The challenge of differentiating fibromyalgia from small-fiber neuropathy in clinical practice

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Abstract

Fibromyalgia and small fibre neuropathy are two diseases leading to chronic widespread pain, and it is difficult to differentiate them in order to provide appropriate care. In this review, we will describe the pathophysiological and clinical differences between fibromyalgia and small fibre neuropathy. In fibromyalgia, pain is increased by dysregulation of central pain processing while small fibre neuropathy pain is related to loss or dysfunction of intraepidermal small nerve fibres. Higher pain intensity; stabbing pain and paraesthesia; allodynia; dry eyes/mouth; changed pattern or sweating on body; skin colour alterations/modifications; reduced hair/nail growth on lower extremities; warm or cold hypoesthesia could be more common in small fibre neuropathy whereas headache or temporo-mandibular disorder point toward fibromyalgia. Length-dependent distribution of pain is common in small fibre neuropathy but can also affect the whole body. Anxiety or depression are common in these two diseases, but post-traumatic stress disorder and physical or sexual abuse in childhood or adulthood suggest fibromyalgia. Inflammatory disease or musculoskeletal disease is frequently reported with fibromyalgia whereas metabolic disorders (especially diabetes mellitus), neurotoxic exposure, Sjogren's syndrome, sarcoidosis, HIV are the main diseases associated with small fibre neuropathy. Skin biopsy, quantitative sensory testing, laser evoked potentials, confocal corneal microscopy or electrochemical skin conductance can help to discriminate between fibromyalgia and small fibre neuropathy.

1. Introduction

Fibromyalgia is characterized by chronic, widespread musculoskeletal pain, fatigue, sleep disturbances, and other cognitive and somatic symptoms. It affects approximately 0.5% to 5% of the general population [1], depending on the diagnostic criteria applied [2]. The prevalence is significantly higher in patients with other chronic diseases, such as inflammatory rheumatic diseases, and fluctuates according to the studies between 10 and 65% of these patients [1]. Chronic widespread pain, the cardinal symptom of fibromyalgia, is common in the general population, with comparable prevalence rates of 7.3% to 12.9% across different countries [1]. Small fibre neuropathy (SFN) is another aetiology of chronic widespread pain. For most experts, SFN is a different disease than fibromyalgia, with different pathophysiological mechanisms [1–6], through some authors claim SFN is a subgroup of

fibromyalgia [7–10]. Although chronic widespread pain is present in both diseases, some clinical or paraclinical features may distinguish them. Differentiating fibromyalgia from SFN has implications for patient management: the main treatments for fibromyalgia are nonpharmacological therapies, while those for SFN are based on neuropathic pain drugs. However, questionnaires used in clinical practice cannot differentiate between fibromyalgia and SFN, especially since the recent classification criteria have increased the prevalence of fibromyalgia. The objectives of this review are a description of the pathophysiological and clinical differences between these two diseases.

2. Pathophysiology of fibromyalgia

The pathophysiology of fibromyalgia is not completely understood. Several directions of research suggest abnormal central pain processing as the primary pathophysiologic mechanism [5]. The first hypothesis involves endogenous pain modulation systems (including endogenous opioid systems and catecholaminergic systems in the brain stem) which have a powerful inhibitory or facilitating effect on the neuronal transmission of nociceptive signals. Dysregulation of pain can occur in the ascending or descending pain pathway. Some of these perturbations include greater neuronal activity in pain-processing brain areas, exaggerated pain responses to experimental stimuli (sensitization), changes in brain morphology, regulation of peripheral or brain receptors, and altered levels of pain-related neuropeptides and neurotransmitters (substance P, brain-derived neurotrophic factor, glutamine, and dopamine) [5]. Hyperexcitable C nociceptors have also been identified in patients with fibromyalgia or SFN compared with controls [11]. These changes may extend to processing of other sensory input, potentially explaining other bothersome symptoms associated with fibromyalgia, such as fatigue, sleep disruption, cognitive problems, and depression [12]. More specifically, dysregulation of conditioned pain modulation (also called diffuse noxious inhibitory control-like effect) which is a powerful inhibitory system from brain stem to spinal cord can lead to hypersensitivity to pain. The presence of depressive symptoms could further accentuate the failure to activate this brain network [13].

