Chronic widespread pain in the spectrum of rheumatological diseases

Fabiola Atzeni, MD, PhD\textsuperscript{a,*}, Marco Cazzola, MD\textsuperscript{b}, Maurizio Benucci, MD\textsuperscript{c}, Manuela Di Franco, MD\textsuperscript{d}, Fausto Salaffi, MD, PhD\textsuperscript{e}, Piercarlo Sarzi-Puttini, MD\textsuperscript{a}

\textsuperscript{a}Rheumatology Unit, L. Sacco University Hospital, 20127 Milan, Italy
\textsuperscript{b}Unità Operativa di Medicina Riabilitativa, Azienda Ospedaliera ‘Ospedale di Circolo’ di Busto Arsizio, Presidio di Saronno, Varese, Italy
\textsuperscript{c}Rheumatology Unit, Ospedale San Giovanni di Dio, ASL 10 Florence, Italy
\textsuperscript{d}Chair of Rheumatology, La Sapienza University of Rome, Rome, Italy
\textsuperscript{e}Rheumatology Department, Politechnic University of the Marche, Ancona, Italy
\textsuperscript{f}Experimental Medicine and Rheumatology, William Harvey Research Institute, Queen Mary University of London, London, UK

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Fibromyalgia (FM) is a rheumatic disease characterised by musculoskeletal pain, chronic diffuse tension and/or stiffness in joints and muscles, fatigue, sleep and emotional disturbances and pressure pain sensitivity in at least 11 of 18 tender points. There are currently no instrumental tests or specific diagnostic markers, and the characteristic symptoms of the disease overlap those of many other conditions classified in a different manner. FM is often associated with other diseases that act as confounding and aggravating factors, including primary Sjögren’s syndrome (pSS), systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). It has been reported to coexist in 25% of patients with RA, 30% of patients with SLE and 50% of patients with pSS.

Its clinical diagnosis is not easy because FM-like symptoms are frequent, and its differential diagnosis with other causes of chronic diffuse pain is difficult. This is even more true in the case of patients who are positive for antinuclear antibodies (ANAs) because, although sensitive, ANA positivity is not specific for SLE or connective tissue diseases, and can also be found in 10–15% of FM patients. Furthermore, composite indices such as the disease activity score (DAS)-28, which are widely used in everyday clinical practice and clinical trials, may be insufficient to evaluate real...
inflammatory activity in patients with RA associated with chronic pain syndromes such as FM, and can lead to an overestimate of disease activity in RA. The presence of diffuse pain in autoimmune rheumatic diseases compromises the quality of life of the patients, although overall mortality is not increased. A misdiagnosis harms the patients and the community. Rheumatologists should be able to recognise and distinguish primary and secondary FM, and need new guidelines and instruments to avoid making mistakes.

Fibromyalgia (FM) is currently defined as chronic widespread pain (CWP) with allodynia or hyperalgesia to pressure pain, and is classified as one of the largest group of soft-tissue pain syndromes [1–3]. Its pathogenesis is not entirely understood, although it is currently believed to be the result of a central nervous system (CNS) malfunction that increases pain transmission and perception [4]. The widespread nature of spontaneous pain in FM involves general mechanisms that may include the spinal or supraspinal modulation of normal peripheral input, or effector mechanisms that alter peripheral pain sensitivity [5–7]. Environmental factors can also affect the development of FM and a number of ‘stressors’ have been found to be temporally related to its onset, including trauma, infections (e.g. hepatitis C virus, HIV and Lyme disease), emotional stress, catastrophes (e.g. war), autoimmune diseases and other pain conditions [7–13]. FM is often associated with other diseases that act as confounding and aggravating factors, such as primary Sjögren’s syndrome (pSS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and thyroid disease (Table 1); it has been reported to coexist in 25% of patients with RA, 30% of patients with SLE and 50% of patients with pSS [14–16].

