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Is fibromyalgia a neuropsychiatric disorder?

¿Es la fibromialgia un trastorno neuropsiquiátrico?

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INTRODUCTION

Fibromyalgia (FM) is a chronic musculoskeletal disorder characterized by generalized pain and tenderness at specific anatomic sites, called *tender points* (1). The condition had been recognized for years under other names (*nonarticular rheumatism, psychogenic rheumatism,* and *fibrositis*), but in 1990 the American College of Rheumatology (ACR) defined criteria for the classification of these patients and FM was "officially" borne; the ACR has recently published revised diagnostic criteria (Table 1) which include a measure of symptom severity reflecting the non-articular manifestations of FM (2). These criteria correctly classified between 89% and 95% of FM patients. Either the 1990 or the 2010 criteria can be used in the clinical and research settings.

FM can occur in isolation or in the setting of other musculoskeletal or rheumatic disorder (primary versus secondary FM) (1). In fact, in some patients with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) the overwhelming clinical manifestations are those of FM, and not the ones attribute to either RA or SLE. These FM symptoms are, by and large, unresponsive to therapies commonly used for the underlying condition.

Patients with FM often present to their physicians complaining of diffuse arthralgias and myalgias as well as of joint swelling, particularly in the small joints of the hands and feet (1). Joint swelling, however, cannot be verified on physical examination. Some patients also complain of morning stiffness lasting from minutes to hours; others exhibit joint hypermobility. These patients may also experience numerous other clinical manifestations. In fact, these other manifestations may be the ones that bring them to seek medical help. In some cases these other manifestations, rather than pain, may be the predominant ones. The most commonly described are fatigue, sleep disturbances, mental fog (inability to concentrate), and others. These patients may be under the care of different physicians for their various symptoms and may be subjected to extensive, expensive, and even invasive tests and procedures, in order to rule out more serious or different disorders. Imaging and nuclear medicine studies, endoscopies, and exploratory surgeries are, unfortunately, not uncommonly performed. Table 2 lists procedures and tests commonly obtained in patients with FM depending on their presenting symptoms.

Rheumatologists see patients with possible FM in consultation in different situations. One scenario is that of patients with FM who have failed numerous treatments and who come seeking a cure for their ailment. A second scenario is that of patients who want to legitimize their diagnosis for legal purposes (1).

Fibromyalgia affects preferentially middle-aged white women; men, children of both genders, and older adults can be also affected (1). FM has been recognized primarily in the middle and upper socioeconomic strata. Whether this reflects only access to health care or true

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Table 1*

Criteria
1. The patient does not have a disorder that would otherwise explain the pain
2. Widespread pain index (WPI) =7 and symptom severity (SS) scale score =5 or WPI 3-6 and SS scale score =9
3. Symptoms have been present at similar level for at least 3 months
Ascertainment
1. WPI: Note the number of areas the patient has had over the last week. Score between 0-19
2. SS Scale Score: Fatigue, Waking unrefreshed, Cognitive symptoms (severity 0-3 for each of them) plus somatic symptoms (0-3, none, few, moderate number, a great deal of symptoms)

*Modified from Wolfe et al (2).

differences in the incidence and prevalence of the disorder among disadvantaged populations has not been determined. Studies from North America and Europe, imperfect as they may be, reveal overall prevalence rates between 1% and 5%, but figures as high as 13% have been reported. In the clinical setting, the frequency of FM depends, to a certain extent, on the degree of awareness about this condition. Figures between 2% and 4% have been reported in the primary care setting. In rheumatology clinics, the frequency of FM fluctuates between 3% and 20%.

ETIOPATHOGENESIS

Like many other rheumatic disorders, the etiopathogenesis of FM is probably multifactorial (1). Susceptible individuals may develop FM as a result of the interaction of peripheral and central factors. Familial aggregation of FM does not of itself prove genetic susceptibility; in fact, it can be argued that familial aggregation only reflects learned behavior among the offspring of adult FM patients. However, the familial pattern of FM (affecting primarily the female gender) suggests an autosomal dominant transmission (1). Animal data indeed suggest that genetic factors may influence pain sensitivity and pain modulation; human data are just emerging (1).