Dysfunction of central pain processing leads to “central sensitization”, which is defined as “Increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input” according to the International Association for the Study of Pain [14]. While older definition of neuropathic pain included “lesion or dysfunction of the somatosensory system”, the new classification of pain separates “nociplastic pain” (related to central sensitization) from “neuropathic pain” (which now includes only lesions of the somatosensory nervous system but not dysfunction) [15]. Therefore, fibromyalgia pain can be classified as nociplastic pain, whereas SFN is categorized as neuropathic pain due to the existence of an individually identifiable lesion.

A complementary line of research concerns the disturbances in the physiological mechanisms involved in the response to stress. The accumulation of physical, psychological, or emotional stress can lead to

disturbances in the two main systems involved in the physiological response to stress: the hypothalamic-pituitary-adrenal axis and the sympathetic system. These two strongly interconnected effectors are connected to the brain structures involved in the perception and modulation of pain. Fibromyalgia is associated with a reduced reactivity of the hypothalamic-pituitary-adrenal axis and the sympathetic system to stress (physical and/or psychological), which could modify modulation of pain [4,13].

Fibromyalgia can be an isolated diagnosis or can be frequently associated with other diseases, such as inflammatory rheumatic diseases, auto-immune disorders, or musculoskeletal disorders. In a systematic review, the median incidence of physician diagnosed fibromyalgia in the general population was 4.3 per 1000 person-years but 14.0 if medical illness was present [6]. Several risk factors were identified, such as musculoskeletal disorders, irritable bowel syndrome, peptic ulcer, diabetes, hypertension, hyperlipidemia, “medical comorbidities”, sleep disorders, anxiety/depression, smoking, heavy or repetitive work, childhood difficulties by the age of 7 [6]. A “bidirectional relationship” was found between fibromyalgia and depression, gastroesophageal reflux disorder, headache, migraine, insomnia, and irritable bowel syndrome; each of these 6 disorders predicted fibromyalgia, which, in turn, was a risk factor for each of them [6]. Potentially traumatic events and post-traumatic stress disorder (PTSD) including childhood adversities are also risk factors for the development of fibromyalgia [16–18]. The link with physical and/or psychological stress can explain the strong correlation between fibromyalgia and other diseases such as inflammatory rheumatic disorders and mood disorders.

The diagnostic criteria of fibromyalgia have significantly evolved: the 1990 criteria required a physical examination [13]. The 2010 and 2016 American College of Rheumatology criteria only need interview data to quantify the Widespread Pain Index (WPI : 19 body area) and Symptom Severity (SS) scores during the past week: fatigue, waking unrefreshed, and cognitive symptoms [19]. An important update between the 2010 and the 2016 fibromyalgia criteria is related to associated diseases. In the more recent criteria, “A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses” whereas in the 2010 criteria “the patient does not have a disorder that would otherwise explain the pain” [19]. The 2016 criteria are useful to include patients with previous or associated disease such as rheumatoid arthritis or spondyloarthritis, especially patients with persistent pain without clinical inflammation, but therefore cannot exclude patients with SFN. The main consequence of these successive changes is a significant increase in the number of patients labelled as fibromyalgia [2] and confusion with diagnoses with close clinical characteristics.

