

The evaluation of the fibromyalgia patients

La valutazione del paziente fibromialgico

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RIASSUNTO

La sindrome fibromialgica (FM) è una condizione di frequente riscontro nella pratica clinica caratterizzata da dolore muscoloscheletrico cronico e diffuso, sensazione di tensione e/o di rigidità muscolare e articolare, affaticabilità, disturbi del sonno, alterazioni del tono dell'umore e dolore alla digitopressione di almeno 11/18 tender points (TPs). Fino ad oggi, non disponiamo né di esami strumentali né di marcatori specifici per effettuare la diagnosi di FM; infatti, la maggior parte degli esami attualmente disponibili sono utili solo ai fini di ricerca. La maggior parte delle diagnosi differenziali può essere effettuata mediante un accurato esame clinico e anamnestico. Se consideriamo il possibile overlap tra la FM ed altre malattie, il medico curante dovrebbe sottoporre tutti i pazienti con sospetta FM a radiografia del torace ed ecografia dell'addome, oltre ad un accurato esame obiettivo. La risonanza magnetica funzionale ha messo in evidenza diverse alterazioni sovraspinali nei pazienti affetti da FM, una condizione clinica a patogenesi sconosciuta. Nei pazienti affetti da FM sono diversi i trattamenti utilizzati, ma valutarne il loro effetto è difficile poiché questa sindrome presenta molteplici aspetti. Al fine di identificare un "core outcome domains", l'iniziativa dell'IMMPACT e il workshop OMERACT ha convocato un meeting per sviluppare le raccomandazioni utili per i trials clinici sul dolore cronico.

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INTRODUCTION

Fibromyalgia (FM) is a rheumatic disease characterized by musculoskeletal pain, chronic diffuse tension and/or stiffness from joints and mus-

cles, easy fatigue, sleep and emotional disturbances, and pressure pain sensitivity in at least 11 of 18 tender points (TP) (1, 2). This disease has an incidence of 2% in the general population, but it is found more often in middle-aged women (3.4%) (3, 4). The etiopathogenesis of FM has not been clarified yet. FM patients have a dysregulation of pain neurotransmitters and neurohormone-mediated association with irregularities in the physiology of sleep. The American College of Rheumatology (ACR)

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criteria diagnostic criteria for FM are based upon chronic widespread pain and tenderness in 11 of 18 defined muscular sites (1). Recent evidence suggests that the tenderness component of FM is not confined to these sites; rather, it is present throughout the body, including non-muscular sites such as the thumb. The widespread nature of spontaneous pain in FM implicates general mechanisms that may involve spinal or supraspinal modulation of normal peripheral input, or effector mechanisms that alter pain sensitivity at the periphery. These mechanisms are likely observed at supraspinal sites. Functional neuroimaging of the brain has opened a window into the supraspinal processes in health and disease (5). With a few exceptions, these methods infer neural activity in the brain by changes in regional cerebral blood flow (rCBF). This inference is based on the principle that localized brain activity signals a discreet increase in rCBF to meet the metabolic demands of this increase in neural activity. The increase in rCBF occurs after a hemodynamic delay of a few seconds and is closely coupled to the magnitude and duration of the activity. Most functional imaging methods are based on the evaluation of the time course of changes in rCBF throughout the brain (6).

The absence of anatomopathological lesions and biohumoral abnormalities, demonstrated with classical instrumental methods, has led to considerable difficulties in diagnosis. The diagnostic criteria frequently overlap with those of other diseases; in fact, some patients with chronic fatigue syndrome (CFS) meet the criteria for FM, and an FM-like framework may be present even in non-rheumatic diseases.

For example, patients with hypothyroidism show musculoskeletal pain that is similar FM. The diagnosis based on the ACR criteria, therefore, must be accompanied by the exclusion of diseases that have symptoms, but not causes, in common with FM as evidenced by the evaluation of markers and humoral scans (miositis, rheumatic polymyalgia, spondyloarthritis, etc.) (7). Often, FM is comorbid with other diseases that act as confounding and aggravating factors (Sjögren, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), thyroid disease). There are no instrumental tests to confirm the diagnosis of FM; and many differential diagnoses may be excluded by an extensive clinical examination and patient history. Considering the overlap of FM with other medical conditions, treating physicians should be vigilant: chest-X-rays and abdominal ultrasonography are the first steps to-

ward general evaluation of all patients with suspected FM. An individualized, multidisciplinary range of treatments should be employed to treat the various symptoms that patients experience. Although some of these therapies have been tested in randomized controlled trials (RCT), there has been little standardization in the approach to these trials and in the outcome measures used. Evaluating therapeutic effects in FM patients is difficult because of the many facets of the syndrome. To address the identification of core outcome domains, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (8) and Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) (9) workshop convened a meeting to develop consensus recommendations for chronic pain clinical trials.

LABORATORY AND INSTRUMENTAL EVALUATIONS IN PATIENTS WITH FM

In clinical studies and observational research studies, FM is usually diagnosed by application of the ACR criteria (1). Moreover, diagnosis is made by a combination of patient history, physical examination, laboratory evaluations and exclusion of other causes for symptoms attributed to FM (10, 11).