Peripheral Factors

Patients with FM describe their pain as being "muscular". It is therefore logical that muscle tissues from these patients have been studied; muscle microtrauma may occur with pain persisting despite apparent healing which may explain the negative results of these studies. An alternative explanation is that healing is slow to occur due to altered growth hormone (GH) production (needed for muscle repair); in turn, these altered levels of GH result from disturbed sleep (sleep modulates the GH axis). However, magnetic resonance (MR) imaging of tender points and muscles has failed to demonstrate structural abnormalities of muscles. Studies of ^{31}P MR spectroscopy, however, suggest alterations of the oxidative capacity of muscle tissue at rest (1), and ultrastructural studies demonstrate increased DNA repair in muscle fibers of patients with FM relative to control subjects (1).

Central Factors

Given the inconsistency and relative paucity of peripheral abnormalities in patients with FM, and the concomitant neuropsychiatric manifestations these patients present, efforts have been directed at the elucidation of the central mechanisms that may be responsible for the musculoskeletal pain these patients present. Of course there are those who consider FM patients to have pain with no organic basis and dismiss them as a nuance to the medical system. In support of their assertion is the well-recognized fact that patients with FM who are cared for at tertiary-level facilities may exhibit a significant degree of psychopathology (1). What appears to prompt FM subjects to seek medical care is not pain *per se*, but the degree of psychologic disturbance they have. The following central factors: neuroendocrine abnormalities, neuropeptide abnormalities, and abnormalities in functional brain activity are now described.

Neuroendocrine Abnormalities

Abnormalities of the hypothalamic–pituitary–adrenal (HPA) axis are now well recognized in patients with FM. It has now clearly been shown that patients with

TABLA 2. Symptoms, diagnostic tests/procedures and diagnoses in fibromyalgia patients seeking health care

Specialist	Reasons for Consultation	Potential Tests/Procedures	Possible Diagnoses[a]
Internist	Malaise, fatigue, weakness	Various	Various
Cardiologist	Palpitations, chest pain, syncope, hypotension	ECG, exercise test, echocardiogram, conventional and MR angiograms, cardiac catheterization, tilt table evaluation	Mitral valve prolapse Atypical angina Dysautonomia
Pulmonologist	Dyspnea, snoring	Pulmonary function tests, arterial blood gases, polysomnogram	Asthma Sleep apnea
Gastroenterologist	Dysphagia, dyspepsia, abdominal pain, bloating, constipation, diarrhea	Upper and lower GI tract endoscopies, radiographs and/or biopsies, abdominal CT and/or ultrasound, abdominal angiogram	Noncardiac chest pain Irritable bowel syndrome Gastroesophageal reflux
Endocrinologist	Weakness, faintness	Fasting blood sugars, serum hormone levels	Hypoglycemia
Rheumatologist	Myalgias, arthralgias, Raynaud phenomenon, weakness, neck and/or back pain, fatigue	Serologic tests, electrophysiologic studies	"Latent", "Variant" or "Pre-lupus" Costochondritis Polymyalgia rheumatica "Undifferentiated" CTD
Dermatologist	Pruritus, hives, skin rashes, "photosensitivity"	Skin biopsies	Dermatitis
Allergist	"Allergies"	Skin tests, suppression tests	Allergies Multiple chemical sensitivities
Neurologist	Dizziness, dysesthesias, vertigo, headache, syncope, seizures	CT scans and/or MRIs, MR angiograms, electrophysiologic studies, lumbar puncture, biopsies	Migraine, restless leg syndrome, dysauto-nomia, anxiety
Gynecologist	Polyuria, dysuria, dyspareunia, "vaginitis," pelvic pain	Cystoscopies, colposcopies	UTI, cystitis, vaginitis, endometriosis
Otorhinolaryngologist	Tinnitus, cough, headache, hoarseness, snoring, vertigo, dizziness	Audiograms, CT scans or MRIs, polysomnogram	Rhinitis, sinusitis, Menière, sleep apnea
Orthopedist	Neck and/or back pain	Radiographs, MRIs, and/or CT scans	"Arthritis"
Neurosurgeon	Headache, neck and/or back pain, dysesthesias	CT scans and/or MRIs, electrophysiologic studies	Spinal stenosis, radiculopathy
Ophthalmologist	Dry eyes, blurred vision, double vision	Shirmer test, fluorescein test	Sicca syndrome
Psychiatrist	Anxiety, depression, insomnia, decreased memory, sexual and/or physical abuse	MMPI, neurocognitive evaluation, other psychologic tests	Anxiety, depression, abuse (sexual and/or physical)
Dentist	Dry mouth	Salivary gland biopsy	Sicca syndrome

