshold; WDT, warm detection threshold; WUR, wind-up ratio.

previous questionnaire survey for small fiber neuropathy in patients with FMS also gave similar results in patient subgroups.[25] Our study underscores that specifically designed pain and neuropathic symptom questionnaires are needed to help differentiating FMS from SFN. For this, our data collection may provide a valuable base.

We report a higher prevalence of impaired glucose metabolism in patients with SFN compared to patients with FMS, which is in line with previous data.[40] Although data are conflicting about the pathophysiological influence of mere prediabetes,[43] we believe that thorough search for potential impairment in glucose metabolism is crucial in the clinical management of patients with FMS and SFN. These data are also of immense importance regarding the underlying pathomechanism in both entities. We suspect nociceptive hyperexcitability because of sensitization and degeneration of sensory neurons.[38]

Multilevel investigation of small fiber pathology revealed that patients with FMS mostly show proximal skin denervation, whereas reduction of lower leg IENFD was most common in patients with SFN.[10,11] This is an intriguing finding also reported by others[52] and remains of unclear pathophysiology. Regarding the proximal denervation in FMS found by us and others,[33,52] we speculate that an impairment of sensory neurons in the dorsal root ganglia may be present. Neuropathies normally show a distal-to-proximal spread; however, predominant proximal denervation was also shown in patients with Sjögren syndrome,[4] celiac disease,[6] or autoimmune hepatitis.[28] Although merely speculative, impairment of ganglionic sensory neurons may play a role in FMS, such that further investigations are needed. It is further of note that in patients with SFN, distal skin denervation was associated with prolonged latencies of electrically evoked A-delta potentials.

As for sensory profiles, QST was normal in almost all patients of both groups when compared with control values. This is

Table 10

Differences between fibromyalgia syndrome and small fiber neuropathy in small fiber tests.

	FMS	SFN
Skin innervation	Proximal denervation	Distal denervation
Corneal innervation	Mostly normal	Reduced NBD
Sensory profiles compared with healthy controls	CPT, MPS, PTT ↑ MDT, MPT↓	CDT↑, MDT ↓ more often pathological
A-delta conductance	PPA ↓	P1 ↑, N1 ↑

CDT, cold detection threshold; CPT, cold pain threshold; FMS, fibromyalgia syndrome; MDT, mechanical detection threshold; MPT, mechanical pain threshold; MPS, mechanical pain sensitivity; N1, first negative peak latency; NBD, nerve branch density; P1, subsequent positive peak latency; PPA, peak-to-peak amplitudes; PPT, pressure pain threshold; SFN, small fiber neuropathy.

Table 11

Subgroup comparison for short disease duration of ≤5 years.

	FMS (n = 33)	SFN (n = 32)	*P*
Median pain intensity during interview (NRS) [range]	5.0 [1–9]	4.0 [1–9]	n.s.
Median pain intensity after medication (NRS) [range]	2.0 [0–4]	1.0 [0–1]	<0.001
Median number of additional symptoms [range]	7.0 [1–28]	4.0 [0–11]	<0.001
Median number of pain aggravating factors [range]	2.0 [1–6]	1.0 [0–3]	<0.01
Median number of pain relieving factors [range]	2.0 [1–4]	1.0 [0–3]	<0.001
Median number of medications [range]	4.0 [1–8]	3.0 [0–10]	n.s.
Median number of nonpharmaceutical therapy attempts [range]	3.0 [0–15]	0.0 [0–4]	<0.001
Psychotherapy in past	7/33 (21.2%)	0/32 (0%)	<0.01
Median IENFD lower leg (fibers/mm) [range]	6.4 [0–14.4]	5.4 [0–11.8]	<0.05
Median IENFD upper thigh (fibers/mm) [range]	8.2 [1.3–16.4]	9.8 [1.5–16.5]	n.s.

