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ORIGINAL ARTICLE

Fibromyalgia syndrome: definition and diagnostic aspects

La sindrome fibromialgica: definizione ed aspetti diagnostici

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RIASSUNTO

Fin dalla prima descrizione la FM è stata considerata tra le diagnosi più controverse in ambito reumatologico, dal momento che non tutti accettano l'esistenza della FM come un'entità clinica indipendente. La sensibilità e la specificità dei criteri diagnostici sono ancora oggetto di discussione tra i vari specialisti (non solo tra i reumatologi), che sollevano come critica principale il fatto che i criteri dell'American College del 1990 identificano solamente un subset di pazienti non rappresentativo della pratica clinica quotidiana. Inoltre, i sintomi caratteristici della FM sono simili a quelli osservati in altre condizioni cliniche. Negli ultimi anni, questo ha portato a considerare la FM sempre meno come un' entità clinica indipendente e sempre più come una possibile manifestazione tipica delle alterazioni del sistema psico-neuroendocrino (lo spettro dei disturbi affettivi) o del sistema di reazione allo stress (sintomi disfunzionali). Recentemente, sono stati sollevati dubbi su queste classificazioni; e attualmente sembra corretto includere la FM tra le sindromi di "sensibilizzazione del sistema nervoso centrale", che considerano il meccanismo patogenetico causa di sindromi muscolari ed extra-muscolari della FM o delle altre sindromi disfunzionali.

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INTRODUCTION

Although the term "fibromyalgia" (FM) is relatively new, the condition characterised by chronic musculoskeletal pain that is accompanied by numerous extra-skeletal symptoms has been described in the medical literature for many years under different names. The term "fibrositis," which was originally used in 1904 by Sir William Gowers to define a type of lumbalgia, became a synonym for diffuse musculoskeletal pain until 1976 (1). In the mid-1970s, Smythe and Moldofsky used the term "fibrositic syndrome" to describe the presence of tender points (TPs), sleep disturbances and other accompanying symptoms such as asthenia

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(2). In the early 1980s, Yunus replaced "fibrositis" with "fibromyalgia" in order to underline the absence of phlogistic alterations in the muscle that were repeatedly reported in published histological studies (3). In 1990, under the aegis of the American College of Rheumatology (ACR), a multicentre study of 558 patients with fibromyalgia was conducted with the aim of standardising the diagnostic criteria of the syndrome (4). This study found that the combination of pain induced by 4 kg./cm^2 of pressure in at least 11 of the 18 considered TPs and a history of diffuse musculoskeletal pain for at least three months provided the most sensitive, specific and accurate criteria for diagnosing both primary and secondary FM.

However, the use of the 1990 ACR criteria in clinical practice soon highlighted their limitations; in particular, they were not able to distinguish FM from other syndromes that are characterised by organ or systemic symptoms without detectable morphological alterations, such as chronic fatigue syndrome (CFS) and myofascial syndromes (5-7). Many of these symptoms overlap to the extent that the same patient will often satisfy the diagnostic criteria for two or more syndromes. In 1989, Pope and Hudson postulated the concept of a "spectrum of affective disorders" based on the observation that many of these conditions showed a certain clinical response only to antidepressants (8). Following similar reasoning concerning the syndromes' clinical characteristics and mutual associations, and considering the most accredited pathogenetic hypotheses for each, Yunus coined the definition of a "spectrum of dysfunctional syndromes" in which the term "dysfunctional" referred to the supposed underlying psycho-neuro-immuno-endocrine alterations (9). More recently, these attempts at classification have been questioned and supplanted by the concept of a "central pain syndrome" or, better, "central sensitisation" (10, 11). Central sensitisation is based on the latest experimental evidence concerning the role that central nervous system modifications, which are induced by the environment in genetically predisposed subjects, play in the onset of many previously defined "algodysfunctional" syndromes, including FM (12).

DEFINITION

In 1989, Wolfe defined FM as "a painful musculoskeletal disorder characterised by core clinical features that are always present (widespread chronic pain and tenderness), features that are present in more than 75% of cases (fatigue, non-refreshing sleep and morning stiffness), and features that are present in more than 25% of cases (for example, paresthesia, irritable bowel syndrome and functional disability)" (13). Constitutional symptoms have not been considered since the 1990 ACR diagnostic criteria; and the main symptom that distinguishes FM is now pain, which must be diffuse (affecting both sides of the body, above and below the waist, and the axial skeleton involving at least one of the cervical, dorsal and lumbar regions of the spine), chronic (present for at least three months), and capable of being evoked by pressure at specific sites (TPs) (4). In our view, developments in our knowledge of the pathogenetic mechanisms of the central pain syndromes, together with the reduced importance of TPs for diagnostic purposes, now allow the definition to be reformulated as follows:

"Fibromyalgia is a central sensitisation syndrome characterised by dysfunctions in the neurocircuits involving the perception, transmission and processing of nociceptive afferents, with the prevalent manifestation of pain at the level of the musculoskeletal system. In addition to pain, there may be a multitude of accompanying symptoms (asthenia, sleep disturbances, abdominal pains…) that are common to other central sensitisation syndromes. Particular genetic characteristics and a reduced individual capacity to tolerate "stressors" predispose individuals to the onset of the disease".

