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Chronic widespread pain in the spectrum of rheumatological diseases

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Chronic pain is very common in all European countries, with musculoskeletal problems predominating. About 1% of the adult population develops a syndrome of chronic muscle pain, fibromyalgia (FMS), characterized by multiple tender points, back or neck pain, and a number of associated problems from other organs, including a high frequency of fatigue. Evidence points to central sensitization as an important neurophysiological aberration in the development of FMS. Importantly, these neurological changes may result from inadequately treated chronic focal pain problems such as osteoarthritis or myofascial pain. It is important for health professionals to be aware of this syndrome and to diagnose the patients to avoid a steady increase in diagnostic tests. On the other hand, patients with chronic widespread pain have an increased risk of developing malignancies, and new or changed symptoms should be diagnosed even in FMS. In rheumatology practice it is especially important to be aware of the existence of FMS in association with immune inflammatory diseases, most commonly lupus and rheumatoid arthritis. Differential diagnoses are other causes of chronic pain, e.g. thyroid disease. The costs of this syndrome are substantial due to loss of working capability and direct expenses of medication and health-system usage. Fibromyalgia patients need recognition of their pain syndrome if they are to comply with treatment. Lack of empathy and understanding by healthcare professionals often leads to patient frustration and inappropriate illness behavior, often associated with some exaggeration of symptoms in an effort to gain some legitimacy for their problem. FMS is multifaceted, and treatment consists of both medical interventions, with emphasis on agents acting on the central nervous system, and physical exercises.

Key words: chronic widespread; fibromyalgia; classification; muscles; differential diagnosis; immuno-inflammatory; recognition; expenses.

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CHRONIC WIDESPREAD PAIN, WHAT IS THE EVIDENCE?

Chronic pain is very common in all European countries¹, and problems with musculo-skeletal pain are particularly prominent.² Pain leads to disability for the individual³, and for society the disease has significant economic implications.^{4,5} In the muscles the most prominent pain syndrome is rather localized and generally referred to as myofascial pain, which may occur in most of the population given the right circumstances (see Chapter 3). The muscles, whether healthy or painful, have the capacity to produce symptoms, and this may be associated with the activation of specific trigger points, possibly by a change the biochemical milieu (see Chapter 4).

What exactly triggers the spread of this pain into hitherto normal functioning areas has yet to be clarified. However, evidence points towards a significant role of the central nervous system, with central sensitization as the presumed underlying mechanism (see Chapter 5). This spread of symptoms (i.e. spread of receptive fields) can be elicited experimentally and is a normal short-lived response of the nervous system. In some patients this normally transient response develops a chronicity which results in a syndrome of chronic pain, which patients commonly attribute to originating in their muscles. When such pain becomes widespread (i.e. involving most of the body) it is called 'fibromyalgia', an enigmatic disorder that is usually referred to as a syndrome (FMS), in view of the fact that these patients often have multiple other symptoms. Many of these associated symptoms are thought to reflect profound changes in the nervous system, as reviewed in Chapter 6. As is the case with many common disorders, the pathogenesis of fibromyalgia probably reflects an interaction of environmental triggering events on the background of a genetic predisposition (Table I; see also Chapter 9).

Whatever the underlying mechanisms of FMS, the disorder tends to run a chronic course, and the widespread musculoskeletal pain has a large impact on the sufferers' quality of life (Chapter 11), their social life, family network, and society. Despite an increasingly impressive research effort, there are many aspects of fibromyalgia which

Table I. Red-flag-symptoms for fibromyalgia syndrome (FMS) in rheumatological practice.