BIOMARKERS IN FM

Serum

Compared to healthy subjects or patients with other diseases, FM patients present with high antipolymer antibodies (APA) (12) and antiserotonin antibody (13) values, with contrasting results in the Italian population. The APA positivity in a recent work appears to be less than that evidenced in the USA, and it appears to correlate with the severity of the disease; this result could be due to a different ethnic origin of the populations studied. Other antibodies (antiganglioside and antiphospholipids) were identified in FM patients compared to healthy subjects, but the sensitivity and specificity was not clear. Patients with FM have a higher frequency of anti-thyroid antibodies, and their values seem to be correlated with the presence of certain symptoms (14). Recent studies have shown higher hyaluronic acid values in FM patients compared to healthy controls, but this data has not been confirmed (15, 16). Alterations of branched-chain amino acids (valine, leucine, isoleucine), pheny-

lalanine (17), and collagen cross links, and particularly, a reduction in the ratio of pyridinoline to deoxypyridinoline as well as decreased levels of hydroxyproline (18) were also found. Neopterin has been suggested as an inflammation marker, which has an inversely proportional relationship with L-tryptophan availability. Other studies showed low serum levels of 5-HT in FM patients compared to both healthy controls and patients with rheumatic diseases such as RA. These studies provide indirect evidence supporting the alteration of 5-HT metabolism in FM subjects. In a recent study, FM patients exhibited a tendency to have lower serotonin levels than patients with RA and healthy controls; but the variation of serotonin levels within the disease groups is too broad to differentiate FM from other conditions, especially depression (19). There is also evidence to suggest that FM patients may have alterations in the expression of 5-HT transporters due to a transcriptional polymorphism in the region that could lead to an increase of the same transcriptional region (20). Another study has suggested that an alteration of the growth hormone (GH), an indirect modulator of the immune system that interacts with the hormonal system, seems to protect the body from the immunosuppressive effects of glucocorticoids during stress (21) and favours IGF1-mediated muscle repair. Altered serum cortisol and melatonin levels were found; these hormone secretions are closely associated with the circadian rhythms. The study also found alterations of 5-HT, somatomedin C, calcitonin gene-related peptide, calcitonin and cholecystokinin which are possible indicators of FM widespread pain (22). Studies conducted on FM patients showed an increase in plasma levels of IL-6 and IL-8 compared to healthy controls, an increased production of IL-1 and TNF-alpha, and a reduced production of IL-2 and IFN-alpha, which highlights an immune activation and a down-regulation of the HPA. A study showed an increase in plasma IL-10, IL-8 and TNF-alpha in FM patients independent of the presence of psychiatric comorbidity; this supports the hypothesis of an activation of the immune system (23). Abnormal levels of ACTH, 5-HT, IGF-1 and FT4 were found, which suggests an alteration of the endocrine system in this disease (14). The role of free radicals in FM is controversial, as this could suggest that FM is also an oxidative disorder; studies have shown high levels of malondialdehyde, markers of oxidative damage, and low levels of superoxide dismutase, an intracellular antioxidant (24) in FM.

Urine

The stress factor is probably crucial in this condition and alterations of the urinary corticotropin-releasing factor (CRF)-L1, catecholamine, cortisol, with the haplotypes of catecholamine COMT gene (25) were recently found; as in the serum, cross-links of collagen, a reduction in the ratio of pyridinoline to deoxypyridinoline and decreased levels of hydroxyproline (18) were found in the urine.

Cerebrospinal fluid

In FM subjects, substance P levels increase in cerebrospinal fluid and this event leads to the release of IL-6. Substance P induces the production of IL-8, a pro-inflammatory cytokine, which stimulates the passage of neutrophils through the vascular walls. Altered levels of serotonin and increased corticotropin-releasing hormone (CRH) and a pool of proteins (alpha-1-macroglobulina, keratin 16, orosomucoide, amyloid precursors etc.) were also found in the cerebrospinal fluid of FM patients (26). Among FM patients, pain, but not fatigue, was associated with the concentration of CRF in the cerebrospinal fluid (27).

These data support the hypothesis that abnormalities in the stress response are associated with FM pain. In FM subjects, a reduction of glial cell-derived neurotrophic factor was also found (28); this result could be related to the role of this neurotrophic factor in preventing and reversing abnormalities that develop in chronic pain conditions.

Somatostatin levels appear to be reduced in the cerebrospinal fluid of FM patients and significantly correlated with reduced levels of neurotrophic factor.

Isolated cells

Alterations of the immune cells have been studied in FM patients, highlighting an abnormal lymphocyte and cytokine (IL-6-8-10 TNF-alpha) response related to FM. Specifically, the number of T lymphocytes and the immunoglobulin M level appear to be altered, and the number of natural killer cells appears to be reduced. In FM patients, reduced activation of T lymphocytes was also found. The cell receptors, especially the peripheral benzodiazepine receptor (PBR), the 5-HT receptors and the 5-HT re-uptake system were altered. Studies conducted on platelets have shown a reduced receptor density and functionality of 5-HT and its carrier, which were identified by lower 5-HT re-uptake rate from the synaptic cleft (29). Other research has shown

an up-regulation of PBR, also related to the severity of illness (30). In the platelets of FM patients increased intracellular concentrations of calcium and magnesium ions and decreased ATP levels were also found. In a recent study (31), a comparison was made between FM patients, subjects with complex regional pain syndrome (CRPS) and healthy controls regarding the influence of pain on subpopulations, lymphocyte number, and the ratio of Th1 to Th2 cytokine in T lymphocytes. The lymphocyte number did not differ between groups, but there was a significant reduction of cytotoxic CD8+ lymphocytes in FM and CRPS patients.