FMS, fibromyalgia syndrome; IENFD, intraepidermal nerve fiber density; NRS, numeric rating scale; n.s., not significant; SFN, small fiber neuropathy.

interesting because several studies have reported elevated thermal perception thresholds in patients with FMS compared with healthy controls.[3,23] The main reason for this discrepancy may be the diversity in the number of subjects investigated keeping in mind that large-enough sample size is necessary to obtain robust QST data.[27] Normal QST profiles in patients with SFN were already reported by several previous studies.[10,37,48] Interestingly, intergroup comparison revealed single parameters that might be of value to distinguish FMS from SFN (**Table 9**).

While our finding of higher NBD on CCM in patients with FMS compared with patients with SFN remains unclear as for its pathophysiological relevance, longer N1 and P1 latencies in patients with SFN is consistent with previous data.[30] These findings may reflect axonopathy as in analogy to data obtained in diabetic neuropathy via laser-evoked potentials.[1,36] Potential influences of disease duration on our data need to be taken into account because intergroup differences varied when assessing short or long periods.

Our study has some limitations. The study cohort consisted of women; hence, our data cannot be transferred to men. The FMS patient group was 3 times larger than the SFN group and group sizes were overall small. However, given the homogeneity in data acquisition during the original monocentric studies, we believe this is of minor influence. Because of the retrospective nature of data collected in 2 independent studies on patients seen at our Department, matching was not possible. Furthermore, the fact that the SFN cohort consisted of patients seen at our department and agreeing to participate in our study, whereas the FMS patient cohort was recruited for study participation needs to be taken into account when interpreting our results. Although inclusion criteria differed naturally investigating patients with 2 different diagnoses,[10,11] exclusion criteria were also not identical between both initial studies: B_{12} hypovitaminosis was an exclusion criterion in patients with SFN. Hence, the finding that vitamin B_{12} levels did not distinguish between patients with FMS and SFN may be biased by

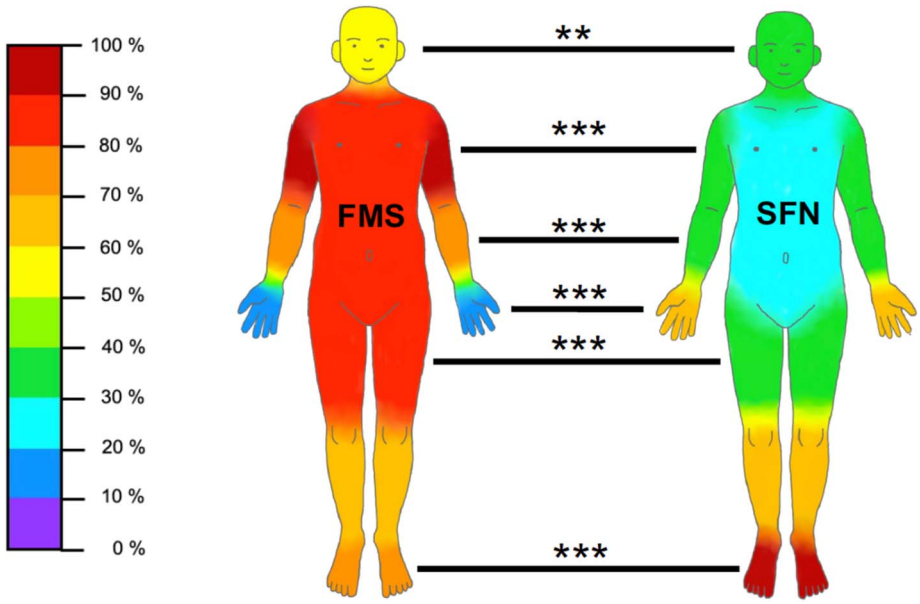

Figure 1. Proportion of patients who reported pain in distinct body areas. The graph depicts the frequency of pain reported in distinct body areas in relation to the FMS (n = 158) and SFN (n = 53) patient groups. For exact data, please see Table 2. FMS, fibromyalgia syndrome; SFN, small fiber neuropathy. $^{**}P < 0.01$, $^{***}P < 0.001$.