Predisposing feature	Principle	Examples
Heritance and constitution	Hypermobility Other	Ehlers–Danlos almost 100% Family occurrence of FMS
Long-lasting pain	Localized or regional pain in extremities	Epicondylitis, carpal tunnel syndrome, frozen shoulder, supraspinatus tendonitis, radicular pain, spinal stenosis
	Neck pain	Whiplash
	Back pain	Degenerative pain, non-specific back, pain without radicular symptoms, spondylitis
Surgery for musculoskeletal pain syndromes	Minor	Carpal tunnel, acromioplasty, transposition of ulnar nerve
	Major	Repeated back surgeries
Medical disease	Immuno-inflammatory	Rheumatoid arthritis, polymyalgia rheumatica, systemic lupus, Sjogren's syndrome

need further clarification. The present knowledge of the disease stems from epidemiological data, psychological profiles, and studies of dysfunction of the autonomic, central and peripheral nervous systems. Interestingly, no specific changes have been found in muscle tissue, despite the common assertion that this is the origin of the patient's pain. This paradox is currently challenging our perspective on FMS (see Chapter 12). The lack of specific disease mechanisms is reflected in the fact that no cure has been found for the disease, and the many interventions which are advocated in FMS are targeted against the more general features of pain and disability. There is an increasing consensus that therapy should include both medical treatment, mainly acting on the central nervous system (Chapter 7), and non-pharmacological measures, which are basic to any rehabilitation program (Chapter 8).

IMPORTANCE FOR THE RHEUMATOLOGIST

For the rheumatologist, chronic widespread pain has always been relevant as it occurs in a significant percentage of the patients in their clinic. It is quite evident that musculoskeletal specialists have reacted very differently with regard to diagnostic and therapeutic strategies for patients with chronic pain syndromes. There are geographic and cultural variations in the attitude to chronic widespread pain, and in some countries only about one in four rheumatologists 'believe' in the diagnosis of fibromyalgia.⁶ In many physicians this may be due to lack of education.^{6,7} Nevertheless, patients with FM should be referred to a specialist to be screened for other causes of their symptoms⁸, as the final diagnosis may differ from FM in some instances.⁹

Whatever the professional inclination may be, pain is an integral part of rheumatology, and some patients have more widespread problems than others.¹⁰ This is all the more important as pain has a definite influence on the reporting of other symptoms and signs, including self-reported instruments widely used in rheumatic diseases, and without knowledge of FM the rheumatologist may get a false impression of the severity of the disease by e.g. Health Assessment Questionnaire (HAQ) and Disease Activity Score 28 (DAS-28) in rheumatoid arthritis¹¹ or Bath AS Disease Activity Index (BASDAI) in spondylarthritis.¹² The issue is all the more relevant as a high prevalence of FMS is found in these chronic rheumatic diseases; concomitant FM is present in about one in five patients with RA¹⁰ and even more frequently in systemic lupus erythematosus (SLE).¹³

Why search for FMS as a diagnosis?

Identification of patients with FMS is important to both the patient and the professional system for various reasons. However, a certain controversy exists concerning the benefit of diagnosis, and some advocate that it be abandoned to avoid an increase in burden for the patients, and possibly for the professionals as well.^{14,15} Recent data suggest otherwise; the average cost of health care for patients with FMS is high, with an estimated average of more than \$2000 per patient per year¹⁶, and in the UK the diagnosis of FMS can stop a steeply rising utilization of both GP consultations and diagnostic tests.¹⁷ On the other hand, the label FMS should not lead to neglect of symptoms in the patient with musculoskeletal pain, who has a greater-than-average risk of acquiring serious complications and diseases.^{18,19}

Indeed, the diagnosis of FMS enables the scientific society to deal in a structured way with the many patho-etiologic questions that need to be answered before relevant therapy may be given to subgroups of sufferers from this syndrome.

IMPORTANCE FOR THE PATIENT

FM patients and physicians often have discordant views upon several matters which may impact on physician–patient collaboration during office visits.²⁰ Persuading a skeptical physician about the validity of a pain complaint may be quite hard work.²¹ If the patient succeeds in adequately describing the problem, the chances of obtaining successful management is enhanced, as the attitude of healthcare professionals can positively add to treatment results. Conversely, denial on the part of the healthcare professional may push the patient into adopting inappropriate illness behaviors.²²