Tissues

In skin biopsies an increase of activated mast cells has been observed (25). It appears that muscle tissue does not exhibit alterations at the cellular level; and while the data appear inconsistent, inflammatory infiltrates have not been found. The skin of FM patients shows unusual patterns of unmyelinated nerve fibers as well as Schwann cells; if these results are replicated in a larger study, these abnormalities may contribute to the lower pain threshold of FM subjects (32).

INSTRUMENTAL STUDIES

Studies that employ existing or innovative testing devices or methodologies are usually negative, and these testing methodologies are not recommended for purposes of screening or diagnosis (33); however, imaging tests can be used to exclude concomitant illnesses that could resemble FM.

The following overview of comorbidities highlights the need for improved instruments for accurate assessment of FM. Environmental factors can influence both the development of FM and a number of "stressors" that are temporally correlated with the onset of the syndrome, including trauma, infections (e.g., hepatitis C virus, HIV, and Lyme disease), emotional stress, catastrophic events (e.g., war), autoimmune diseases and other pain conditions (34, 35). FM has been reported to coexist in 25% of patients with RA, 30% of patients with SLE and 50% of patients with Sjogren's syndrome (36-38).

The most common rheumatic diseases that could overlap and be confused with FM are: osteoarthritis (OA), RA, ankylosing spondylitis (AS), polymyalgia rheumatica (PMR), SLE, Sjogren's syndrome, osteomalacia, polymyositis.

OA is observed most often in people over age 50 (most of them are asymptomatic); OA, together with FM, is among the most prevalent (7%) rheumatic syndromes in clinical practice (39). OA can be confused with FM because it causes arthralgias of the whole body and could be associated with significant limitation of activity. It has a clear predilection for certain joints, in particular, the first carpometacarpal joints, cervical and lumbar spine, hips, knees and metatarsophalangeal joints (40). Radiographically, OA has classic changes that include osteophyte formation, joint space narrowing, subchondral sclerosis, and subchondral cysts (41). It may seem reasonable to study the painful region on radiograph, but radiographs are not necessarily correlated with clinical symptoms and must be interpreted correctly in the clinical context.

RA is an inflammatory arthritis; the patients present with inflammatory symptoms. The historical evaluation and the physical examination are fundamental to determine, for example, if real synovitis is present. The radiographic manifestations of RA have been well described (marginal erosions, joint space narrowing, joint destruction), and disease-specific alterations that can be seen during the clinic visit (e.g., soft tissue swelling, deformities, subluxations) could be partially found on radiographs. In fact, it takes months or years to develop these alterations, which emphasizes the importance of developing new instrumental assessments that will facilitate early diagnosis of RA. Magnetic resonance imaging (MRI) is the gold standard for confirming the diagnosis of RA, but is too expensive for normal management. Musculoskeletal ultrasonography is easy to perform, can be repeated without X-ray exposure risks for patient, and represents the best compromise between cost and result (42-44). The ultrasonography evaluation of the patient could help the clinician to identify the elements for RA or FM diagnosis.

AS usually begins with an insidious onset of chronic inflammatory back pain symptoms in adolescence or early adulthood (45). AS can be easily mistaken for FM, because both diseases occur in young patients who may have constitutional symptoms such as malaise, fatigue and impaired sleep (45). The hallmark of AS is sacroiliitis as identified radiographically via conventional pelvic X-ray, although this condition may not be evident in the early stages of the illness (46). Sacroiliitis does not occur in FM, though, so its presence is fundamental in distinguishing AS from FM. Recent reports indicate that the role of MRI has become

clearer and it may be a better tool for early identification of these patients (47).

PMR is characterized by widespread pain and profound morning stiffness. Patient's historical factors (age, distribution of pain and stiffness) and laboratory tests can help to distinguish FM from PMR. The response to prednisone therapy is dramatic in PMR (24 to 48 hours), whereas no response is present in FM. Instrumental tests are not helpful to diagnose both diseases.

FM could mimic SLE as demographic and clinical features overlap: young women, fatigue, dermatological involvement, arthralgias (48, 49). However, organ system involvement such as malar rash and photosensitivity, fever, serositis, haematological alterations, and neurological signs typically occur in SLE whereas these elements are not present in FM (50). Conventional X-rays, ultrasonography, computed tomography, MRI help clinicians to diagnose SLE and to distinguish SLE from FM.