[a]Some of these diagnoses represent true associations. Others, unfortunately, are given to patients in an effort to explain their symptoms, but lack organic basis.

CT, computerized tomography; CTD, connective-tissue disease; ECG, electrocardiograms; GI, gastrointestinal; MMPI, Minnesota Multiphasic Personality Inventory; MR, magnetic resonance; MRI, MR imaging; UTI, urinary tract infection.

Modified from Alarcón GS. *Wmn Health Pri Care* (Orth Ed) 1999;2:11–22.

FM exhibit a reduced 24-hour excretion of free cortisol; these patients also respond with an exaggerated excretion of ACTH but a blunted cortisol response to the administration of corticotrophin-releasing hormone. The infusion of ACTH is followed, however, by a normal cortisol response. Abnormalities of the autonomic nervous system (e.g., response to orthostatic stress), which have been well documented in patients with FM, may be related to an altered HPA axis and abnormal sympathoadrenal responses (1). There is also a reciprocal interaction between the HPA axis and brain limbic system structures. These interactions may explain the high levels of aversiveness that characterizes the pain of FM (1).

Neuroendocrine abnormalities in FM go beyond the HPA axis, the sympathoadrenal responses, and limbic system structures; they include the HP-thyroid, the HP-gonadal (G), and the GH axis. The study of the hypothalamic–pituitary–gonadal (HPG) axis, including pain perception and stimulation during the different phases of the menstrual cycle, for example, may provide insights into the predominant female distribution of FM or explain the variability of symptoms patients usually describe in conjunction with the occurrence of menses. Sleep abnormalities may disturb the secretion of GH, necessary for muscle homeostasis. This disturbance, in turn, may contribute to poor healing when muscle microtrauma occurs and to the perpetuation of nociception (1).

Neuropeptide Abnormalities

It has been demonstrated that patients with FM exhibit abnormalities in neuropeptides, suggesting that indeed pain in FM involves abnormalities in pain modulation (1). Abnormalities that have been consistently found include low serum levels of serotonin and its metabolite, 5-hydroxyindolacetic acid (5-HIAA), and high CSF levels of substance P. Other neuropeptides found to be abnormal in patients with FM include nerve growth factor, dynorphin A, and calcitonin-related gene peptide. These neuropeptides could contribute to increased excitability of dorsal horn neurons after injury. This increased excitability results in increased neural input (which is mediated by neurons with *N*-methyl-D-aspartate, or NMDA, receptors). By this process, called *central sensitization*, the receptive area of nociception experiences an enlargement in quantity (increased peripheral perceptive field) and quality (responsive to all kinds of stimulation). This increase in nociceptive transmission may result in functional alterations of brain structures involved in pain modulation. It has also been proposed that the hyperexcitability of the NMDA receptors may lead to increased synthesis of nitric oxide which in turns contributes to maintaining abnormal muscle tissue and leads to increased nociception, and to a vicious cycle that is difficult to interrupt.