CHARACTERISTICS OF FMS

The core diagnostic feature of FMS is a reduced threshold for pain in the muscles, generally identified by an increased sensitivity to pressure, with hyperalgesia and sometimes allodynia. Usually this feature is tested clinically with a pressure of about 4 kg/cm² applied by the examiner's fingertip.²³ The test is somewhat biased by examiner expectations, but is reasonably reproducible in daily clinical practice.²⁴ For research purpose, a more elaborate instrument (such as an algometer) may be used to test local tenderness and provide more quantitative measurements.²⁵ Whatever the method used, repetitive measurements during follow-up in longitudinal studies should be performed by the same examiner.²⁶

There are indications that FMS patients, while definitely having lower pain detection thresholds, in principle have a normal pattern of reaction to pain as measured by the patients' endurance to computerized pressure muscle pain – deep muscle pain – with normal absolute values for pain tolerance limits.²⁷

A patient with FMS may very well have local changes in the muscles, which should be detected clinically and treated in parallel with more localized musculoskeletal pain, i.e., myofascial pain syndromes (see Chapter 3). Some of the treatments for myofascial pain (e.g. trigger-point injections) must be used with caution in FM patients in order to avoid the patient developing an undue dependence on such interventions to the exclusion of other therapeutic modalities such as medications and exercise.

FMS is often part of a wider syndrome encompassing many symptoms from organs other than muscle. These associated features include fatigue, sleep disturbance, headache, migraine, variable bowel habits, diffuse abdominal pain, and urinary frequency.²⁸ The fatigue is especially prominent, and a common overlap between chronic fatigue and FMS has been noted.

In a recent population-based study involving the Swedish Twin Registry, a highly increased odds ratio (OR) of >20 for chronic fatigue was found in a population of identical twins who had been diagnosed with FM. In comparison, non-identical twins had an increased OR of ~10. These results strongly suggest that both genetic and environmental influences play a role in the coexistence of these two common syndromes.²⁹

Mild psychiatric disturbances – e.g. depression and anxiety – are found in about one third of FMS patients³⁰, and this may contribute to the severity of the symptoms.³¹ It has been suggested that certain personality traits predispose for the development of FMS³², however, in parallel with other chronic pain conditions, the personality may change under

the duress of chronic pain.^{33,34} There is no doubt that FMS patients in general have pain as demonstrated by central nervous system reactions^{35,36}, while in their quest for acceptance of their problems they may be driven to exaggerating their symptoms.²² Somatization is an aspect to be considered in all chronic pain states, including FMS.³⁷ However, most evidence in this field has been gathered from patients referred to tertiary centers with a specific interest in FMS; such patients may have an over-representation of psychiatric problems and diagnoses. It is quite possible that FMS only strikes after a long period of subclinical disease, in which the patient may not yet have reached the point of no return. Even in subjects with severe chronic pain, but lacking features of full-blown FMS, reversibility of symptoms may still be possible.³⁸ In line with these observations, patients may exhibit reduced biochemical indices of central sensitization, such as a reduction of substance P in cerebrospinal fluid, after removal of a source of pain, as in arthroplasty for osteoarthritis.³⁹

Muscles in FMS

Most information on FM has been gathered from studies on patients with long-standing disease. Over the course of several years many FM patients develop varying degrees of impaired muscle function with low perceived strength.^{40,41} Several studies have observed non-specific degenerative changes in the muscles, which can be explained by prolonged reduction of activity.⁴²⁻⁴⁶ A low content of intramuscular collagen may make the muscle more prone to micro-injury⁴⁷, which in turn may make the FMS patient especially prone to developing delayed-onset muscle soreness.

This implies that on top of the background pain, FM patients have post-exercise intolerance which acts as a deterrent to regular strength and endurance training. Post-exertion pain in FM patients is not always associated with reduced cardiovascular fitness⁴⁸; indeed, recently it has been possible to motivate a group of FM patients to persist with heavy-resistance training in the same way as healthy controls.⁴⁹

PREVALENCE OF FMS

Epidemiological data indicate that FM is fairly prevalent in all age groups in all cultures; the typical prevalence varies from about 1% to 10% (see Chapter 2).