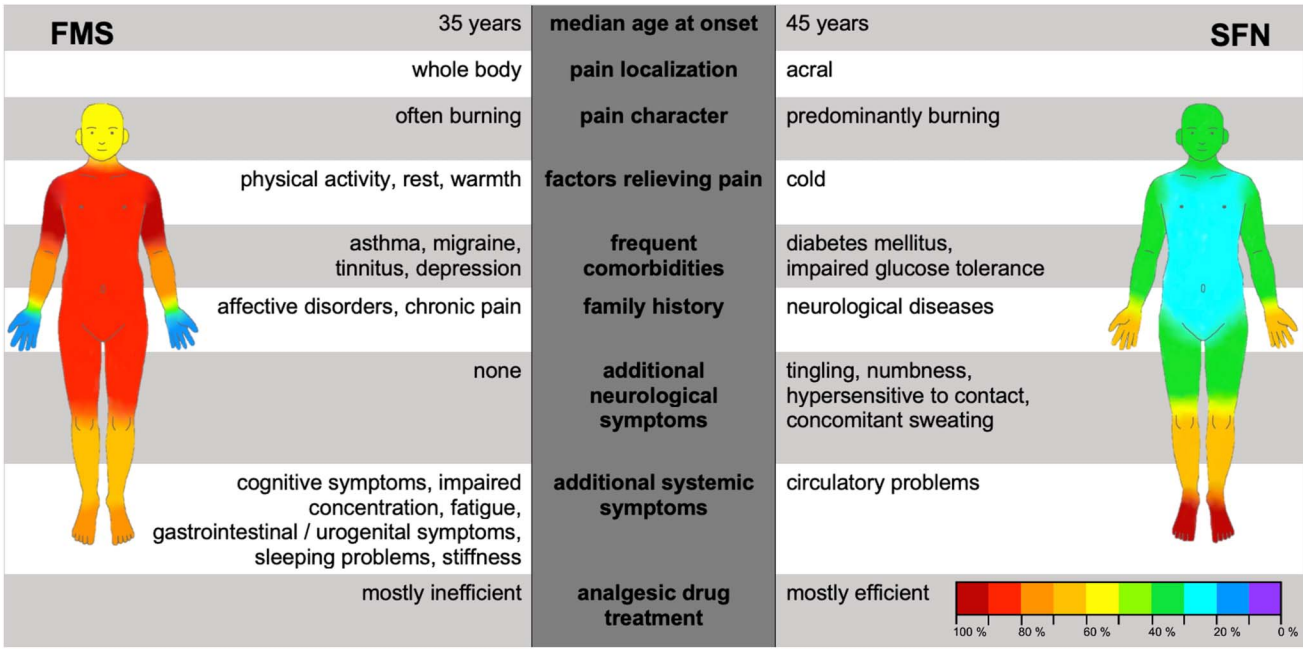

Figure 2. Clinical aspects distinguishing FMS and SFN. The plot summarizes the most important opposing aspects that can be collected during interview. The figurines showing the pain localization are taken from Figure 1. The exact data can be found in Tables 1, 2, 4, 5 and 7. FMS, fibromyalgia syndrome; SFN, small fiber neuropathy.

the fact that patients with SFN with already diagnosed vitamin B_{12} deficiency were not enrolled. Similarly, patients with FMS with severe depression currently requiring treatment were not included such that data on the frequency of depression in the 2 cohorts may be biased. Furthermore, our data on the prevalence of impaired glucose metabolism may be biased because previously diagnosed diabetes mellitus was an exclusion criterion.

Still, we performed the first head-to-head comparison of a rich set of monocentrically collected clinical data between patients with FMS and SFN and provide clinical guidance directly applicable in daily practice.

Disclosures

The authors have no conflict of interest to declare.

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