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Fibromyalgia: A Clinical Update

Fibromyalgia Syndrome: Definition

In clinical practice the diagnosis of “fibromyalgia” is often given to individuals with chronic widespread pain for which no alternative cause can be identified. The 1990 classification criteria of the American College of Rheumatology (ACR) for fibromyalgia syndrome (FMS) combine chronic widespread pain (CWP), which indicates pain on both sides of the body, above and below the waist, and axial pain for at least 3 months, and tenderness on manual palpation in at least 11 out of 18 defined tender points.⁶¹ Most clinicians would recognize that FMS, in its typical manifestation, is accompanied by a combination of additional symptoms such as sleep disturbance, fatigue, and anxiety, and by other clinical manifestations such as depression, gastrointestinal symptoms, and headache. In addition, FMS is often associated with chronic fatigue syndrome, irritable bowel syndrome (IBS), irritable bladder syndrome or interstitial cystitis, and temporomandibular disorder.¹¹ The common theme is that patients have chronic pain and other somatic symptoms, but without apparent tissue damage or inflammation.

The debate whether fibromyalgia is a rheumatological, psychiatric, somatoform, or neuroendocrine disorder, or no distinct clinical entity at all, is ongoing. However, the focus of fibromyalgia research has shifted to research on epidemiology, risk factors, and biomarkers, and to controlled trials testing drugs or other interventions in FMS. Furthermore, there is consensus that FMS is a heterogeneous condition and that subgroups may exist that have different pathophysiologies with different response characteristics to treatment.⁵⁵ Heterogeneity has been confirmed, for example, based on sensory symptoms and comorbidities⁴³ and on patterns of tender point responses.⁵⁹

Epidemiology

A review of 10 studies from different Western countries reported a prevalence of FMS according to the ACR criteria in the general adult population of between 0.7% and 3.3%,²⁰ with a prevalence in women between 1.0% and 4.9%, and in men between zero and 1.6%. It has been suggested that the male-female ratio reported in the literature may be biased, because most of the data come from tertiary care centers. In the United States, about 5 million people are thought to be affected.³⁵ A recent retrospective survey of American employees found a prevalence of 0.73%.³⁰ In this study, patients with FMS had significantly lowered annual work output, comparable to those with osteoarthritis. A recent large retrospective cohort study from Canada identified a high prevalence of comorbidities among patients with a diagnosis of FMS and emphasized the substantial economic burden of the disorder.³²

Typical Presentation

Most patients complain of widespread musculoskeletal pain. The pain is typically diffuse or multifocal, and its intensity varies over time. Patients also may complain of morning stiffness and swelling of joints or limbs, resembling symptoms of rheumatoid arthritis. Other frequently encountered symptoms are fatigue, reduced energy and drive, and disturbed sleep. Many patients complain of problems with concentration, attention, or memory. In fact, cognitive impairment was found in FMS patients in neuropsychological studies. Often, gastrointestinal symptoms and bladder disturbances are reported. FMS may present concomitantly with other disorders, which does not exclude the diagnosis. Commonly associated diseases are chronic autoimmune disorders such as rheumatoid arthritis or lupus erythematosus, and a variety of functional disorders such as IBS or palpitations. Patients with FMS seen in tertiary pain centers often give the physician elaborate descriptions of their complaints. It has been suggested that patients aim at controlling the dialogue by means of lengthy but vague descriptions of their somatic complaints, and the resulting difficult physician-patient interaction has been regarded

as a diagnostic criterion.²⁹ This difficult interaction pattern may lead to the finding that patients feel isolated from health care professionals and find it difficult to convince them that they have a real disease.⁴⁵

Diagnostic Workup

Patients presenting with multifocal pain that cannot be explained on the basis of a lesion or inflammation in the affected regions should be suspected to have CWP or FMS. A pain diagram helps to identify patients with CWP. Further key symptoms of FMS (fatigue or nonrestorative sleep and increased morning stiffness or swelling of the fingers or the hands) should be actively explored. Patients should be screened for symptoms of other functional somatic syndromes and mental disorders as well as current psychosocial stressors. Moreover, restrictions of daily activities and subjective illness attributions should be discussed. Medication used by the patient should be assessed because arthralgia, myalgia, and fatigue can also be side effects of medication. Misuse of medication should be actively explored.