DIAGNOSTIC CRITERIA

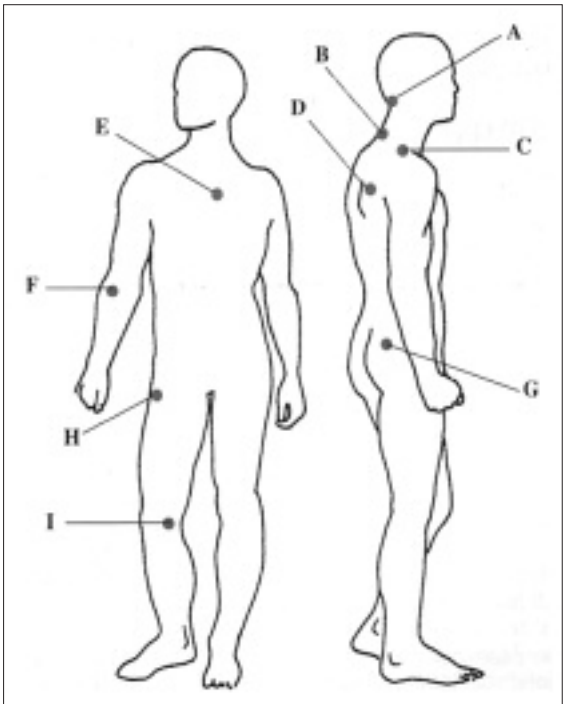
In 1990, the ACR carried out a study involving 558 FM patients attending 16 centres with the aim of standardising the syndrome's diagnostic criteria (4); this study identified the most sensitive, specific and accurate criteria for diagnosing FM:

1) A history of widespread pain: chronic, widespread, musculoskeletal pain lasting longer than three months in all four quadrants of the body ("widespread pain" was defined as pain above and below the waist, and on both sides of the body), with the additional presence of axial skeletal pain in the cervical spine, anterior chest, thoracic spine or low back.

2) Pain in 11 of 18 tender sites upon digital palpation: there are 18 TPs that doctors assess to confirm the diagnosis of FM (see Figure 1), and according to the ACR requirements, a patient must

endorse at least 11 as painful upon application of approximately four kg/cm^2 of pressure.
As the ACR criteria suggest, a diagnosis of FM requires the "hands-on" evaluation of a patient by a skilled medical professional, typically a rheumatologist, although other specialists are becoming quite knowledgeable in this area. Patients are usually aware of the specific anatomical origins of the pain in their bodies; however, self-diagnosis is not advised.
The authors also stated that, from a clinical perspective, primary and secondary FM were indistinguishable and, therefore, they proposed abolishing the term "secondary fibromyalgia". A diagnosis of FM may be present concomitant with other rheumatic diseases, but in this way, the "secondary" FM remains clinically indistinguishable from the primary form and is an unnecessary classification.
In the absence of diagnostic laboratory tests or X-rays, the ACR diagnostic criteria were a milestone in the recognition and study of FM. For the first time, researchers around the world could identify and study FM patients using standardised measures, thus enabling comparison of results. In the clinic setting, patients who had fallen through the cracks of medical science could finally be diagnosed.
Nevertheless, the criteria were not without their drawbacks:

- the TP paradigm suggested that FM patients only experienced pain in anatomically-specific sites, but later studies (such as those reported by Granges and Littlejohn in 1993) suggested that they were sensitive to painful stimuli throughout the body. Today, widespread body pain is commonly associated with FM (14);
- it quickly became evident that tenderness varied from day to day and from month to month, which meant that TP counts fluctuated above and below the required 11 depending on when the count was made. Furthermore, patients did not always manifest pain in all four body quadrants: some had unilateral pain, and/or pain solely in the upper or lower half of the body;
- Staud has shown that, although everyone with FM has TPs, the number of TPs does not reflect the level of pain patients experience; in short, TPs do not correlate with pain (15);
- Clauw and Crofford have commented that the ACR criteria focus only on pain and do not include many other FM symptoms (fatigue, cognitive disturbance, irritable bowel syndrome, etc.); as a result, the criteria "fail to capture the essence of the FM syndrome" and allow for "greater variability in studies of physiologic mechanisms other than pain processing" (16);
- the number of TPs is greatly influenced by the demographic and psychological characteristics of patients with FM. Women are only 1.5 times more likely to experience chronic widespread pain but are 11 times more likely to have 11 or more TPs, which means that they are approximately 10 times more likely to satisfy the ACR criteria. However, most men who experience chronic widespread pain but are not tender