Abnormalities in Functional Brain Activity

Patients with FM have abnormalities in the functional activity of specific brain structures (thalamus and caudate nucleus) as demonstrated by different investigators (1,3). These studies support the contribution of central mechanisms to the pathogenesis of pain in FM. These abnormalities are found in the resting state but also after stimulation. In normal individuals such stimulation is followed by activation not only of the contralateral thalamus but also of the anterior cingulate (AC) cortex, the primary and secondary somatosensory (SS) cortices, and the insula. In contrast, in FM patients there is bilateral activation of the SS cortices and of the right AC cortex. The level of painful stimulation utilized in these studies was tailored to the patients' own threshold levels of pain. Thus, by and large, patients received lower levels of painful stimulation than the controls (1). More recently, investigators from Harvard have used resting state functional magnetic resonanace imaging (FMRI) and have demonstrated that resting brain activity within multiple brain networks is associated with clinical pain in FM (3). These studies support the role of central factors in the etiopathogenesis of FM.

PRECIPITATING FACTORS

In some patients FM evolves in an insidious manner. It is impossible to determine precisely when symptoms really started. Other patients, however, can time the onset of their symptoms to a traumatic event (physical or emotional), or to a well-defined infectious process. With regard to trauma, the nature of the trauma does not really matter (severity of injury or even if the event was predominantly physical, but perceived as emotional by the patient) (1). Numerous infectious processes have been described as capable of precipitating FM. They include infections with the human immunodeficiency virus, hepatitis C virus, Coxsackie virus, and Parvovirus B19 (1). Infections with *Borrelia burgdorferi* (Lyme disease) and Brucellosis have also been recognized as capable of precipitating FM. It should be noted that, unfortunately, cases of post-Lyme and post Brucellosis

FM are erroneously diagnosed as chronic ongoing infections and patients subjected to costly, unnecessary, and lengthy treatments.

In summary, central factors appear to be important in the etiopathogenesis of pain in FM.

A theoretical model of FM pathogenesis is depicted in figure 1.

PATIENT EVALUATION

A careful history (multitude of somatic complaints, fatigue, poor sleep, and impaired cognition) and a complete physical examination (not limited to tender points) should point to the correct diagnosis. At this time the inclusion of either imaging brain studies (particularly SPECT) or the study of serum and CSF levels of neuropeptides in all FM patients is not recommended. As useful as these studies have been and continue to be in clarifying the nature of this compex and intriguing condition, their diagnostic properties (sensitivity; specificity; and negative, positive, and overall predictive value) have not been determined; furthermore their risk and cost make them currently unjustifiable. Other ancillary studies including laboratory tests should be ordered only as clinically indicated.

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TREATMENT GUIDELINES

Given that the nature of this disorder is just beginning to be understood, it should come as no surprise that we have limited effective therapies to manage these patients. Primary care physicians (PCPs) have the