3. Pathophysiology of small fibre neuropathy

SFN is a disease characterised by a selective or predominant impairment of peripheral afferent thinly myelinated Aδ-fibres and unmyelinated C-fibres [20]. In the somatosensory nervous system, small nerve fibres transmit information about temperature, pain, and itch, and in the autonomic nervous system, they mediate sudomotor, thermoregulatory, cardiovascular, gastrointestinal, urogenital, and other autonomic functions. They participate in inflammation and injury responses to help protect the body from external and internal dangers. The clinical presentation of SFN is heterogeneous, with no single clinical pattern fitting all presentations. However, the two most common presentations are a length-dependent polyneuropathy and a non-length dependent ganglionopathy, or mononeuropathy. Autonomic symptoms are present in nearly half of the patients with SFN. The length-dependent SFN is easier to diagnose because symptoms are close to large fibre neuropathies whereas the non-length-dependent SFN symptoms are closely related to fibromyalgia. Skin biopsy is frequently used as gold standard in studies to evaluate intraepidermal nerve fibre density (IENFD), even if other diagnosis procedures exist. In 2010, guidelines on the use of skin biopsy in the diagnosis of small fibre neuropathy were published [21]. For length-dependent SFN, a 3-mm punch skin biopsy performed at the distal leg (10 cm above the lateral malleolus) is recommended for quantification of intraepidermal nerve fibres density. An additional biopsy from the proximal thigh may provide information about both length-dependent and non-length-dependent processes. A biopsy can be performed in clinical routine but requires sterile and haemostasis procedures. Immunohistochemistry or immunofluorescence with polyclonal anti-PGP 9.5 must be performed in a laboratory with experience in the interpretation of this diagnosis. Normative reference values of intraepidermal nerve fibre depend on age and gender [21] but are not used in all the studies [22]. Moreover, a recent small-scale study showed that the IENFD at the distal leg appeared influenced by the ethnicity : IENFD is lower in Chinese Americans than in non-Chinese Americans [23], but normative data depending on ethnicity are not available.

Multiple diseases are associated with low IENFD and SFN, especially diseases with neurologic involvement or toxicity. Most of the studies find approximately fifty percent of idiopathic SFN, even if some “idiopathic” SFN could be of genetic origin [24]. The main diseases frequently associated with SFN are those with neurological impairment, suggesting direct damage to these fibres. However, another study suggests a link with increase excitatory neurotransmitter (glutamate) in insula, which is identified as one of the mechanisms of fibromyalgia, could reduce IENFD. So central modification of central nervous system could lead to SFN [7]. This article questions the separation between fibromyalgia and SFN, which remains a debate not completely settled.

Even if the most sensitive and specific examination for SFN is skin biopsy, the correlation between reduced IENFD and pain remain unclear. A decrease of the number of fibers is a structural change but could differ with functional changes [25]. Other factors such as inflammation could also play a role: increase of Langerhans cells are thought to play a role in diabetic neuropathy (there is an increase of these cells in patients with painful neuropathy compared with patients with non-painful neuropathy) [26]. An increase in macrophages in the epidermidis [20], and CGRP-positive fibers [25] are other hypothesis to explain pain. Another argument in favour of a problem of fibre function, rather than a simple decrease in density, is the existence of gain-of-function variants of sodium channels Nav1.7, Nav1.8 and Nav 1.9, which give pain by altering the functioning of these NaV channels [24,27]. However, some patients with mutations of S*CN11A* gene encodes the $Na_v1.9$ sodium channel do not have typical SFN [28]. In conclusion, pain in SFN is not just linked with decrease number of fibers but is probably linked with the dysfunction of the remaining fibers, can thus be sensitised, hypofunctional, or normal.

Diagnostic criteria for idiopathic SFN has been proposed in 2020, based on expert consensus [29]. A diagnosis requires the presence of one characteristic painful or non-painful SFN (e.g., spontaneous or intermittent pain, paresthesias) present in a symmetrical, length-dependent distribution, at least one small fiber sign on the basis of a physical examination (e.g., allodynia, hyperalgesia, abnormal pinprick perception), absence of muscle weakness, absence of diseases with neurological impairment and abnormalities in IENFD skin biopsy or sensory nerve conduction studies and a disease duration of at least 3 months