The most common and characteristic symptoms of FM are generalised pain, stiffness, fatigue and poor sleep [1]. However, the defining symptom is widespread chronic pain lasting at least 3 months, usually in all four limbs and the upper or lower back. The pain may be described as any combination of burning, searing, tingling, shooting, stabbing, deep aching, sharp or ‘feeling bruised all over’ and, like stiffness, it is often aggravated by cold or damp weather, anxiety or stress, excessive or too little physical activity, poor sleep and noise [1,7]. About two-thirds of the patients say they “hurt all over”, and this symptom can be useful in differentiating FM from other conditions [17].

Table 1
Main differential diagnoses of fibromyalgia.

1. Inflammatory rheumatic diseases
   SLE/SS/CTD
   RA/polyarthritis/PsA
   Polymyalgia rheumatica
   Inflammatory idiopathic myopathies
2. Degenerative rheumatic diseases
   Localised myofascial pain
   Osteoarthritis
   Tendinitis
3. Other medical diseases
   Thyroid dysfunction
   Chronic fatigue syndrome
   HCV infection
   Lyme disease
   Osteomalacia
   Malignances
   Others

Its clinical diagnosis is not easy because FM-like symptoms are frequently found, and differential diagnoses against other causes of chronic pain are essential [18] (Table 2). When pain involves a large number of joints, it may be confused with the widespread pain of FM, but the degree of pain measured by means of a visual analogue scale (VAS) is not helpful in distinguishing FM from conditions such as RA or osteoarthritis (OA) [19]. Furthermore, as it can coexist with immunoinflammatory diseases, many rheumatic and nonrheumatic diseases can easily be misdiagnosed as FM. There are no instrumental tests to confirm the diagnosis, but many of the differential diagnoses can be excluded by means of an extensive clinical examination and patient history. A recent study [20] has provided evidence concerning inaccurate diagnoses of FM in a cohort of patients referred to a rheumatology clinic: FM was confirmed in only 34% of the patients presenting with musculoskeletal pain—a 66% diagnostic error rate. The symptoms discriminating FM from non-FM patients were tender points (TPs) ($p < 0.0001$) and fatigue ($p = 0.0003$), whereas prolonged early morning stiffness was a clinically discriminating feature of non-FM patients (although it was also present in a quarter of the patients with FM). Given the high rate of error in diagnosing FM, the authors concluded that a wider spectrum of diseases should be considered in the differential diagnosis of ill-defined aches and pain.

### Fibromyalgia and rheumatic diseases

FM may occur alone (primary FM) or in combination with other diseases (secondary FM): 44–55% of FM patients have been found to have pSS [7]. Although it is a major feature of FM, it has been found that fatigue is not a sensitive discriminator and so it is not included in the classification criteria, which rely on the presence of widespread pain and mild or more severe tenderness in at least 11 of 18 specific TPs [21]. It has been shown that these factors are equally sensitive and specific in identifying primary and secondary FM, and so a coexisting autoimmune rheumatic disease should not be seen as excluding a diagnosis of FM. However, the new FM criteria that are currently being studied do not include TPs [22].

The most common rheumatic diseases that may overlap and be confused with FM are OA, RA, ankylosing spondylitis (AS), polymyalgia rheumatica (PMR), SLE, pSS, osteomalacia and polymyositis; however, all autoimmune rheumatic diseases are possible aetiologies for symptoms of vague and diffuse musculoskeletal pain associated with marked fatigue [1].

### Fibromyalgia and SLE

The differential diagnosis of SLE and FM may raise some problems as the two diseases may lead to common symptoms [23,24], including musculoskeletal pain, fatigue and stiffness, cold-induced vasospasm, sicca symptoms, cognitive dysfunction and depression [25]. Up to 65% of patients with SLE attending one rheumatology clinic met the American College of Rheumatology (ACR) criteria for FM [21]. Wallace et al. [26] reported a 22% prevalence of FM in 464 SLE patients, and Middleton [10] and Morand [25], respectively found a prevalence of 22% and 25%. Akkasila [27] observed the presence of more than 11/18 TPs in 17% of 173 SLE patients, and Romano et al. found that 40% of 75 SLE patients had coexisting FM that adversely affected their quality of life [28].