FMS, like most descriptive syndromes, cannot be regarded as a truly discrete entity; rather it is best envisaged as being at one extreme of a continuous spectrum of pain intensity and distribution. Many adults have been observed to have three to six tender points without significant pain complaints⁵⁰, and it is now evident that the distribution of tender points is a continuum in both the general population and rheumatologic patients.^{10,50}

FMS symptoms (and diagnosis) may be seen in patients with less than the 11 of 18 tender points, while most patients with more than this number may be classified as having FMS. Another question to be clarified is the changes in number and intensity of tender points over time. A too-rigorous view on number of tender points as a criterion may lead to the discarding of an otherwise soundly founded clinical diagnosis of FMS.

Fibromyalgia has been categorized as a 'female syndrome'; however, it should be realized that men may develop FM as well. It may be that FM in men is under-diagnosed for a number of reasons, such as gender differences in seeking medical help, men being less likely to report pain when palpated, psychosocial influences⁵¹, and sex-related differences in pain perception.⁵²

CLASSIFICATION OF FMS

For research purposes, it has been of huge importance to have definite criteria for these patients.

In 1990 the American College of Rheumatology (ACR) published classification criteria for FMS.²³ These are the most commonly used classification criteria in clinical and therapeutic research. They stipulate that an individual must have both chronic widespread pain for at least 3 months involving at least three quadrants of the body as well as the axial skeleton, and the presence of 11 or more of 18 tender points on examination (Table 2).

Importantly, these criteria specifically state that FM is not a diagnosis of exclusion. Thus the finding of abnormal serology or radiographic changes does not 'rule out' a diagnosis of FM. This is an important point, as FM is a common accompaniment of rheumatic disorders such as rheumatoid arthritis, SLE, and Sjogren's syndrome.

It has been suggested that certain subgroups within fibromyalgia could be distinguished on the basis of e.g. their myalgic score, i.e., the sum of the grades of tenderness of the tender points, using a scale of 0–3 according to patient reaction: 0 = no reaction, 1 = tenderness, 2 = withdrawal, 3 = verbal exclamation of pain. With 18 tender points, this results in a range of 0–54. The myalgic score correlates significantly, albeit weakly, with muscle strength.⁵³ Tender points and tenderness of some muscles are part of life, and most individuals have at least a few tender points, which are in the same muscles and locations as those tested for in patients with FMS.⁵⁴ Indeed, the number of tender points in ordinary adults is in the range 3–6, with females having more than males.⁵⁰ Tenderness on palpation is not enough to create patient status; the tenderness must be combined with a complaint of pain and, in the case of musculoskeletal tissue, the distribution of these complaints is crucial for the diagnosis. Myofascial pain syndromes are confined to certain regions, and a patient may exhibit several of these. While pain drawings cannot be recommended as a tool for distinguishing patients with various psychological states of pain⁵⁵, they do represent a fast and simple way of discerning widespread from more regionally defined pain (Figures 1 and 2).

As with other rheumatological diseases, fibromyalgia patients may be further scored for disease impact by using the fibromyalgia impact questionnaire⁵⁶, which has been translated into and validated in several languages. The prognostic value of these classifications remains to be clarified.

It is possible that patients with spread of pain to non-muscle tissue have a more severe disturbance of the nociceptive system; however, the so-called control points on the forehead and nail-bed of the thumb are not regularly used and are not included in the classification of ACR.²³

Table 2. The American College of Rheumatology (ACR) criteria for the classification of fibromyalgia.²³

- Widespread pain on both right and left sides, above and below the waist on both sides of the body
- Axial skeletal pain (cervical, thoracic or low back)
- In combination with:
 - tenderness at 11 or more of 18 specific tender points
 - the tenderness is estimated by palpation with a force of approximately 4 kg