4. Clinical findings to differentiate fibromyalgia from small fibre neuropathy.

The incidence and prevalence of SFN are unknown. The only based-population study in Netherlands has found an overall minimum incidence of 11.7 cases/100,000 inhabitants/year and prevalence of 53.0 cases/100,000, but is probably underestimated [30]. In this study, 55.7% of patients were male. Most other studies found a majority of women [31]. However, most of them evaluated patients with associated diseases or a previous diagnosis (such as fibromyalgia), so the sex ratio is difficult to determine and depends on possible associated diseases. Fibromyalgia is also more common among women. Nevertheless, when the 1990 criteria were used, the sex ratio was 9 women to 1 man. Since the use of the 2010 ACR/EULAR criteria, the sex-ratio was lower (approximatively 3-4 women to 1 man, depending on the study) [32,33].

Associated diseases can help in the diagnostic workup: diseases, toxins or drugs that can favour an involvement of small fibres suggest SFN. Fibromyalgia is more frequently associated with a disease with chronic pain, such as rheumatoid arthritis, spondyloarthritis and intestinal functional disorders (Table 1)

Psychologic or psychiatric associated diseases can also guide the practitioner. Fibromyalgia and SFN, like all diseases that lead to chronic pain, can be associated with anxiety or depression [10]. However, fibromyalgia is also strongly associated with PTSD [16] and self-reported physical or sexual abuse, both in childhood and adulthood [18]. The impact of those abuses (who led to the development of a PTSD) could favour the onset of fibromyalgia [17].

Family history can also be useful to discriminate between fibromyalgia and SFN. Fibromyalgia is not a genetic disease, but polymorphisms of genes in the serotoninergic, dopaminergic and catecholaminergic systems could play a role in fibromyalgia [34]. In a study assessing 30 female patients with fibromyalgia and 117 of their close relatives (parents, brothers, sisters, children and husbands), the prevalence of fibromyalgia among the blood relatives of patients with fibromyalgia was 26%, compared to 19% among their husbands [35]. Fibromyalgia prevalence was 14% in male relatives and 41% in female relatives. The authors suggested that the higher prevalence of fibromyalgia in relatives could be attributed to genetic and environmental factors [35]. A recent study found a heritability of fibromyalgia phenotype of 13.9%, with highest heritability in individuals ≤ 50 years of age (23.5%) [36]. The authors' hypothesis is that “primary” fibromyalgia has a higher heritability than “secondary” fibromyalgia (related to another disease), which is more often found in the elderly.

A genetic cause of SFN must be considered when the disease onset is young and/or a positive family history is present. Gain-of-function mutation in the voltage-gated sodium channels Nav 1.7, Nav1.8 and Nav 1.9 encoded by the SCN9A, SCN10A and SCN11A genes can lead to hyperexcitability neurons [37,38]. In a study with 28 patients with idiopathic biopsy-confirmed SFN, 8 were found to carry gain of function Nav 1.7 mutation [24].

The characteristics of pain as well as the associated signs are close in these two diseases but may have discriminatory characteristics. In the largest study available (170 women with fibromyalgia diagnosis and evaluation of IENFD), patients with SFN had higher pain intensity, impairment due to pain, higher disease burden, more stabbing pain and paraesthesia than fibromyalgia patients with normal IENFD [10]. Muscle soreness was not a discriminating criterion [10]. In a study of 39 patients referred for multisymptom illnesses including chronic widespread pain and suspicion of SFN [8], patients underwent objective evaluation of SFN using skin biopsy with altered density of epidermal nerve fibres or diagnostic composite Autonomic Function Testing. Patients with proven SFN underwent more