A) Occiput: bilateral, at the suboccipital muscle insertions.
B) Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
C) Trapezius: bilateral, at the midpoint of the upper border.
D) Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.
E) Second rib: bilateral, at the second costochondral junction, just lateral to the junctions on upper surfaces.
F) Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
G) Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
H) Greater trochanter: bilateral, posterior to the trochanteric prominence.
I) Knee: bilateral, at the medial fat pad proximal to the joint line.

Figure 1 - Fibromyalgia tender points identified by the American College of Rheumatology in 1990 (*at digital palpation with an approximate force of 4 kg*).

enough to meet FM criteria probably have the same underlying pathophysiology;
- another unintended consequence of diagnosing FM on the basis of chronic widespread pain and at least 11 TPs is that many people with FM experience high levels of distress. Wolfe has described TPs as a "sedimentation rate for distress" because population-based studies have shown that TPs are more common in distressed individuals (17). Distress is considered a combination of somatic and anxiety and/or depression symptoms, and it has been assumed that, as TPs are associated with distress, the same is true of tenderness (i.e., sensitivity to mechanical pressure). However, recent evidence suggests that the association is probably due to the standard TP technique of applying steadily increasing pressure until reaching 4 kg and, in this situation, people who are anxious or "expectant" have a tendency to "bail out" and report tenderness;
- TP examinations require skill and, when performed incorrectly (in the wrong place or with too much or too little digital pressure), they lead to erroneous results. Unfortunately, the TPs of FM are also sometimes confused with the trigger points of myofascial pain syndrome (MPS), and the two are not uncommonly mistaken for each other.

To complicate the clinical picture further, FM patients often have symptoms that overlap with those of other systemic syndromes (CFS, psychogenic syndrome, etc) or localised syndromes (MPS, irritable bowel syndrome, etc.), and many rheumatologists doubt that the current 1990 ACR criteria define a specific disease.

CLINICAL SUBSETS

In 2003, first Hazemeijer and Rasker (18), and then Ehrlich (19), raised considerable doubts about the very existence of FM. In particular, Ehrlich considered it only a mental construct: "When one has tuberculosis, one has tuberculosis, whether or not it is diagnosed. The same is true for cancer, rheumatoid arthritis, hookworm infestation - really, of the gamut of diseases. But not for FM. No-one has FM until it is diagnosed."

However, given the indisputable existence of people affected by a central painful syndrome, the positivist position of Wolfe has a point: "fibromyalgia will always exist regardless of the name given to the syndrome" (20).

Setting aside the philosophical issue raised by Hazemeijer and Rasker concerning the need for a specific change in the social setting, or "therapeutic dominion", it has always been clear that patients diagnosed as having FM on the basis of the 1990 ACR criteria fall into a series of heterogeneous subgroups.

Fukuda, et al., studied Air Force veterans from the first Gulf War in 1990-1991, and defined the complex of symptoms as "*chronic multisymptom illness*" (21). In 1996, Turk, et al. (22), first demonstrated the existence of "subsets" of FM patients that could be identified using the Multidimensional Pain Inventory (MPI) and that would respond to different therapies. In addition to psychosocial and cognitive factors, they identified a number of specific neurobiological factors that could better explain the fundamental mechanism of the pain causing hyperalgesia and allodynia.

In 2003, Giesecke, et al. (23), more precisely separated FM patients on the basis of differences in their perception of pain and other psychological factors. They studied 117 FM patients aged 18-60 years (88% women) by evaluating the characteristics and perception of pain (VAS, individual pain thresholds, the number of tender points), and the way in which it was interpreted emotionally (anxiety, depression and catastrophising) (see Figure 2). They quantitatively analysed six parameters for each patient (anxiety, depression, catastrophising, ability to control pain, pain scale, and tenderness to a light touch) and identified three different clusters.