Fibromyalgia-positive patients suffer significantly more frequently from headache, morning stiffness, diffuse alopecia and arthralgias. FM is more frequent in SLE patients than in other lupus subsets [29]. In a Canadian study, 21% of the SLE patients were diagnosed as having FM, and its presence was not related to the overall scores of any of the components of the SLE Disease Activity Index (SLEDAI) or Damage Index, but closely correlated with all eight domains of the Short Form 36 questionarie (SF-36) [30]. In another study, 30 out of 75 Israeli patients with SLE were found to have FM [31].
Differential diagnosis is even more difficult when a patient with FM is positive for antinuclear antibodies (ANAs) because, although sensitive, ANA positivity is not specific for SLE or connective tissue diseases (CTDs) [23], and one review of 422 patients with high ANA titres found that a significant proportion had no CTD at the time of testing [32].

In a recent study of 450 FM patients, Kotter [33] did not find any significant difference in the frequency of ANAs or thyroid antibodies between patients and controls, and concluded that there is no predisposition for autoimmune diseases in FM; on the other hand, to avoid overlooking early CTD, other specific differential diagnostic tests should be considered in ANA-positive FM patients. FM does not correlate with SLE disease activity, but the clinical features of FM may lead to its misinterpretation [14].

Organ system involvement, such as malar rash and photosensitivity, fever, serositis, haematological alterations and neurological signs, typically occur in SLE but not FM patients.

Sjogren’s syndrome, rheumatoid arthritis and FM

pSS is a chronic autoimmune rheumatic disease whose cause is unknown. It is characterised by lymphocytic infiltration of the exocrine glands, and leads to xerostomia, keratoconjunctivitis sicca and extraglandular (systemic) disease.

FM is mainly discussed in the literature as an early symptom of pSS, but the published data are controversial [11]. The incidence of FM in pSS range from 44% to 55% [11,15], and a prevalence of 47% was found by Vitali et al. in 1989 [34].

Although studies show that overall mortality is not increased among patients with pSS, they have a significantly poorer quality of life and a higher prevalence of fatigue, pain and depression than the general population [7,11,34].

In FM patients with pSS features, Schirmer and Saxon’s test, salivary gland biopsies, capillary microscopy and specific laboratory tests should all be considered for the differential diagnosis [14,33]. Patients with pSS probably have concomitant dominant FM, which may therefore be diagnosed before SS. This has also been described in the case of other inflammatory rheumatic conditions such as RA and AS in which pain, fatigue and stiffness are common [12,35]. Wolfe and Michaud [36] reported that 17% of their RA patients had FM and that their RA was more severe as measured by subjective and objective indices.

One very interesting study found that patients with RA and concomitant FM had significantly greater disease activity as measured by the 28-joint Disease Activity Score 28 (DAS-28), but significantly more severe joint destruction was found in the patients with RA alone. A study of 120 patients with RA (including 25 with concomitant FM) found significantly higher tender joint counts (TJC) and global health VAS values, which are the subjective measurements that contribute most to the differences in disease activity assessments in RA patients with and without FM; however, the doctor’s global health VAS values incorporated in a simple disease activity index (SDAI) and a clinical disease activity index (CDAI) were also markedly higher in patients with both the diseases [37].

Composite indices such as DAS-28, SDAI and CDAI are widely used in everyday clinical practice and clinical trials, but they may be insufficient to evaluate real inflammatory activity in cases of RA associated with a chronic pain syndrome such as FM; rheumatologists need to be aware of these limitations [37,38].

Finally, ultrasonography can identify the elements characteristic of RA or FM, and therefore help clinicians to make the correct diagnosis [7].

Other rheumatic diseases and FM

Many other rheumatic diseases may be confused with FM [13]. Polymyalgia rheumatica (PM) is a rheumatic disease characterised by widespread pain and morning stiffness, and a high erythrocyte sedimentation rate (ESR). However, it has been reported that ESR was not increased in 20% of patients with PM, and so a differential diagnosis may be difficult [39,40]. Inflammatory myopathies and osteomalacia may be confused with FM, but a correct diagnosis can be aided by clinical and laboratory findings and diagnostic procedures (creatinine kinase levels, muscle biopsy, hypophosphatemia and radiographic changes) [41].