Fatigue and generalized arthralgias are common for Sjogren's syndrome and FM. The fundamental clinical features of Sjogren's syndrome are dry eyes and dry mouth. In FM mucosal dryness is related to sympathetic hyperactivity (51). Sjogren's syndrome is also characterized by damage to the eye epithelium whereas no damage is evident in patients with FM. Rose bengal and/or fluorescein dyes are used by ophthalmologists to identify this hallmark feature. In recent years, salivary gland ultrasonography became a simple and noninvasive test for the detection of gland involvement in Sjogren's syndrome; color doppler sonography can also increase diagnostic accuracy (52). Both methods are important to differentiate Sjogren's syndrome from FM.

The radiographic evidence of osteopenia with pseudofractures distinguishes osteomalacia from FM (24). Bone density in FM patients is comparable to healthy controls (53).

Profound proximal muscle weakness with mild pain is typical of polymyositis. The muscle biopsy is the gold standard in the diagnosis of this inflammatory myopathy. The histological features of polymyositis include variability in muscle fiber size, scattered necrotic and regenerating fibers and endomysial inflammation with invasion of non-necrotic muscle fibers (54). Use of electromyography increases spontaneous and insertional activity with fibrillation potential, complex repetitive discharges, positive sharp waves, small polyphasic motor unit potentials and early recruitment (54). Muscle biopsy and electromyography are normal in FM patients.

Nonrheumatic syndromes that could overlap and be confused with FM include thyroid dysfunction and hepatitis B and C virus infection.

Thyroid dysfunction. Hypo- and hyperthyroidism are characterized by profound fatigue and muscle weakness. Anxiety may be presented in hyperthyroidism.

There are significant similarities between the clinical findings in FM and the symptoms of thyroid dysfunction (55). Many studies report that a considerable proportion of FM patients has problems in the production or utilization of thyroid hormones (56); therefore, signs of thyroid dysfunction must be investigated in FM patients. When clinically indicated, thyroid function tests may be performed. Gland ultrasonography can be helpful, but the instrumental results are not necessarily indicative of disease as thyroid tissue abnormalities can be present in healthy subjects, too.

Hepatitis B and C virus (HBV/HCV) infection. Patients with HCV infection may frequently present some rheumatologic manifestations such as FM (57). Diffuse musculoskeletal pain is present in approximately half of HB antibody positive patients and approximately 25% of HB antigen positive patients present with FM syndrome (58). Hepatic ultrasonography indicates liver alterations and is an important test for differentiating FM from hepatitis B or C infections.

Generalized pain is a feature of many malignant diseases, including multiple myeloma, and metastatic breast, lung and prostatic cancer (59). Usually FM does not predict cancer, but an increased risk of breast cancer was found among those female patients that did not satisfy the ACR criteria for FM (60). Clinicians must be vigilant of those patients that develop any symptoms of breast malignancy and thoroughly screen using procedures such as mammography.

Tilt test

The tilt table test is another useful tool to study orthostatic intolerance and syncope. The method is based on the physiological changes that occur after adopting an upright posture with pooling of approximately 700 ml blood in the lower parts of the body. In normal circumstances, the autonomic nervous system quickly compensates for this relative volume loss by increasing vascular tone and cardiac output. This mechanism serves to prevent hypotension and inadequate cerebral perfusion. Tilt table testing examines this response in a controlled environment.

With passive orthostasis, additional stress is exerted on the sympathetic nervous system by blocking the influence of muscle contraction that could increase venous return. Subjects are supine for 30 minutes in the first step. The subject is then tilted upright for 30-45 minutes at an angle of 60-80°. Pharmacological stimulation with isoproterenol is sometimes used as an additional step. The normal responses to tilting consist of an increase in heart rate of 10-15 beats per minute, an elevation of diastolic blood pressure of about 10 mmHg, and little change in systolic pressure. There are two types of abnormal responses. One response is orthostatic hypotension, defined as a reduction of systolic blood pressure of at least 20 mmHg or a reduction of diastolic blood pressure of at least 10 mmHg. This hypotension may induce syncope (61). The other type of abnormal response is postural orthostatic tachycardia, which consists of a sustained increase in heart rate of at least 30 beats per minute or a sustained pulse rate of 120 beats per minute. Tilt table testing has been used mostly to study syncope in patients with no evidence of structural heart disease. Furlan et al. (62) showed that, while recumbent, patients with FM seemed to experience a global increase of central cardiovascular sympathetic activity and a blunted enhancement of sympathetic activity. A blunted enhancement of sympathetic modulation to the vessels and impaired cardiac vagal withdrawal characterized their autonomic profiles during gravitational stress and may have accounted for the excessive rate of syncope they experienced upon standing.

Polysomnography

Patients with FM often complain of poor sleep quality. Polysomnography (PSG) is a recording of sleep stages and architecture that is used to investigate underlying pathology, including sleep apnea. Sarzi-Puttini et al. (63) reported that FM patients complaining of daytime hypersomnolence had a higher number of TPs, a greater score of subjective pain and more fatigue than FM patients with no daytime hypersomnolence. Moreover, hypersomnolent patients slept significantly less efficiently, had a lower proportion of stages 3 and 4 sleep, and had twice as many arousals per hour of sleep compared to patients with no hypersomnolence. Rizzi et al. (64) reported that FM patients experience an increased cyclic alternating pattern (CAP) rate, which indicates poorer quality of sleep. Further, these data are strongly correlated with severity of symptoms.