The most frequent (51.5%) was cluster 1 (long dashed line), in which all levels of all parameters

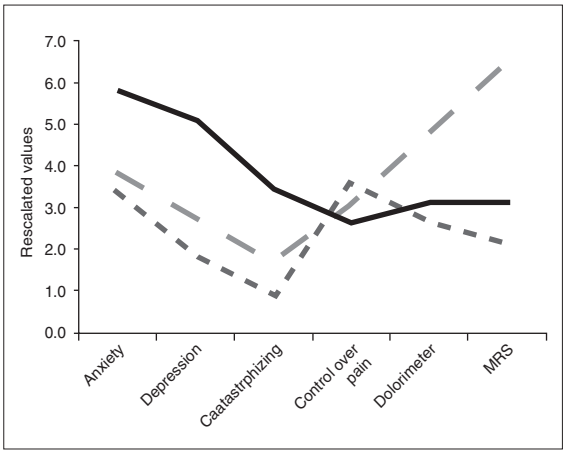


Figure 2 - Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors (23).

were medium. This probably represents the majority of patients who consult a general practitioner (GP) because of widespread pain and who generally respond better to prescribed medical therapy.
Cluster 2 (continuous line) represents 32% of the enrolled patients, a group that was characterised by high levels of anxiety, depression and catastrophising, the lowest level of control over pain, and significant tenderness to light touch.
Cluster 3 (dotted line) accounted for only 16.5% of the patients, a group that showed the lowest levels of anxiety, depression and catastrophising, but also the lowest pain threshold (see Figure 3).
This study showed that patients diagnosed on the basis of the 1990 ACR criteria fall into different categories and may have different reactions to the available therapeutic options.
However, it also strongly suggested that, although they had represented an unquestioned diagnostic platform for more than ten years, the 1990 ACR criteria alone were not sufficient to define FM patients and, therefore, necessitated further research.
At the beginning of 2006, the ACR criteria were used by Katz, et al. (24) to verify their concordance with the clinical diagnosis alone and with the "survey criteria." To this end, they studied 206 patients evaluated on the basis of TPs using the pooled diagnosis of FM (Regional Pain Scale score >8 and fatigue score >6) and clinical history, and found that 49% met the criteria for a clinical diagnosis, 29.1% met the 1990 ACR criteria, and 40.3% met the survey criteria. The clinical and survey criteria were concordant in 74.8% of cases; the clinical and 1990 ACR criteria were concordant in 75.2% of cases; and the survey and 1990 ACR criteria were concordant in 72.3% of cases. Tenderness to light touch of at least 11 of the 18 ACR TPs was not present in the clinical and survey diagnostic criteria but was shown to be very useful in the clinical diagnosis. Therefore, the authors concluded that the three sets of criteria (clinical, ACR and survey) were moderately concordant (72-75%).
As there is no diagnostic "gold standard" for FM, all of the mentioned criteria are equally useful, and the survey criteria have the undoubted advantage of not requiring a physical examination.

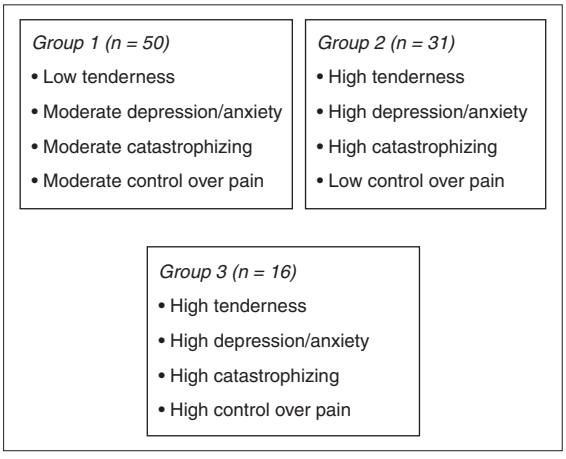


Figure 3 - Subgrouping of fibromyalgia patients on the basis of pressure-pain thresholds and psychological factors (23).

DIAGNOSIS

It is clear that a diagnosis of FM cannot be based exclusively on the 1990 ACR criteria. Many subjects may not have pain throughout the body or at least 11 TPs upon physical examination, but their psychological characteristics and associated symptoms clearly suggest a form of FM or, at any rate, a central sensitisation syndrome of which FM is clearly a part. As there are no specific laboratory markers, imaging techniques or objective signs, constitutional symptoms are the only parameters that can be used.