There is an ongoing debate on the utility of the tender point examination in clinical practice. The ACT criteria were intended for research use, and their use in clinical practice to diagnose individual patients was not originally intended. The practicability and validity of the tender points for clinical diagnosis have never been tested in a primary care setting. Despite efforts to standardize the procedure of tender point counting, such as the manual tender point survey,⁴² the procedure has not been shown to be reproducible across different clinical settings. A recent study assessed the discriminative value of all tender points, alone and in combination, by investigating the appropriate pressure magnitude that should be applied during tenderness examination. It was found that all tender points with determined pressure cutoff values significantly discriminated FMS from controls. The lateral epicondyle and second rib point had the best sensitivity and specificity.⁵² The recently suggested new FMS criteria abolish the need for tender point evaluation and instead introduce a “widespread pain index” and a “symptom severity score.”⁶⁰ Their usefulness in clinical practice remains to be explored.

A complete physical examination including orthopedic and neurological examination is recommended to reveal signs of internal or neurological disorders mimicking the key symptoms of FMS.¹⁶ Blood tests should exclude a systemic inflammatory disorder, renal and hepatic failure, hypothyroidism, myositis, and other diseases, if suggested by the patient’s history. Antibodies associated with inflammatory rheumatological diseases in patients with a history of CWP and fatigue in the absence of joint swelling, typical rashes, or organ involvement have no predictive value.⁵⁰ Similarly, imaging studies are of little value in patients with CWP, unless complaints point to a specific differential diagnosis that can be confirmed or ruled out by imaging studies.³⁶

Risk Factors, Etiology, and Pathophysiology

The prevalence of FMS is increased in family members of patients suffering from FMS. For example, the frequency of FMS among the first-degree relatives of patients was 6.4%.² There are findings indicating a role for polymorphisms of genes in the serotonergic, dopaminergic, and catecholaminergic systems in the etiology of FMS. These polymorphisms all affect the metabolism or transport of monoamines, so they might lead to disturbed sensory processing and an altered stress response.⁹ However, there are negative and positive findings regarding the associations between these polymorphisms and FMS. Thus, it is likely that the development of FMS is influenced by multiple genes, as in other complex genetic diseases.⁶ Furthermore, the gene polymorphisms found are not specific for FMS, but have also been studied in other chronic pain syndromes, as well as in major depressive disorder. Rare missense variants of the familial Mediterranean fever gene increase the risk of FMS and are present in about 15% of FMS patients. These patients have high plasma levels of the proinflammatory cytokine IL-1 β ,¹⁷ indicating that this subtype of FMS might be more closely related to rheumatoid disorders than other subtypes. Recently, there has been increased interest in resilience, or factors that protect against chronic disease. For example, non-affected relatives of FMS patients had a reduced frequency of the met/met genotype of the catechol-*O*-methyl transferase (*COMT*) gene, which may protect them from developing the disorder.¹²

Along with a certain genetic susceptibility, environmental factors may have a large impact in modulating the variance encountered, and external events may trigger the development of FMS. Such triggers consist of physical trauma, a regional myofascial pain syndrome, psychological distress or emotional trauma, or an acute illness.^{5,10} Some factors that have previously been thought to trigger FMS could be shown to be unrelated to the disorder, such as silicon breast implants or whiplash injury.⁵⁴ In women, the frequency of abuse correlates with the prevalence of FMS.⁴⁶ Among psychosocial stressors, there is the highest evidence for those related to the workplace.²¹ Certain lifestyle factors also seem to promote the occurrence of FMS. For example, overweight and obesity are associated with an increased risk of FMS, especially among women with low levels of physical exercise.³⁹ In contrast, regular physical activity appears to promote a favorable long-term outcome of FMS.¹⁴

A number of biological abnormalities have been described in FMS, with possible relevance to its pathophysiology. The major caveat is that in most of these studies no disease controls were investigated, such that the specificity of a certain finding for FMS cannot be determined. Furthermore, there are few longitudinal studies. The hypothalamus-pituitary-adrenal (HPA) axis has frequently been studied, with the hypothesis that patients with FMS have a reduced stress response and hypocortisolism. While there is no evidence for reduced baseline cortisol secretion in patients with FMS, different authors have variously found enhanced or reduced glucocorticoid sensitivity, and this issue remains open.⁵¹ There is some evidence for reduced sympathetic activity in patients with FMS under stress, and capillary microvascularization is altered. There is some support in the literature for an altered cytokine system in FMS, similar to the findings in major depression, but in most studies there were no correlations with the severity of symptoms.³⁷ In particular, anti-inflammatory cytokines were found to be decreased in patients with FMS, indicating that a reduction in these protective, anti-inflammatory mediators may be an additional risk factor for FMS.⁵⁶ Interestingly, cytokine profiles could be modified by multidisciplinary pain therapy.⁵⁷