FUNCTIONAL NEUROIMAGING

The first studies that used functional neuroimaging to evaluate brain processing in fibromyalgia patients used the method of single photon emission computed tomography (SPECT). SPECT quantifies regional cerebral blood flow (rCBF) by detecting the distribution of a radioactive tracer that is infused before the scan. Mountz et al. (65) evaluated baseline levels of rCBF in ten patients with FM and in seven healthy control subjects. After the tracer infusion the participants sat quietly for the duration of the 32-minute SPECT scan. This method produced images with a resolution of about 8.5 mm in predefined regions of interest (ROI) corresponding to the right and left thalamus and right and left head of the caudate nucleus. Patients, relative to controls, had lower rCBF in both the right and left thalamus and in both the right and left caudate nucleus. Kwiatek et al. (66) subsequently performed a similar study using SPECT in 17 patients with FM and in 22 healthy control subjects and found decreased rCBF in the right thalamus but no decreases in either the left thalamus or in the caudate nuclei of FM patients. Additional activations were found in the inferior pontine tegementum and near the right lentiform nucleus of patients. The consistent finding of reduced baseline rCBF in the right thalamus was replicated by Cohen-Gadol et al. (67) and has been observed in patients with pain associated with traumatic peripheral neuropathy (68) and metastatic breast cancer (69).

During the time of these initial SPECT studies in FM, functional magnetic resonance imaging (fMRI) methods were being developed to assess brain activity with greater temporal and spatial resolution than either SPECT or positron emission tomography (PET). The commonly used fMRI method of blood oxygen level dependent (BOLD) imaging has the further advantage of not requiring the infusion of a radioactive tracer. The first study to apply fMRI to the evaluation of FM evaluated brain responses to painful blunt pressure applied to the thumb (6). This study assessed the pressure pain sensitivity in patients and control subjects before and during the fMRI experiments. For each of 16 FM and 16 control participants, this study determined pressures that evoked pain described as near "slightly intense" on a calibrated pain scale (6, 70). The comparison of the effects of these subjectively equal evoked pain sensations (produced by approximately half the pressure in the fibromyalgia patients) defined the *equal pain* contrast. The

healthy control subjects received an additional scan in which they received the same low pressures that were delivered to the patients (*equal pressure* contrast). These pressures provoke ratings of “slightly intense” pain by the FM patients, and ratings of “not painful” or “faintly painful” by the control subjects. Pressures were applied to the thumbnail by a 1-cm diameter hard rubber probe attached to a hydraulic cylinder. The thumb site was chosen for its dense innervation and its large representation in the primary somatosensory cortex. The thumb was also chosen to test the concept that tenderness in FM is not due to muscle sensitivity or confined to muscles at specific tender point sites, but rather, it is a property of deep tissue and is found throughout the body in these patients.

The patients underwent an fMRI scan during which 30 seconds of painful pressure (e.g., 2 kg) was alternated with 30 seconds of non-painful pressure (e.g., 0.5 kg) for the duration of the 10-minute scan. Control participants underwent the same type of scan whereby painful pressure alternated with nonpainful pressure (*equal pain* control), and an additional scan in which the painful pressure was reduced to the values delivered to the patients (*equal pressure* control). All participants also received a conventional anatomical MRI of the head to facilitate localization of the fMRI-derived brain activity. During the anatomical session complete functional images of the entire brain and cerebellum were obtained every 5 seconds, with a resolution of 3 mm in all three dimensions. These data were processed by standard methods (6), and the result is a statistical volume, or map, of each subject’s brain that represents the statistical results of the difference between painful and nonpainful pressure. To perform group analyses, each of these volumes was converted to standard coordinates and presented as group activity for each group or as a statistical difference between groups. The results show that a similar experience of pain (the *equal pain* contrast), which was produced using about half the amount of pressure in patients compared to controls, was associated with similar activations in a number of brain regions that are usually activated in pain imaging experiments. These include contralateral primary (SI) and secondary (SII) somatosensory cortex, insular cortex and inferior parietal lobule. In this case the brain response appears to be consistent with the verbal reports of the subjects. A second analysis evaluated the effects of the *equal pressure* contrast by identifying regions in which the same pressure produced greater effects

in one of the groups. The relatively low pressure of 2 kg evoked significantly greater activity in a number of brain regions in FM patients, including both regions found in the first analysis and additional regions such as anterior cingulate cortex.

This result with painful pressure has been found with painful heat as well. Cook et al. (5) administered similarly painful, 10-second heat stimuli to the left hand of nine female FM patients and nine female healthy controls. The reduced heat tolerated by patients (mean 47.4°C) compared to controls (48.3 °C) resulted in no significant differences in brain activation. This study also showed evidence of increased activity in the contralateral insular cortex of patients.

Additional studies have characterized regions that show graded responses to stimulus intensity and regions that appear to show a binary response to painful stimulation, i.e., turning on at some threshold level of stimulation (71). Both patients and controls have shown graded responses to stimulus pressure in regions that are involved in processing the sensory-discriminative dimension of pain sensation, including contralateral (right) thalamus, and primary (SI) and secondary (SII) somatosensory cortex.