Characteristics of pain

In clinical practice, FM should be suspected in all patients describing multifocal pain that has an origin which is not justified by the presence of tissue damage or inflammation at the painful sites. In many cases, the main clinical manifestation is musculoskeletal pain; but it may be much more generalised because it is known that mechanisms of sensory amplification underlie pain of central origin. This explains why chronic headache, atypical chest pain, and chronic abdominal or pelvic pain are very common findings in FM patients; FM should be suspected in all patients who complain of chronic pain *sine materia* at these sites. As pain is the fundamental element of FM, it is necessary to investigate its characteristics and to differentiate it from pain induced by other diseases. Fibromyalgia pain is typically diffuse or multifocal, varies in intensity during the course of the day, and sometimes migrates from one body region to another; its exacerbations are influenced by various external physical and/or psychological factors. These are the characteristics of *central pain*, which differ from the more constant localization and intensity of *peripheral pain*. Patients sometimes perceive stimuli

Table I - Characteristics of central and peripheral pain.

	Central	*Peripheral*
Site	Diffuse	Localised
Intensity	Variable	Constant
Stimulus/response ratio	Non-proportional	Conserved
Modifying factors	Environmental and/or psychological factors	Mechanical factors
Concomitant sensitivity alterations (dysesthesia/paresthesia)	Present	Absent

that are usually innocuous, such as wearing clothes, as painful; if adequately questioned, they frequently report associated paresthesia or dysesthsia (Tab. I).

Other symptoms

Pain may be accompanied by numerous other symptoms that are apparently unrelated. Asthenia, sleep disturbances, weakness, labile attention and memory deficits, intolerance of cold or heat, visual and hearing disorders, vestibular symptoms, the sensation of dry mucosae, and inexplicable changes in weight are only the most frequent. "Allergic" phenomena such as rhinitis, sinusitis, nasal congestion and lower respiratory airway symptoms are reported more frequently by FM patients than controls, although these are almost always due to hypersensitivity and not immunoglobulin E (IgE)-mediated immune reactions. The most frequent comorbidities in women are dysmenorrhea, interstitial cystitis, vestibulitis and vulvodynia; in men, non-bacterial prostatitis is most common.

Physical examination

Physical examination is usually negative with the exception of hyperpathia upon pressure, particularly at the TPs. However, the semiology of the musculoskeletal system must always be completed for the purposes of differential diagnosis.

Laboratory tests

Generally, lab tests are not useful except for differential diagnosis. One criterion for deciding which and how many laboratory tests to perform is the duration of the disease: if the diagnosis was made several years ago, it is possible to limit the number of tests, whereas more recent or current diagnosis may require thorough investigation for accuracy (Tab. II).

Other investigations

These are not usually necessary unless indicated on the basis of findings from the physical examination and laboratory screening (see Figure 4).

Table II - Laboratory tests recommended at first observation.

Symptom onset <12 months	*Symptom onset >12 months*
ESR	ERS
CRP	Hemochrome
Hemochrome	TSH
ANA	
CPK	
TSH	
Liver and renal function	

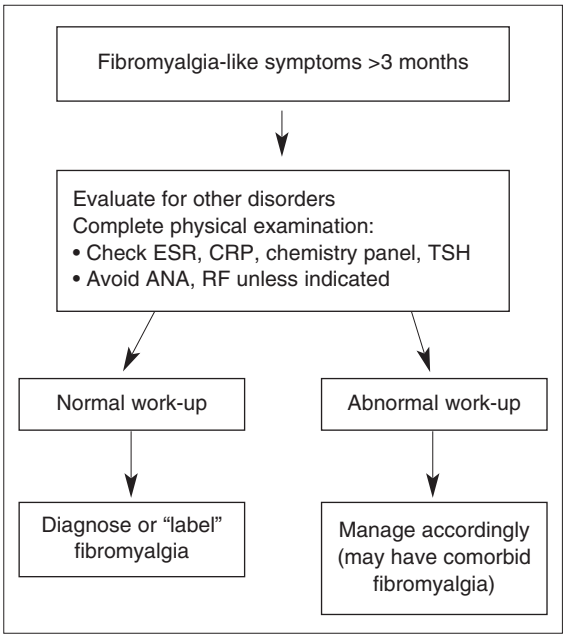


Figure 4 - Algorithm for the diagnosis of fibromyalgia. Modified from: Clauw D. Fibromyalgia: defining the disorder and its diagnostic and treatment approach. www.medscape.com, 2007.

DIFFERENTIAL DIAGNOSIS

FM is often part of a wider syndrome encompassing many symptoms from different organs other than muscles. Its clinical diagnosis is not easy because fibromyalgia-like symptoms are frequently found, and differential diagnosis with other causes of chronic pain is essential (Tabs. III, IV). When

the pain involves a large number of joints, it may be confused with the widespread pain of FM. The degree of pain as measured by a visual analogue scale is not helpful in distinguishing FM from other conditions such as arthritis or osteoarthritis (25). Furthermore, as FM can exist in association with immunoinflammatory diseases, many rheumatic and non-rheumatic diseases can easily be misdiag-

Table III - Possible causes of muscle pain.