Elevation of the neuropeptide substance P in the cerebrospinal fluid was one of the first biochemical findings in FMS⁴⁴ and was confirmed in later studies. However, substance P was also elevated in patients with osteoarthritis and in full-term pregnant women, and therefore high levels cannot be regarded a specific biomarker for FMS. Similarly, the neurotrophic factors brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) were increased in cerebrospinal fluid from FMS patients, but also in persons with chronic migraine.⁴⁷

Structural and functional imaging studies of the central nervous system have led to the concept that FMS is a disorder of central sensitization or a defective pain inhibitory system.⁴⁹ The evidence of central augmentation in FMS has recently been reviewed.⁵⁸ Functional brain-imaging studies reveal enhanced activation in pain related areas and thus corroborate the patients’ reports of increased pain.¹⁹ A recent study using mu-opioid-receptor positron emission tomography (PET) demonstrated reduced mu-opioid receptors in several pain-related brain regions.²² These results may indicate altered endogenous opioid analgesic activity in FMS and may explain why therapeutic opiates have so little efficacy in FMS patients.

As in other chronic pain conditions, studies have shown both increases and decreases in regional gray matter density in FMS patients (for review see Schweinhardt et al.⁴⁹). FMS patients had less total gray matter volume, less gray matter density, and an age-associated decrease in gray matter that was three times greater than in healthy controls,³¹ which led to the hypothesis of premature aging in FMS. Regional gray matter density analyses revealed gray matter loss in regions associated with pain modulation or stress, such as the cingulate, insular, and medial frontal cortices, the parahippocampal gyri, the thalamus, and the amygdala. Increased gray matter in the left orbitofrontal cortex, left cerebellum, and bilateral striatum was also described.^{7,48} Again, this finding is more likely to be related to chronic pain as such than specifically to FMS, and the underlying cellular and molecular processes are unknown.

Treatment

The aim of treating FMS is to decrease pain and the associated symptoms and to increase function and quality of life. Currently, FMS cannot be cured by any therapy, and overall treatment effects of single interventions are modest at best. Coping with symptoms includes the acceptance of symptoms and of some limitations as well as continuous self-management (e.g., stress management). Recently, a large number of drugs and interventions have been tested in controlled trials for their efficacy in FMS, and meta-analyses have been written on most of these interventions. It is well known that some antidepressants are effective in FMS; they reduce pain, fatigue, and depression and improve sleep and quality of life.²⁴ It must be considered that not every antidepressant affects these symptoms equally, and that overall effect sizes are small. However, it appears that even moderate reductions in pain may lead to considerable increases in quality of life.³⁸ A meta-analysis of the trials with gabapentin and pregabalin also showed effects on reduction of pain, improved sleep, and quality of life.²⁵ Comparing the drugs licensed by the U.S. Food and Drug Administration (FDA) for FMS—duloxetine, milnacipran, and pregabalin—we found that the three drugs were superior to placebo, except for duloxetine for fatigue, milnacipran for sleep disturbance, and pregabalin for depressed mood. Adjusted indirect comparisons indicated no significant differences for 30% pain relief and dropout rates due to adverse events for the three drugs. Side-effect profiles differed, as we had expected.²⁶ Thus, which drug to start with is an individual choice, depending on the patient's symptoms, comorbidities, and preferences. There is weaker evidence for the effect of some other drugs, such as tramadol, and for some drugs there is good evidence that they are not effective (Table 1). It must be noted that comorbid depression is not specifically treated by some of the agents mentioned or in the doses given for FMS. Thus, depression may have to be treated separately.