paraesthesia (« tingling »). Their component sub score for dysautonomia symptoms was also worse. Other characteristics (sensation of "swelling in hands or feet", changed pattern of sweating on body, less hair growth on lower legs or feet, skin that hurts after gentle contact (touch, breeze), skin that has less sensation (numbness)) were also more common, but without reaching statistical significatively in this small study. All those items are issued from the MGH Small-Fibre Symptom Survey. Based on those results, another study selected 8 items suggestive of SFN: dry eyes/mouth; allodynia; changed pattern or sweating on body; skin colour alterations/modifications; reduced hair/nail growth on lower extremities; warm hypoesthesia; thermal allodynia; cold hypoesthesia. Forty-six percent of patients presented 3 or more of those signs suggestive of SFN in an online survey of 854 patients [39]. Dry eyes/mouth, discoloration of the skin and sweating are the most common symptoms related to autonomic disturbance in SFN [40]. Sudomotor dysfunction is common in SFN, but can also be related to other diseases such as sudomotor neuropathy, myelopathy, α-synucleinopathies, autoimmune autonomic ganglionopathy, antibody-mediated hyperexcitability syndromes, and a host of medications [41]. To detect subtle sensory disturbances, the Utah Early Neuropathy Scale (which evaluates motor examination, pin sensation, allodynia/hyperesthesia, large fiber sensation and deep tendon reflexes) is a sensitive (92%) and reproducible clinical measure of sensory and small-fiber nerve injury [42].

Decreased motility of the intestinal track and the urinary system are also common autonomic signs but difficult to discriminate in clinical practice from irritable bowel and lower urinary track symptoms (such as frequent urination or bladder spasm) associated with fibromyalgia. Conversely, headache and temporo-mandibular disorder are frequently reported only in fibromyalgia (Table 2). Muscle pain, temporomandibular joint pain, and masticatory muscle tenderness on palpation are frequent among fibromyalgia patients [43].

Multiple questionnaires have been developed for screening fibromyalgia (such as FIRST questionnaire [44]) or SFN (Small-fibre Symptom Survey [45], small fibre neuropathy screening list [46]) but none of them can discriminate between those two diseases.

5. Neurophysiological test and biopsy can help to discriminate between fibromyalgia and SFN.

No laboratory exams are required for fibromyalgia diagnosis. However, complete blood count, C-reactive protein levels, serum calcium levels, creatine phosphokinase levels, thyroid-stimulating hormone levels and other exams depending on clinical presentation and are often performed to eliminate differential diagnoses.

The tests for SFN may include complete blood count, comprehensive metabolic panel, 2-hour oral glucose tolerance test, lipid panel, erythrocyte sedimentation rate, thyroid-stimulating hormone, free T4, antinuclear antibodies, extractable nuclear antigens, serum / urine immunofixation, and B12 level. Performing 2-hour oral glucose tolerance test is required because SFN can be diagnosed before diagnosis of diabetes mellitus [47]. If there is a history of gastrointestinal symptoms, gliadin antibody, tissue transglutaminase antibodies, and small bowel biopsy may be pursued to evaluate for celiac disease. HIV or hepatitis C virus serology should be ordered if risk factors are present. If there is a significant family history or erythromelalgia, further genetic testing should be considered [24]. Lip biopsy or bone marrow biopsy should be considered if clinical suspicion is high for Sjögren's syndrome, seronegative sicca syndrome or amyloidosis [37].

Electromyography is a procedure frequently performed to exclude large nerve fibre damage but is normal in both fibromyalgia and SFN, unless there is an associated disease that affects the large fibres, such as systemic lupus erythematosus.

Skin biopsy is considered as the gold standard for instrumental investigation of SFN, in the foreleg (10 cm proximal to the lateral malleolus) and if required at the thigh (20 cm distal to the iliac crest), preferentially on the body side with more prominent clinical symptoms. Only two side effects are noted: minor bacterial inflammation of the wound, which can be treated with antibiotics, and bleeding which does not require suturing. Specificity and sensitivity of the method range from 88 to 92%, depending on the diagnosis criteria used for SFN [40,48]. Advantages of biopsies include representativeness and reproducibility, and, unlike nerve biopsy, this method does not lead to the development of sensory disturbances at the site of biopsy sampling. However, it requires laboratory equipment, cost and time to read the IENFD. It is performed only with normal electromyography because nerve compression or polyneuropathy of large fibre can also reduce the IENFD.