Causes of focal muscle pain	*Causes of generalised muscle pain*
With swelling or induration	**With muscle weakness**
Neoplasm	Inflammation (dermatomyositis and polymyositis)
Trauma (hematoma)	Infection
Torn tendon	Toxoplasmosis
Ruptured Baker's cyst	Trichinosis
Thrombophlebitis	Toxic myopathy (viral infections, leptospirosis,
Infection	Gram-negative infections, toxic shock syndrome,
Streptoccal myositis	Kawasaki's syndrome)
Gas gangrene	Poliomyelitis
Pyomyositis	Toxic and metabolic disorders
Trichinosis, hydatid cyst, sparganosis	Acute alcoholic myopathy
Painful weakness in children with influenza	Hypophosphatemia
Inflammation	Potassium deficiency
Localised nodular myositis	Total parenteral nutrition
Proliferative myositis	Carcinoma-induced necrotic myopathy
Pseudo-malignant myositis ossificans	Hypothyroid myopathy
Eosinophilic fasciitis	Drugs (e-aminocaproic acid, clofibrate, emetine)
Sarcoidosis (nodular)	Carnitine palmitoyltransferase deficiency
Ischemia	Amyloidosis
Muscle necrosis due to arterial occlusion	Bone pain and myopathy (osteomalacia,
Diabetes (thigh muscle infarction)	hyperparathyroidism)
Embolism (marantic endocarditis)	Acute polyneuropathy (Guillain-Barré syndrome, porphyria)
Azotemic hyperparathyroidism	
Toxic and metabolic disorders	**Without muscle weakness**
Acute alcoholic myopathy	Rheumatic polymyalgia
Myoglobinuria in drug-induced coma	Painful muscle fasciculation syndrome
Drug-induced damage	Myalgia in infections or fever
Effort-induced muscle damage (in normal subjects	Myalgia in collagenovascular disease
or subjects with metabolic myopathies)	Discontinuation of steroids
Motor unit hyperactivity (stiff man syndrome, tetanus,	Hypothyroidism
strychnine poisoning)	Primary myalgia
	Fabry's disease
Without swelling or induration	Parkinsonism
Effort myalgia	
Normal subjects	
Claudicatio intermittens	
Metabolic myopathies	
Acute brachialgia	
Ischemic mononeuropathy	
Parkinsonism	
Resting leg pain of obscure cause	
Growing pains	
Restless legs	
Painful legs and tips of the fingers	
Idiopathic leg pain	

Modified from: Layzer RB: Muscle pain, cramps and fatigue. In Engel AG, Banker BQ (eds.): Myology. New York, McGraw-Hill, 1986, pp. 1907-1922.

Table IV - Conditions that simulate fibromyalgia.

Common	*Less common*
Hypothyroidism	Hepatitis C
Polymyalgia rheumatica	Sleep apnea
Early in course of autoimmune disorders: e.g. rheumatoid arthritis or SLE	Chiari malformation
Sjogren's syndrome	

nosed as FM. A recent study (26) has provided some evidence concerning inaccuracy in diagnosing FM in a cohort of patients referred to a rheumatology clinic: FM was confirmed in only 34% of patients presenting with musculoskeletal pain, with a 66% diagnostic error rate. TPs ($p<0.0001$) and fatigue ($p=0.0003$) were the symptoms that discriminated FM from the non-FM patients, whereas prolonged early morning stiffness was a clinically discriminating feature of the non-FM patients (although this feature was present in a quarter of those 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.

There is a general agreement about this. Rheumatic autoimmune diseases such as Systemic Lupus Erythematosus (SLE), Sjögren's syndrome, other connective tissue diseases (CTDs), rheumatoid arthritis (RA) and spondyloarthritis, and non-rheumatic diseases such as hypothyroidism, anemia, Lyme disease, hepatitis C virus infection (HCV), chronic fatigue syndrome (CFS) and occult malignancy, are all possible etiologies for symptoms of vague and diffuse musculoskeletal pain associated with marked fatigue (27).