A review of 46 exercise treatment studies in FMS reported that the strongest evidence was in support of aerobic exercise.²⁸ Busch and coworkers systematically reviewed 34 studies. Meta-analysis of six studies provided moderate-quality evidence that aerobic-only exercise training at intensity levels recommended by the American College of Sports Medicine has positive effects on global well-being, on physical function, and possibly on pain.⁸ A recent study showed that self-selected physical activity reduces FMS symptoms in minimally active adults.¹⁸ Interestingly, certain biomarkers including proinflammatory cytokines and cortisol were decreased after exercise, specifically after an aquatic program in warm water over a period of 4 months,⁴¹ suggesting that exercise may work by its anti-inflammatory effects and by better regulation of the cytokine-HPA axis feedback. A meta-analysis found moderate evidence that hydrotherapy has short-term beneficial effects on pain and health-related quality of life in FMS patients.³⁴

Among the psychotherapeutic interventions, the best evidence is available for cognitive-behavioral therapy (CBT). The rationale behind the

use of CBT in treating FMS hinges on the concept that the experience of pain results from a complex interplay between biological factors, cognition, affect, and behavior.¹ The modification of these factors would thus be expected to affect an individual's pain experience. CBT is effective, and the different programs have been reviewed.^{4,53} Recently, the mechanisms of action of CBT have been explored. It appears that CBT reduces nociceptive responding via descending inhibition of nociception.¹

Multimodal or multidisciplinary treatment programs are recommended for difficult-to-treat patients. The existing systematic reviews on multimodal treatment agree that it should include at least one educational or other psychological treatment and at least one kind of exercise therapy. A recent meta-analysis on multimodal treatment in FMS came to the conclusions that there is strong evidence for beneficial short-term effects of multicomponent treatment on the key symptoms of FMS, and that strategies to maintain the benefits in the long term need to be developed.²³ A recent report on a 3-month outpatient program integrating physiotherapy, occupational therapy, nursing, and CBT came to the conclusion that the predictors for long-term improvement in disability were an increase in self-efficacy for pain and better general adherence during treatment.¹⁵ Interestingly, a very short multicomponent program lasting only a day and a half, including evaluation, education, self-management, physical therapy, and occupational therapy, tested in 521 participants, reported mild but significant reductions in the Fibromyalgia Impact Questionnaire total score and subscores, even at 6 and 12 months' follow-up.⁴⁰ In spite of the caveats regarding this study (self-report measures, follow-up by questionnaires, and a low response rate), it might be worth reproducing in a different setting.

Being dissatisfied with classical medicine, many patients with CWP or FMS may turn to alternative medicine. The evidence for efficacy of complementary or alternative drugs in FMS was considered insufficient in a recent systematic review.¹³ Another paper reviewed 23 trials for acupuncture, balneotherapy, thermotherapy, magnetic therapy, homeopathy, manual manipulation, mind-body medicine, diet therapy, and music therapy.³ The average methodological quality of the identified studies was considered low. Best evidence was found for balneotherapy or hydrotherapy in multiple studies, and positive results were also noted for homeopathy and mild infrared hyperthermia. Acupuncture may be helpful, but this seems to depend on the patient's cultural background.^{27,33}

Future Developments

A major goal in FMS research will be to better identify subgroups and to more clearly explain the pathophysiology of the syndrome so that individualized treatment can be developed and administered. Better outcome measures are needed to do justice to the complex array of symptoms in FMS.

Table 1
Drugs with positive effects on FMS in randomized controlled trials

Drug	Strength of Evidence*	Recommended Dose Range	Comments
Amitriptyline	1a	10–50 mg	Large body of evidence, frequent side effects
Duloxetine	1a	30–60 mg	FDA approved, long-term efficacy shown
Milnacipran	1a	25–200 mg	FDA approved
Pregabalin	1a	150–450 mg	FDA approved, long-term efficacy shown
Gabapentin	1b	1200–2400 mg	One large RCT
Cyclobenzaprine	2a	10–40 mg	An antidepressant and muscle relaxant. Not widely available outside the United States. RCTs included in this meta-analysis were short-term and of low quality.
Fluoxetine	2a	20–60 mg	Three small RCTs
Paroxetine	2b	20 mg	One large RCT
Tramadol	2b	50–300 mg	Two RCTs of tramadol 150 mg/acetaminophen (paracetamol) 1300 mg

* Oxford classification of levels of evidence: 1a: systematic review (with homogeneity) of randomized controlled trials (RCTs); 1b: individual RCT; 2a: systematic review of cohort study or low-quality RCT; 2b: Individual cohort study or low-quality RCT.

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