Quantitative sensory testing (QST) can be performed by measuring warm, cold, and pain threshold by non-invasive tests, but requires costly equipment. Temperature threshold variation is related with SFN. The overall sensitivity describe in studies is 65–80%, and the specificity is 37–94% [49] but these data represent a comparison between the presence and absence of SFN, not between SFN and fibromyalgia. QST can also be used to evaluate conditioned pain modulation, which is an evaluation of the central inhibitory system from brain stem to spinal cord. Conditioned pain modulation has good specificity (79%) but low sensitivity (46%) to discriminate between fibromyalgia and healthy controls [50]. This investigation is sometimes performed to measure the degree of "fibromyalgianess" in patients with another painful disease [51]. QST are a valid test to assess the diagnosis of SFN but are time consuming and determination of warm threshold alone could be a reasonable compromise [48].

Laser evoked potentials test the function of A-delta and possibly C-type fibres in peripheral tissues. The response to laser stimulation is a non-invasive, reproducible, and measurable for estimating SFN

with a sensitivity of 65–80% and specificity of 87%. Like quantitative sensory testing, it is not specific to the peripheral nervous system [40] and requires normal electromyography to interpret the results. Confocal corneal microscopy is a non-invasive method performed by an ophthalmologist for evaluating the density of small C-fibres originated from the trigeminal nerve in the cornea of the eye, which is reduced in SFN. Sensitivity and specificity (91% and 93% respectively) are good for SFN related to diabetes mellitus, but data are lacking for other SFN [40]. Patients with FM and SFN could both have abnormalities in corneal confocal examination, but the abnormalities are different depending on the disease [52].

Electrochemical skin conductance using a Sudoscan® is a quick and non-invasive method evaluating sudomotor dysfunction. It has a good specificity (92%) but poor sensitivity (50%) for SFN [53].

Diagnostic criteria for SFN often used a combination of clinical data, QST or skin biopsy results. Devigili et al. criteria proposed in 2008 was based on the combination of at least two abnormal findings of the following: (i) clinical signs of small fibre impairment (pinprick and thermal sensory loss and/or allodynia and/or hyperalgesia); (ii) abnormal warm or cold thresholds, or both, at the foot as assessed by QST; and (iii) reduced IENFD at the distal leg. Exclusion criteria were any clinical sign of large fibre impairment or abnormality at nerve conduction studies [48]. The other diagnostic criteria issued from the European Association for the Study of Diabetes is based on a grading as: (i) possible, if symptoms or clinical signs of small fibre damage, or both; (ii) probable, if clinical signs of small fibre damage, and normal sural nerve conduction study; and (iii) definite, if clinical signs of small fibre damage, normal sural nerve condition study, and abnormal QST thresholds at the foot or reduced IENFD at the ankle, or both. Other criteria have also been suggested [20]. There is no consensus on the criteria to be used.

6. Therapeutic consequences of differentiating fibromyalgia from small fibre neuropathy.

EULAR guidelines for the management of fibromyalgia published in 2016 [54] focus on non-pharmacological therapies, such as patient education, graduated exercise, psychological therapies such as cognitive behavioural therapies, meditative movement, mindfulness/mind-body therapy and for severe disease a multimodal rehabilitation programme. Pharmacological management should include amitriptyline, duloxetine or milnacipran, tramadol, pregabalin or cyclobenzaprine if patient suffer from severe pain or severe sleep problems.

There are several evidence-based guidelines for management of painful neuropathy, but without individualising SFN [55]. Antidepressants (nortriptyline, amitriptyline, duloxetine, milnacipran, venlafaxine), anticonvulsants (gabapentin, pregabalin, lamotrigine, oxcarbazepine, carbamazepine,

sodium valproate, lacosamide, topiramate), mexiletine, topical agents (capsaicin, lidocaine), opioids are frequently suggested, given their modest efficacy in large fibre neuropathy. Intravenous immunoglobulin (IVIG) was reported to reduce pain and paraesthesia in immune-mediated diseases SFN, especially in Sjogren's syndrome, systemic lupus erythematosus and sarcoidosis-associated small-fibre neuropathy[56]. Potentially treatable causes could be identifiable in one-third to one-half of patients with SFN [57]. The effectiveness of non-pharmacological therapies in SFN is not known, although it could probably contribute to the improvement of symptoms as in the most chronic pain.