The differential diagnosis of SLE and FM may pose a dilemma as such patients may have common symptoms (28, 29), including musculoskeletal pain, fatigue and stiffness, cold-induced vasospasm, sicca symptoms, cognitive dysfunction, and depression (30, 31). Furthermore, some studies have reported the coexistence of SLE and FM. Middleton (30) and Morand (31), respectively, found a prevalence of FM of 22% and 25% in their groups of SLE patients, and Akkasilpa (32) reported the presence of more than 11/18 TPs in 17% of 173 SLE patients. Differential diagnosis is more difficult when a patient with FM is positive for antinuclear antibodies (ANAs) because, although sensitive, ANA positivity is not specific for SLE or CTDs (28). In a recent study of 450 FM patients, Kotter 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, in order not to overlook early CTD, other specific differential diagnostic tests should be considered in ANA-positive FM patients (33). Finally, FM does not correlate with SLE disease activity, but the clinical features of FM may contribute to a misinterpretation of such activity (34).

FM is mainly discussed as an early symptom of Sjogren's syndrome in the literature, but the data are rather controversial (35). In FM patients with Sjögren's syndrome features, Schirmer and Saxon's test, salivary gland biopsies, capillary microscopy and specific laboratory tests should be considered for the purposes of differential diagnosis (33, 34). Patients with Sjögren's syndrome probably have concomitant FM, which may dominate their complaints and, thus, be diagnosed before Sjögren's syndrome. This has also been described in the case of other inflammatory rheumatic conditions such as RA and spondylitis in which pain, fatigue and stiffness are common (30, 34, 36, 37).

Many other rheumatic and non-rheumatic diseases may be confused with FM (28). Polymyalgia rheumatica is characterised by widespread pain and morning stiffness, but the hallmark is the erythrocyte sedimentation rate (ESR); it is reported that ESR was not increased in 20% of patients (38-39). Inflammatory myopathies and osteomalacia may be confused with FM, but a correct diagnosis can be helped by clinical findings, laboratory findings and diagnostic procedures (creatine kinase levels, muscle biopsy, hypophosphatemia, and radiographic changes) (40, 41).

Other medical diseases associated with widespread pain should be considered in the differential diagnosis of FM (25) as they may be confused with FM or truly overlap it. Patients with thyroid dysfunction may experience profound fatigue, muscle weakness and general achiness (28); and a recent study of thyroid abnormalities and autoimmunity in FM patients found the presence of thyroid antibody in 41% of the patients, thus, suggesting an association between autoimmune thyroiditis and FM (42).

In a cohort of 287 patients with Lyme disease that was followed for 3.5 years, 8% of patients had associated FM; although the differential diagnosis is based on serological testing, Lyme disease may trigger FM (43).

FM has been reported in 5-19% of patients with HCV infections. However, it is still debated

Table V - Clinical criteria for a diagnosis of myofascial pain syndrome caused by active trigger points.

To make a clinical diagnosis of myofascial pain syndrome, the findings should include the five main criteria and at least one of the three minor criteria. The *five main criteria* are:
1. Reported symptom of regional pain.
2. Symptoms of pain or altered sensation in the expected distribution, or pain transferred from a myofascial trigger point.
3. Palpable tense fascia in an accessible muscle.
4. Point of great tenderness along the tense fascia.

A certain limitation in the amplitude of movement, when measurable.

The three *minor criteria* are:
1. Clinical symptom of pain or altered sensitivity reproduced by pressure on the tender point.
2. Provocation of local contraction response by means of sharp transversal palpation on the tender point, or the insertion of a needle in the tender point of the tense fascia.
3. Pain relived by lengthening (stretching) the muscle or by injecting the tender point (trigger point).

Note: Additional symptoms are often present, such as sensitivity to the weather, disturbed sleep and depression, but they are not diagnostic because they may be attributable to chronic severe pain perpetuated by numerous mechanical and/or systemic factors. From: Simons AG: Muscular pain syndromes. In : Friction JR, Awad EA (eds.), Advances in Pain Research and Therapy, Vol. 17: Myofascial Pain and Fibromyalgia. New York, Raven Press, 1990, p. 18.

whether HCV infection is associated with FM, since there is no proof of an epidemiological link between the two (44).

CFS frequently overlaps FM (Tab. VI). 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).

Myofascial pain syndrome has been defined as chronic pain accompanied by trigger points (TrPs) in one or more muscles or group of muscles (Tab. V). TrPs may easily be mistaken for TPs and, thus, lead to the overdiagnosis of FM; therefore, physicians must be able to distinguish TrPs and TPs with the aid of a pain drawing (25).

Table VI - Diagnostic criteria for chronic fatigue syndrome.

- Clinically ascertained, persistent, recurrent and unexplainable chronic fatigue
- of recent onset or temporally identifiable
- not due to an ongoing period of effort
- not relievd by rest
- occupationally, socially or personally disabling.