Other medical diseases associated with widespread pain should be considered in the differential diagnosis of FM [8] because they may be confused with FM or overlap it. Patients with thyroid dysfunction may experience profound fatigue, muscle weakness and general achiness, and a recent
study of thyroid abnormalities and autoimmunity in FM patients found that 41% had thyroid antibodies, which suggests that there may be an association between autoimmune thyroiditis and FM [42]. One study found that 8% of a cohort of 287 patients with Lyme disease followed up for 3.5 years had associated FM [43] and, although the differential diagnosis is based on serological testing, Lyme disease may trigger FM [43]. FM has also been reported in 5–19% of patients with hepatitis C virus (HCV) infections, but it is still debated whether HCV infection is associated with FM because there is no evidence of an epidemiological link between the two [44]. Chronic fatigue syndrome (CFS) frequently overlaps FM (Table 3): more than 70% of FM patients have CFS symptoms, and the patients who meet the criteria for both FMS and CFS have a worse overall health status [45,46]. Myofascial pain syndrome has been defined as chronic pain accompanied by trigger points (TrPs) in one or more muscles or group of muscles. As TrPs may easily be mistaken for TPs and lead to the overdiagnosis of FM, physicians should distinguish them with the aid of a pain drawing [19].

AS can also easily be mistaken for FM because both occur in young patients who may have constitutional symptoms such as malaise, fatigue and impaired sleep [47]. The hallmark of AS is sacroiliitis, which can be identified early by means of magnetic resonance imaging (MRI) [48] and does not occur in FM. OA can be confused with FM because it causes arthralgia of the whole body and may be associated with the significant limitation of activity. Patient age and radiological imaging can help distinguish the diseases, although the two may coexist [49].

As in many chronic diseases such as RA and SLE, fatigue is also an important symptom in patients with psoriatic arthritis (PsA) as it interferes with daily activities and causes disability [50]. Furthermore, as polyarthritic PsA is sometimes difficult to distinguish from FM, secondary FM in PsA patients and PsA in FM patients can be misdiagnosed. In a multicentre cross-sectional study of 262 PsA patients and 96 FM patients, Marchesoni et al. [51] found that 18 (6.9%) PsA patients met the classification criteria for FM and univariate logistic regression showed the odds ratios (ORs) of morning stiffness, anxiety and depression were not statistically different between the two groups. However, the number of FM-associated symptoms, the number of TPs and the patients’ response to non-steroidal anti-inflammatory drugs (NSAIDs) can help distinguish polyarthritic PsA and FM.

**Conclusion**

FM is common in patients with autoimmune rheumatic diseases and may be the cause of many of their symptoms and much of their disability. Misdiagnosis is harmful for the patients and the community, and so rheumatologists and general practitioners need to be able to recognise and distinguish primary and secondary FM.
# Research agenda

- To develop new laboratory and clinical indices to distinguish FM from other autoimmune rheumatic diseases in order to reduce misdiagnoses.
- To evaluate the adequacy and appropriateness of measures for diagnosing primary and secondary FM.
- To determine whether new instrumental methods such as ultrasonography distinguish FM from RA or PsA.
- To develop new recommendations to differentiate diffuse pain in the context of rheumatic diseases.
- To promote future multicentre studies and registries for diffuse pain in autoimmune rheumatic diseases.

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# Practice points

- Chronic widespread pain (CWP) is prevalent and coexists with many autoimmune rheumatic diseases, such as SLE, RA and pSS; it is therefore difficult to distinguish and treat adequately.
- Fatigue, diffuse pain and other symptoms are common in FM and in pSS and/or SLE.
- The presence of diffuse pain in autoimmune rheumatic diseases compromises the quality of life of the patients, even though overall mortality is not increased.
- Composite indices for evaluating inflammatory activity in RA, such as DAS-28, SDAI and CDAI (all widely used in everyday clinical practice and clinical trials), are available but may be insufficient in cases of RA associated with chronic pain syndromes such as FM; all rheumatologists should be aware of these limitations.
- FM is common in patients with autoimmune rheumatic diseases and may be the source of many of their symptoms and much of their disability.
- A careful evaluation of the patient associated with instrumental methods can help to reduce misdiagnoses, incorrect treatment, social impact and costs.

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# References