7. Conclusion

The updated diagnostic criteria for fibromyalgia have greatly increased the proportion of patients diagnosed with fibromyalgia, but those criteria do not include any physical examination and do not differentiate between fibromyalgia and SFN. There are several clinical signs which can guide the clinician to distinguish between these two diagnoses, but none of them are pathognomonic, therefore additional examinations such as skin biopsy, laser evoked potentials or QST are frequently performed. Corneal confocal microscopy is a recent non-invasive examination that could also be used. Defining the correct diagnosis allows appropriate information to be given to patients and allows pharmacological and non-pharmacological treatments to be adapted. Additional studies individualising these two diseases are required to improve patient care.

Conflict of interest statement

The author has declared that he has no conflicts of interest in relation to this article

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Table 1: Main medical conditions associated with fibromyalgia or small fiber neuropathy

	Fibromyalgia	Small fibre neuropathy
Main medical conditions associated	Inflammatory joint diseases (rheumatoid arthritis, ankylosing spondyloarthritis) Osteoarthritis Spine diseases Headaches Irritable bowel sleep disorders	Metabolic causes (diabetes, impaired glucose tolerance, hypothyroidism, hypertriglyceridemia, uraemia Vitamin B12 deficiency Neurotoxic exposure (Alcohol, antiretroviral agents, chemotherapeutic agents, pyridoxine, statins, organic solvents) Infections (Hepatitis C virus, HIV, Influenza, Lyme disease) Immunological causes (Sjogren's syndrome, celiac disease, systemic lupus erythematosus, paraneoplasic syndromes, sarcoidosis) Cryoglobulin Ehler Danlos syndrome Neurologic disorders (Rapid eyes movment sleep behavior disorder, amyotrophic lateral sclerosis, Parkinson disease, postural tachycardia syndrome) Auto-antibodies targeting neuronal antigens trisulfated heparin disaccharide (TS-HDS) and fibroblast growth factor 3 (FGFR3) Genetic causes (mutation of sodium channels, familial amyloid neuropathies), especially if associated with erythromelalgia

Table 2: Comparison of main characteristics of fibromyalgia and small fiber neuropathy

	Fibromyalgia	Small fibre neuropathy
Type of pain	Nociplastic	Neuropathic
Prevalence	0.5 to 5% of the population	Unknow
Diagnosis criteria	2016 ACR Criteria of fibromyalgia	Various criteria exist, without scientific consensus. All required at least clinical signs of small-fiber neuropathy and at least abnormal quantitative sensory testing or reduced intraepidermal nerve fiber density at skin biopsy
Distribution of pain	Diffuse	Length-dependant for 80% of patients, non-length-dependant for 20% of them
Discriminative clinical criteria	Headache Temporo-mandibular disorder	Stabbing pain Paraesthesia Autonomic dysfunction: dry eyes/mouth; changed pattern or sweating on body; skin colour alterations/modifications; reduced hair/nail growth on lower extremities Allodynia, warm hypoesthesia, thermal allodynia, cold hypoesthesia Erythromelalgia
Psychological disease associated	Anxiety Depression Post-traumatic stress disorder Physical or sexual abuse in childhood or adulthood	Anxiety Depression
Workup	If required to exclude comorbidities or other diagnoses	Skin biopsy Quantitative sensory testing Laser evoked potentials

		Confocal corneal microscopy Electrochemical skin conductance Genetic testing if significant family history or erythromelalgia
Management of the disease	Mainly non-pharmacological therapies	Antidepressant or antiepileptic associated with topical agents if possible