These initial studies explored the effects of the amount of painful stimulation on the pattern and magnitude of brain responses. A large body of evidence indicates that pain perception and behavior are much more complex and influenced by a number of variables such as mood and cognition. An additional group of studies have begun to investigate this complexity by using fMRI to evaluate the modulation of evoked pain by mood or cognitive variables that have been shown to influence pain and pain behavior.

Depression is a significant factor in the expression of pain and response to treatment. Giasecke, et al. (72) evaluated the effects of depression on brain response to pressure pain in FM. Thirty FM patients and 7 control participants received fMRI scans during alternating pressure and no pressure stimulation using methods similar to the initial fMRI study described above by Gracely, et al. (6). However, instead of comparing two groups, the first analysis compared three groups: 7 age- and gender-matched control subjects, 7 FM patients diagnosed with major depressive disorder, and 7 matched fibromyalgia patients without major depressive disorder. Equally painful stimuli, produced by significantly lower stimulus pressures in the FM patients, resulted in similar activations in all three groups.

These activations were in regions implicated in processing the sensory-discriminative dimension of pain, including contralateral SI and SII. The patients with major depressive disorder showed additional activations in bilateral amygdala and in a specific region of the contralateral anterior insula. A second analysis examined the influence of depression using a correlational method in all 30 FM patients in which the level of pain-induced brain activation for each subject was correlated with the symptoms of depression, as measured by the Center for Epidemiological Studies Depression Scale (CES-D). No associations between depression and pressure pain sensitivity were found in brain regions associated with processing the sensory discriminative dimensions of pain. CES-D scores, however, were significantly associated with pain-evoked activity in brain regions implicated in processing the motivational-affective dimensions of the pain experience, specifically the contralateral anterior insula and bilateral amygdala, the same regions identified in the between groups analysis. These results suggest that depression modulates pain-evoked activity in structures involved in processing affective characteristics of pain experience. Similar correlation analyses have been applied to the cognitive variable of catastrophizing, which is emerging as a significant variable predicting pain chronicity and poor treatment response (73). Since this cognitive style has been linked to depression, the analysis controlled for depression statistically. The results correlating catastrophizing with pain-evoked activity in each subject found significant associations in brain regions related to the anticipation of (contralateral medial frontal cortex, ipsilateral cerebellum) and attention to (contralateral anterior cingulate gyrus, bilateral dorsolateral prefrontal cortex) pain, and to both emotional (ipsilateral claustrum, interconnected to the amygdala) and motor (contralateral lentiform nuclei) responses (74). These results suggest that the effects of negative cognitions are mediated through a number of separate mechanisms. Successful treatment may involve identification of the relevant and most responsive mechanisms.

The field of brain neuroimaging continues to advance at a fast pace, and both old and new methods have been applied to the evaluation of FM. In an application of the older method of structural MRI, Kuchinad, et al. (75) have found that the size of specific brain regions is significantly reduced in patients with FM. A PET study of opioid receptors showed significant differences in endogenous opi-

oid activity in FM (76), and the neuroimaging method of magnetic resonance spectroscopy (MRS) showed differences in the concentrations of metabolites related to neural activity in the insula (Harris, unpublished observations). Newer fMRI methods such as arterial spin labeling (ASL) have identified insular mechanisms in patients that are related to increased activity at rest in the absence of painful stimulation and differences in the interconnections of the pain network at rest. A recent multi-center European trial has found that long term treatment with milnacipran results in changes in pain-evoked brain activity not observed with placebo treatment.

CLINIMETRIC APPROACHES IN FIBROMYALGIA

A range of treatments are employed to treat the various symptom facets of FM. Although some of these therapies have been tested in randomized controlled trials (RCT), there has been little standardization of an approach to trials or of the outcome measures used, and evaluating therapeutic effects on widely varying symptoms is difficult. To address the identification of core outcome domains, the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (9) and Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) (8) workshop convened a meeting to develop consensus recommendations for chronic pain clinical trials. The consensus of these groups has been that key outcomes should include pain, physical functioning, emotional functioning, patient global ratings of satisfaction, health-related quality of life, and adverse events (8, 9).

Pain Assessment

Chronic generalized pain is a core feature of FM (77, 78). A number of tools are available for the assessment of pain, including the visual analogue scale, the daily pain diary, and the McGill Pain Questionnaire (MPQ). Important issues that may influence assessment of pain in patients with FM include recall bias, use of paper versus electronic diaries to assess pain experiences, and pain scaling methods (79). The standard visual analogue scale is a 10 cm scale with a border on each end. The left end may be anchored by a numeric (i.e., "0") and/or verbal (e.g., "No pain at all") indicator. The right end may be anchored by a numeric (e.g., "10")

and/or verbal (e.g., “Pain as bad as it could be”) indicator. There are occasional distortions through photocopying and printing, but adjustments can be made so that the highest score is 10. Huskisson et al. (80) also suggested that an alternative descriptive pain relief scale based on the indications “complete relief” “moderate relief,” “slight relief” and “no pain relief” was possible, but this would be much less sensitive than the visual analogue scale. A number of studies have established that data from self-report visual analogue scales are reproducible. With the development of optical scanning technology for the automated computer entry of scores, visual analogue scales can be presented in a format of 11 small boxes or circles for patients to assess their pain from 0-10 (or 100) (81). Although formal direct comparative studies have not been performed to analyze the results of automated optical scanning, this scaling format appears to have criterion validity.