The concomitant presence of at least four of the following symptoms, each of which must have been present continuously or have recurred occasionally for at least six or more consecutive months of disease, and not prevailing over the fatigue:
- patient report of a deterioration in short-term memory that is sufficiently severe as to cause a reduction in previous working, scholastic, social or personal activities
- pharyngodynia
- cervical or axillary lymphadenopathy
- muscle pain
- polyarticular pain without tumefaction or reddening
- headaches with new characteristics or of different severity
- unrefreshing sleep
- malaise following effort and lasting more than 24 hours.

CONCLUSIONS

In the light of current knowledge, we can define FM as a "central sensitisation syndrome characterised by dysfunction in the neurocircuits involving the perception, transmission and processing of nociceptive afferents, with the prevalent manifestation of pain at the level of the musculoskeletal system".

Together with pain, which is characterised by hyperalgesia and allodynia, symptoms of debilitating fatigue, disrupted or non-restorative sleep, functional bowel disturbances, and a variety of neuropsychiatric problems including cognitive dysfunction, anxiety and depressive symptoms combine to define FM (46). Women are the most affected, and the disease has a familial connection linked to genetic variances in the serotonin, dopamine and catecholamine intracerebral system (47). The physical symptoms of FM express themselves primarily in the presence of a psychological condition that reduces the individual capacity to tolerate stessors (48).

Despite widespread criticism, the diagnostic criteria of FM are still based on the 1990 ACR recommendations, which require a specific case history (widespread pain lasting more than three months, sleep disturbance, debilitating fatigue, paresthesia), and tenderness upon pressure (4 kg/cm^2) in at least 11 of the 18 TPs distinguishing the disease, on both sides of the body and simultaneously above and below the waist. On the basis of these diagnostic cri-

teria, three subsets of FM patients can be identified based on individual pain-emotional and neurobiological characteristics that respond differently to specific therapeutic strategies.

Many common musculoskeletal conditions can mimic FM and, thus, may be misdiagnosed as FM. Moreover, many patients do not completely satisfy the FM criteria; rather, they only present with a few symptoms. FM may co-occur or overlap several rheumatic and non-rheumatic conditions. In patients with widespread pain and fatigue, it is necessary to rule out the presence of any other medical condition or disease known to cause these symptoms (27, 28).

A simple and rational approach to evaluating these patients should include a complete clinical history, a physical examination and laboratory tests; and patients with a history that suggests FM should undergo further investigation of their vital signs; TPs; joints and tendons; neurological, abdominal and thyroid status; and signs of connective tissue or other concomitant diseases (49). Laboratory assessments should include a complete blood cell count for common anemias, infections and bone marrow diseases. Although ESR and C-reactive protein are non-specific, they can help to confirm systemic inflammation or infection. Patients presenting with fatigue and widespread pain should undergo routine thyroid function tests. A standard chemistry panel (liver and kidney function, serum fasting glucose, blood lipids) is useful to evaluate overall systemic health. If the physical examination findings suggest joint involvement and soft tissue inflammation, additional serological tests such as rheumatoid factor, ANAs or others should be performed (27). There is agreement that the differential diagnosis of FM should be ruled out as far as possible by adding a number of simple blood tests to the physical examination, which would be justified if the history and physical examination suggest another concomitant or associated condition. Finally, FM should be diagnosed on the basis of its own characteristics and not just by exclusion; the presence of a concomitant disease such as arthritis or hypothyroidism does not exclude a diagnosis of FM (25,49).

SUMMARY

Ever since it was first defined, fibromyalgia (FM) has been considered one of the most controversial diagnoses in the field of rheumatology, to the point that not everybody accepts its existence as an independent entity. The sensitivity and specificity of the proposed diagnostic criteria are still debated by various specialists (not only rheumatologists), whose main criticism of the 1990 American College of Rheumatology criteria is that they identify subsets of particular patients that do not reflect everyday clinical reality. Furthermore, the symptoms characterising FM overlap with those of many other conditions classified in a different manner. Over the last few years, this has led to FM being considered less as a clinical entity and more as a possible manifestation of alterations in the psychoneuroendocrine system (the spectrum of affective disorders) or the stress reaction system (dysfunctional symptoms). More recently, doubts have been raised about even these classifications; and it now seems more appropriate to include FM among the central sensitisation syndromes, which identify the main pathogenetic mechanism as the cause of skeletal and extra-skeletal symptoms of FM and other previously defined "dysfunctional" syndromes.

Key words - Diagnosis, ACR criteria, overlap syndrome, dysfunctional syndromes.
Parole chiave *- Diagnosi, criteri ACR, sindrome da overlap, sindromi disfunzionali.*

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