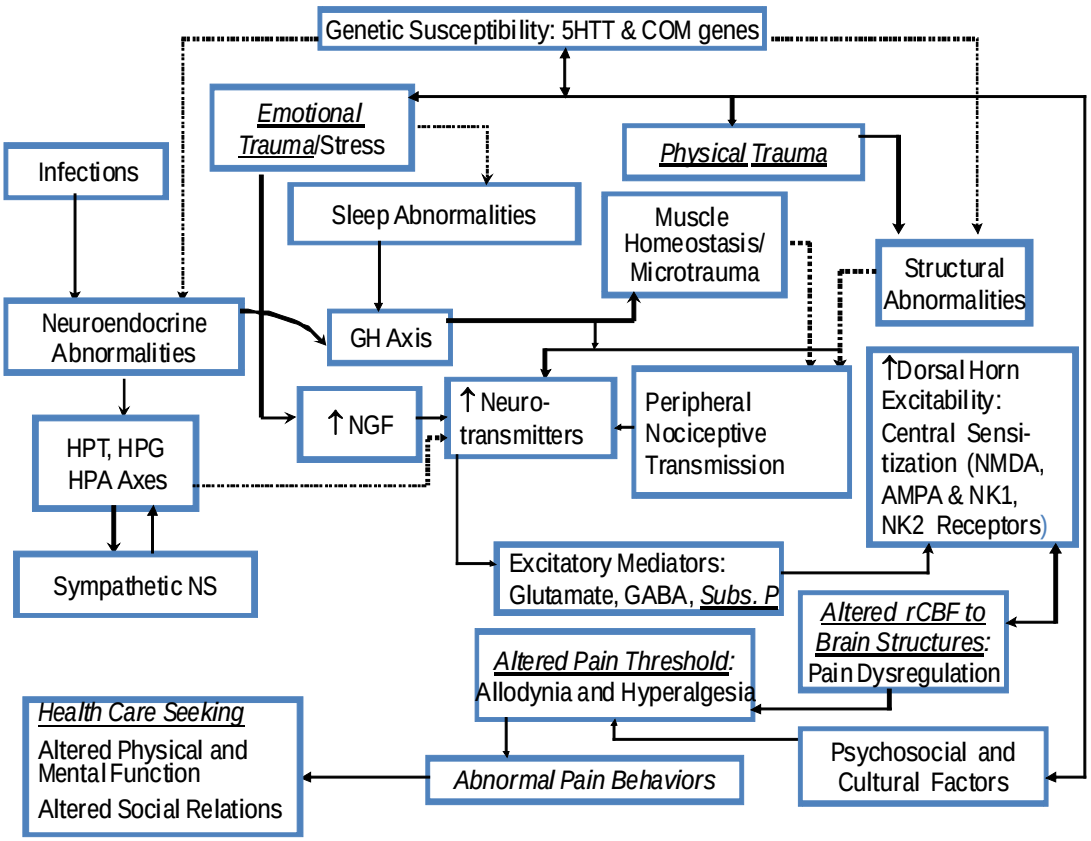

Figure 1. Model of abnormal pain perception in fibromyalgia. *Broken lines* are proposed mechanisms; *solid lines* are defined mechanisms. *HPT*, hypothalamic–pituitary–thyroid axis; *HPG*, hypothalamic–pituitary–gonadal axis; *HPA*, hypothalamic–pituitary–adrenal axis; *GH*, growth hormone axis; *NGF*, nerve growth factor; *NS*, nervous system; *NO*, nitric oxyde; *rCBF*, regional cerebral blood flow. (Modified from Weigent DA, Bradley LA, Blalock JE, et al. *Am J Med Sci* 1998;315:405–412.)

tremendous responsibility of steering patients away from unproved (and often risky) treatments. Patients with FM need first to believe that we, their health care providers, acknowledge that their pain is real and causes suffering (1). Second, realistic goals should be established from the outset. Third, it should be emphasized that pharmacologic compounds constitute only one element of the overall treatment plan. Other elements include a balance between exercise and rest; a diet aimed at achieving or maintaining an ideal body weight; avoidance of alcohol, caffeine, nicotine, and recreational drugs; and modification of abnormal sleep behaviors/habits (4).

Patients with FM are so often overweight and deconditioned that they have to start an exercise program very gradually. Aquatic exercises rather than land exercises are better tolerated; unfortunately, year-round aquatic programs exist only in urban areas and are not accessible to all patients. If these facilities exist, however, patients should be strongly advised to enter aquatic exercise programs under proper supervision (these facilities may have limited to access to the general public, however). Low-impact aerobics are an alternative for these patients. Recently, favorable results in terms of the Fibromyalgia Impact Questionnaire and the SF-36 have been reported with classic Young style Tai Chi in a small 12-week single blinded study; although a larger and longer confirmatory study is needed these data are certainly relevant (5).