The visual analogue pain scale has proven to be a great advance in the assessment of pain. A daily diary has been used to assess the impact of pain in patients with FM and has been reported to be useful for demonstrating the manner in which pain influences activities of daily living in these individuals. The MPQ can provide detailed information on the characteristics of pain in FM (82). It includes 78 pain adjectives that are divided into 4 major categories (sensory, affective, evaluative, and miscellaneous sensory) (82, 83). This index takes 10 to 15 minutes to complete. Tender point assessment is a demonstrably useful part of the official ACR criteria for the diagnosis of FM. However, TPs are not unique to the syndrome. Tenderness is widespread in patients with FM rather than being confined to specific anatomic regions, and these individuals may also demonstrate more hypersensitivity to heat, cold, and electrical stimulation. Some methods of assessing tenderness (e.g., dolorimetry) may demonstrate increased pain sensitivity in patients with FM more objectively than palpation and are relatively independent of biasing factors or patient distress. In addition to tender point count, assessment of tender point intensity or score has been developed as an assessment tool. For example, the FM Intensity Score (FIS) is obtained by averaging the pain intensity scores (on a 0-10 scale) for the 18 sites assessed in the Manual Tender Point Survey (84).

Psychological and behavioural assessment

Psychological evaluation of the patient can provide useful information about the psychological and be-

havioural features that may influence their pain and dysfunction and, conversely, provide a sense of the impact of pain, fatigue, and other symptoms on their psychological health (85, 86). It is often presumed that patients with greater psychological impairment and/or psychiatric pathology may be more symptomatic or resistant to improvement with therapeutic intervention. However, this assumption may be true only in some cases. Both in clinical practice and in drug trials, it is important to diagnose and effectively treat concomitant depression, anxiety, bipolar states, and especially, suicidal tendencies. In addition to a careful history, a number of screening tools are available for both clinical and research purposes, including the Multidimensional Pain Inventory, the Pain Behaviour Scale, the Dartmouth Pain Questionnaire, the Coping Strategies Questionnaire, the Ways of Coping Scale and the Illness Behaviour Questionnaire (79, 85).

Fatigue assessment

Fatigue is one of the core features of FM, and its measurement is important in both research and clinical settings. A variety of measures exist and have proven useful in measuring fatigue in other rheumatic diseases, such as RA and AS (87). These include the Multidimensional Fatigue Index, which measures various types of fatigue including physical and emotional (87); the Functional Assessment of Chronic Illness Therapy (FACIT) system, which has been validated in a number of disease states and may be customized to certain disease indications (88); And the Fatigue Severity Scale, which was originally developed for multiple sclerosis and lupus fatigue assessment (89). The advantage of such tools is their ability to explore the multiple dimensions of fatigue. More simple, single-question fatigue assessments are embedded within such composite instruments as the FM Impact Questionnaire (FIQ).

Sleep assessment

Multiple dimensions of sleep quality have been assessed in FM trials, including quantity, quality, ease of falling asleep, frequency of waking, and feeling refreshed upon awakening. Sleep quality can be assessed on a 100 mm linear scale with “sleep is no problem” at one extreme and “sleep is a major problem” at the other extreme. Similar scales can be used to rate number of awakenings, and “restedness” on awakening in the morning. The Medical Outcome Study (MOS) sleep scale is an example of an instrument used in an FM trial.

Quality of life and functional assessment

Measurement of global sense of well being, quality of life, and functional capacity in multiple dimensions (physical, vocational, social, emotional) is a key area of assessment and is considered essential by regulatory agencies when contemplating approval of medications for chronic pain states (90, 91). Assessment with the MOS Short Form-36 (SF-36) Health Survey (SF-36) has shown that patients with FM have reduced physical functioning, physical role functioning, body pain, general health, vitality, and social functioning compared to healthy subjects.

The SF-36 is a generic instrument with scores that are based on responses to individual questions, which are summarized in eight scales (bodily pain, physical functioning, general health perception, role function - physical aspect, role function - emotional aspect, vitality, social functioning, and mental health), each of which measures a health concept (92). These scales, weighed according to normative data, are scored from 0 to 100, with higher scores reflecting a better quality of life. The SF-36 has been validated for use in Italy, and it can be completed within 15 min by most people. The Nottingham Health Profile (NHP) is intended for primary health care to provide a brief indication of a patient's perceived emotional, social and physical health problems (93).

The questionnaire consisted of two parts, but only part I is now used: it contains 38 yes/no items that can be grouped into 6 domains (physical mobility, pain, sleep, social isolation, emotional reactions, and energy level) with each question weighted for severity. The sum of all weighted values in a given domain represents a continuum between 0 (best health) and 100 (worst health). The FM Impact Questionnaire (FIQ) is an assessment instrument designed to measure the components of health status that are believed to be most affected by FM patients. It is composed of 20 items and is used to measure FM patient status, progress and outcomes (93, 94). The FIQ is a brief, self-administered instrument that takes approximately 5 minutes to complete (90, 91).