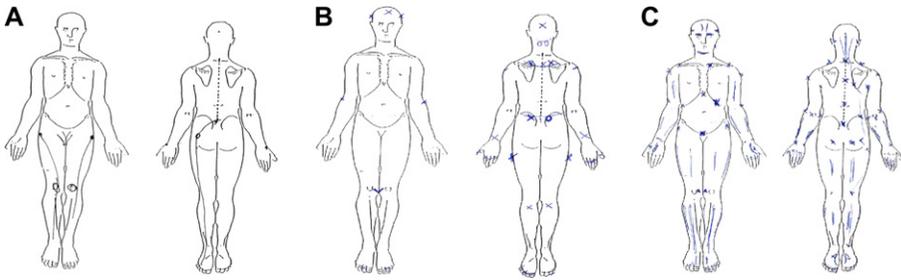


Figure 1. Pain drawings from three patients, all with a clinical diagnosis of fibromyalgia (FMS). It may be suspected that the disease is more pronounced in case B than in case A, and more severe in case C than in case B. A prognostic value for pain drawings remains to be demonstrated.

DIFFERENTIAL DIAGNOSIS

The case history of any patient with a complaint of musculoskeletal pain must include questioning about symptoms from other parts of the body, if possible supplemented by a pain drawing. Even chronic widespread pain has fluctuations, and this is especially the case in different areas, of which some will be the main problem at a given time.

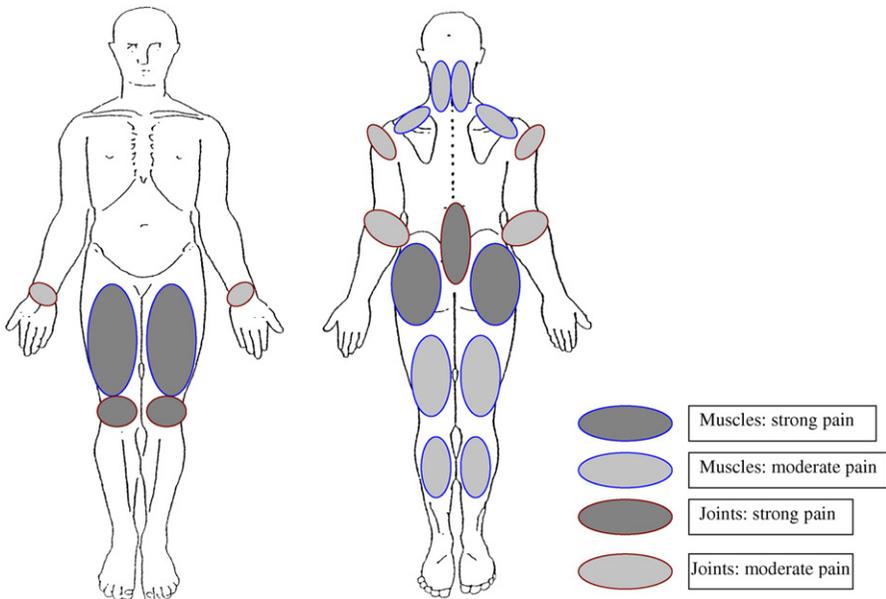


Figure 2. A 60-year-old businessman with his own computer firm contacted the clinic of rheumatology for a second opinion. He had for years had pain in both legs, and within the last year both hips had been diagnosed as osteoarthritic and replaced with alloplasties, with no effect on the symptoms. Spinal stenosis had been disconfirmed by an almost normal magnetic resonance image (MRI), and now replacement of a knee was suggested, again as a radiogram had shown light signs of osteoarthritis. The patient had multiple tender points and filled in the pain drawing at his own computer. The patient chose therapy in a specialized pain clinic instead of surgery.

The objective examination will as a matter of course include a palpatory evaluation of muscles, in this case including the well-defined 18 points of the ACR criteria.

Medical conditions associated with muscle pain

The most obvious diseases to be distinguished from FMS are degenerative and inflammatory joint diseases, which are all associated with pain. With a sufficiently large number of joints involved, this may in fact give rise to widespread pain of the same nature as fibromyalgia. The degree of pain experienced by patients with FMS is in the high range as estimated by a visual analog scale⁵⁷, and per se this is not helpful in distinguishing this disease from e.g. arthritis or osteoarthritis, which are reported to have pain in the same range.⁵⁸ Other medical diseases associated with widespread pain should be excluded, primarily by using a standard set of blood tests for such patients: most importantly, thyroid abnormalities and, in several countries, vitamin-D deficiency (Table 3).