Unfortunately, many patients with FM have reached a level of polypharmacy which is extremely difficult to deal with. Moreover, the rationale for the use of some compounds is virtually lacking. That is the case, for example, for nonsteroidal antiinflammatory drugs (NSAIDs) used as panacea for "arthritis" and prescribed quite often to FM patients (6); other than their possible central effect (purely analgesic), there is no reason for their use. Narcotic analgesics (of different strength and quality) are, unfortunately, also commonly used, even in children and young adults and rarely can be discontinued. Muscle relaxants are also commonly used for a prolonged time. NSAIDs, narcotic analgesics, and muscle relaxants, if used, need to be prescribed judiciously, and for limited time periods (e.g., during exacerbation of background pain or after trauma in patients with joint hypermobility). Patients need to understand that FM per se does not produce physical deformities and that despite pain a relatively normal life is possible. Living with pain, can however, exert a toll on patients and families with studies suggesting that FM is a risk factor for self-inflicted death (7,8).

Pharmacologic compounds found to be beneficial in patients with FM include the tricyclic antidepressants (TCAs) as well as the selective serotonin reuptake inhibitors, or SSRIs, independent of whether patients are depressed or not (1). Among the TCAs, amitriptyline is the most commonly used (1), the starting dose varying between 10 and 25 mg/day; it can be escalated to 50 to 75 mg/day. In terms of the SSRIs, the most commonly used is fluoxetine; the most frequent dose is 20 mg/day, but higher doses have been used. Other SSRIs—including citalopram, sertraline hydrochloride, and venlafaxine—have also been used. Double re-uptake inhibitors such as milnacipran and duloxetine have also been shown to be of benefit in FM patients (9). Finally, a meta-analysis of the effectiveness of anti-depressants in FM for the outcome of pain has shown them to be benefitial (10). The newest "kid on the block" is pregabalin (11). In the landmark 2005 study of Crofford et al 529 FM patients were randomized to either 150 mg, 300 mg, 450 mg or placebo, with the 450 mg group demonstrating improvement in terms of pain, fatigue and sleep. A number of other pregabalin studies have now been performed with one of them being of longer duration (12); overall, these studies support the original report of Crofford et al. Anxiolytics and other psychopharmaceuticals should be restricted to patients with clear-cut indications for their use (concomitant psychopathology).

Other Treatment Modalities

The role of liniments and other topical preparations (substance P antagonists, such as capsaicin) in the treatment of FM is probably limited to those circumstances in which there is definite added local pathology to a region/area of the musculoskeletal system. In the past, rheumatologists frequently injected several tender points with corticosteroids and anesthetics every so often. Some patients indeed reported these injections to be beneficial. This effect probably relates to the use of steroids and their systemic absorption, rather than to their local effect. The rationality for performing periodic soft-tissue injections in all FM patients is nonexistent, other than perhaps "needling" these patients, in much the same way as is done with acupuncture, now a recognized alternative treatment for FM (1). The role of soft-tissue massages, hypnotherapy, relaxation, and spinal manipulations for the treatment of FM is undetermined for now.

Claims have appeared on the Internet of the successful treatment of FM with decompressive surgery of the craniocervical junction based on the

reported possible association of FM with Chiari malformation (protrusion of the tonsils below the level of the foramen magnum) (1). Although patients with cervical spinal stenosis may exhibit some FM-like manifestations, searching for this association should be done only if clinical manifestations indicative of canal stenosis and compressive myelopathy exist (1). Unfortunately, the Internet has favored the dissemination of unfiltered information capable of directly reaching many more patients than with methods used in the past (millions of websites are found). PCPs should be properly informed so that patients receive adequate counseling and unnecessary and risky surgical procedures are avoided.

IMPACT OF FIBROMYALGIA

Although FM patients do not develop obvious physical deformities or impairments, this disorder can impact several domains of their lives (pain, iatrogenesis, employment, and financial and family stability) (1, 7, 8). Patients who remain employed, physically active, and trim; take few medications; and have adequate coping skills and a supportive family tend to do better than those who are physically inactive, unemployed, overweight, and already taking many medications. Neurologists and psychiatrists should be aware of this pervasive condition, manage the associated symptoms and refer the patient back to the PCP for follow up. When in doubt about the diagnosis, an evaluation by a dermatologist may clarify it and treatment guidelines offered. Expensive and invasive ancillary tests are NOT indicated.

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