Response criteria

It is not known whether improvement in pain intensity alone should define response to treatment in FM, given that the syndrome is characterized by multiple and varying symptoms. In an attempt to develop a multi-component criterion for response to treatment in FM patients, Simms, et al. (95) proposed that a meaningful response to treatment should be consid-

Table 1 - Proposed preliminary response criteria for fibromyalgia.

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| <p>Improvement in at least 3 of the 4 measures; and at least 3 of the post-treatment scores must satisfy the respective cutoffs:</p> <ol style="list-style-type: none"> 1. FIQ score <5 (range 0 = no impact to 80 = maximum impact) 2. Pain intensity rating <5 (11 point numeric rating scale; 0 = no pain, 10 = very severe pain) 3. Tender point count <14 (4 kg/cm² pressure is applied with a dolorimeter and the patient rates pain from 0 [no pain] to 10 [worst pain ever experienced]; positive tender point defined as pain intensity at >2) 4. Total tender point pain intensity score <85 (sum of pain intensity scores for the 18 ACR defined sites; range 0 to 180) |
|--|

FIQ: Fibromyalgia Impact Questionnaire. ACR: American College of Rheumatology

ered to have been achieved if patients met 4 of the 6 following criteria: 50% reduction in pain, sleep, fatigue, patient global assessment, or physician global assessment; and an increase of 1 kg in mean total myalgic score. Application of these criteria in a trial that compared amitriptyline, cyclobenzaprine, and placebo in patients with FM indicated that about one-third of patients had at least short-term responses to active treatment. These authors attempted to improve the definition for a response to FM therapy by testing criteria using a known, effective treatment as a gold standard (96).

A set of preliminary criteria was developed using data from a placebo-controlled clinical trial of amitriptyline versus naproxen. The outcome measures with the highest sensitivity in discriminating between patients receiving amitriptyline versus placebo or naproxen were change in physician global assessment, change in tender point score, and patient sleep assessment.

This analysis resulted in the response criteria composed of physician global assessment, patient-assessed sleep score, and tender point score. More recently, Dunk, et al. (97) proposed preliminary criteria for identifying responders in FM clinical trials that were based on a study of magnetic therapy in patients with this disease (Table I). These preliminary criteria identified responders with a sensitivity of 70.5% and specificity of 87.5%; however, these criteria have not been validated in other clinical trials.

CONCLUSIONS

At present, there are no specific markers for FM; in fact, many of the existing factors are significant

for study purposes only. The presence of these factors, however, helps researchers and clinicians to understand the pathogenetic mechanisms and to identify patient subgroups. Some of these factors could be used as indices of disease severity. The current literature is engaged in identifying and suggesting serological alterations or instrumental investigations as new, specific markers of FM; but it is necessary to identify precise biomarkers of disease in accordance with the criteria of feasibility and reproducibility for diagnostic and therapeutic purposes. Unfortunately, the symptoms of FM are not specific and there are no instrumental diagnostic tests for FM. Many differential diagnoses may be excluded via extensive clinical examination and patient history, and considering the overlap of FM with other medical conditions, treating physicians

should be vigilant: chest-X-rays and abdominal ultrasonography are the first steps of general evaluation for all patients with suspected FM. Functional neuroimaging methods have revealed a large number of supraspinal effects in FM, a disorder mediated by mechanisms that are essentially unknown. The goal of future studies will be to assess whether these findings are associated with the mechanisms that initiate and maintain this disorder, or whether they represent supraspinal consequences of these unknown mechanisms. Evaluating therapeutic effects in FM is difficult because of the many facets of the syndrome. To address the identification of core outcome domains, the IMMPACT and OMERACT workshops are working to develop consensus recommendations for chronic pain clinical trials.

SUMMARY

Fibromyalgia (FM) is a rheumatic disease characterized by musculoskeletal pain, chronic diffuse tension and/or stiffness in joints and muscles, easy fatigue, sleep and emotional disturbances, and pressure pain sensitivity in at least 11 of 18 tender points. At present, there are no instrumental tests or specific diagnostic markers for FM; in fact, many of the existing indicators are significant for research purposes only. Many differential diagnoses may be excluded by an extensive clinical examination and patient history. Considering overlap of FM with other medical conditions, the treating physicians should be vigilant: chest-X-rays and abdominal ultrasonography are the first steps of general evaluation for all the patients with suspected FM. Functional neuroimaging methods have revealed a large number of supraspinal effects in FM, a disorder mediated by mechanisms that are essentially unknown. Many treatments are used in FM patients, but evaluating their therapeutic effects in FM is difficult because the syndrome is so multifaceted. To address the identification of core outcome domains, the Initiative on IMMPACT and OMERACT workshop convened a meeting to develop consensus recommendations for chronic pain clinical trials.

Key words - Biomarkers, functional magnetic resonance, clinimetric approaches, polysomnography, tilting test.

Parole chiave - Biomarkers, risonanza magnetica funzionale, clinimetria, polisomnografia, tilting test.

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