CONCLUSION, TREATMENT STRATEGY

The 1990 ACR classification criteria for fibromyalgia were developed as a result of a large blinded multicenter study in North America which included patients with presumed fibromyalgia as well as patients with other chronic pain conditions.²³ It is now apparent that these classification criteria, developed for epidemiological studies, while showing high diagnostic specificity, are sometimes lacking in sensitivity in the clinical

Table 3. Differential diagnoses for fibromyalgia in musculoskeletal conditions.

Diagnosis	Suggested tests for differentiation, supplementary to the clinical examination including tender points
<i>Degenerative diseases</i>	
Localized myofascial pain	Pain drawing
Tendonitis	Ultrasound examination
Osteoarthritis	Radiograms of affected joints
<i>Inflammatory immune diseases</i>	
Rheumatoid arthritis	Radiographs and ultrasound examination of affected areas Blood tests: CRP, anti-CCP, ESR, IgM-rheumatoid factor
Systemic lupus erythematosus	Blood tests: CRP, ANA, anti-DNA
Sjögren's disease	Blood tests: ANA, Shirmer's test, lip biopsy of salivary glands
Polymyalgia rheumatica	CRP, treatment response to prednisolone
Connective tissue diseases	ANA, anti-DNA
Polymyositis/dermatomyositis	S-creatinine kinase, S-myoglobin
<i>Metabolic diseases</i>	
Liver diseases, malignances	Transaminases, CT scan, hepatitis C screen, biopsy
Anemia, infection, leukemia	Hemoglobin, leucocytes, differential count
Hypo/hyperkalemia	Serum potassium and sodium
Kidney diseases	Creatinine, biopsy
Hypo/hyperthyroid diseases	TSH
Hypo/hypercalcemia	Serum Ca ²⁺
CRP, C-reactive protein; CCP, cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; ANA, antinuclear antibody; TSH, thyroid-stimulating hormone.	

setting. As such there are now renewed efforts to develop clinically validated diagnostic criteria which would eventually supplant the 1990 ACR classification criteria.

Over the years there has been continuing controversy as to whether FM should be considered as mainly a psychiatric or a somatic disorder. In this respect, contemporary pain research is providing an integrated understanding of the role of higher cortical centers in pain perception which persuasively negates the old concepts of mind-body dualism.

It is anticipated that useful progress will be gained in standardizing FM therapy if subgroups can be identified in the early stages, in order to focus therapy on the key features that are important in disease progression. It must be realized that 'fast' cures (e.g. prolonged physical therapy, injections, acupuncture etc) do not have sufficient impact on the long-term outcome of FM. The all-encompassing nature of the disorder points towards the necessity for a holistic approach to therapy. Current pharmacological interventions have limited efficacy, and need to be combined with non-pharmacological interventions such as gentle exercise, pacing techniques and, in some cases, cognitive behavioral therapy.⁵⁹ Lastly, as in many chronic disorders, well-educated health-care providers who are both empathetic and supportive must provide the essential backbone for the effective management of FM.

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Practice points

- increased awareness among professionals treating co-morbidities, e.g. myofascial pain, rheumatoid arthritis and SLE
- trigger points should be tested for in cases with chronic pain, especially when this involves neck and back
- chronic widespread pain may result from any long-lasting pain condition in the musculoskeletal system in predisposed individuals
- FMS may occur in both females and males at any age, though there is a preference for middle-aged women
- differential diagnoses should be ruled out as far as possible by adding to a thorough clinical examination a number of blood tests for, among other conditions, thyroid disease

Research agenda

- definition of subgroups of FMS aiming at more focused therapy
- prevention in susceptible individuals with high risk of FMS (e.g. hypermobility) with long-lasting localized pain syndromes (e.g. epicondylitis)

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