29 - 385 Fibromyalgia

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Fibromyalgia ■ ■DEFINITION Fibromyalgia (FM) is characterized by chronic widespread musculo skeletal pain and tenderness. Although FM is defined primarily as a pain syndrome, patients also commonly report associated neuropsy chological symptoms of fatigue, unrefreshing sleep, cognitive dysfunc tion, anxiety, and depression. Patients with FM have an increased prevalence of other syndromes associated with pain and fatigue, including myalgic encephalitis/chronic fatigue syndrome (Chap. 461), temporomandibular disorder, chronic headaches, irritable bowel syn drome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes. These are collectively referred to as chronic primary or chronic overlapping pain conditions. Available evidence implicates the central nervous system as key to maintaining pain and other core symptoms of FM and related conditions. The presence of FM is asso ciated with substantial negative consequences for physical and social functioning. ■ ■EPIDEMIOLOGY Worldwide prevalence is ~2%, with a prevalence of ~4% in women and <1% in men. There is some variability depending on the method of ascertainment; however, the prevalence data are similar across world regions and socioeconomic classes. Cultural factors may play a role in determining whether patients with FM symptoms seek medical atten tion; however, even in cultures in which secondary gain is not expected to play a significant role, the prevalence of FM remains in this range. In clinical settings, a diagnosis of FM is far more common in women than in men, with a ratio of ~8:1. In population studies, the ratio of women to men is closer to 3:1. The prevalence of FM is much higher in patients with rheumatic diseases such as rheumatoid arthritis or systemic lupus erythematosus, where up to 30% have comorbid FM. Additional risk factors include sleep disturbances, physical inactivity, and overweight or obesity. ■ ■CLINICAL MANIFESTATIONS Pain and Tenderness At presentation, patients with FM most commonly report “pain all over.” Widespread pain is operationalized as being present both above and below the waist on both sides of the body and involving the axial skeleton (neck, back, or chest). The pain attributable to FM is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity. For a diag nosis of FM, pain should have been present most of the day on most days for at least 3 months. The pain of FM is associated with tenderness and increased evoked pain sensitivity. In clinical practice, this elevated sensitivity may be identified by pain induced by the pressure of a blood pressure cuff or skin roll tenderness. More formally, an examiner may complete a tender-point examination in which the examiner uses the thumbnail to exert pressure of ~4 kg/m2 (or the amount of pressure leading to blanching of the tip of the thumbnail) on well-defined musculoten dinous sites. Previously, the classification criteria of the American College of Rheumatology required that 11 of 18 sites be perceived as painful on exam for a diagnosis of FM. In practice, tenderness is a continuous variable, and strict application of a categorical threshold for diagnosis is

not necessary. Newer criteria eliminate the need for identi fication of tender points and focus instead on patient-reported clinical symptoms of widespread or multisite pain and neuropsychological symptoms (Fig. 385-1). The newer criteria perform well in clinical set tings in comparison to the older, tender-point criteria. When subjective criteria are applied to populations, the result is an increase in preva lence of FM and a change in the sex ratio (see “Epidemiology,” earlier). Patients with FM often have peripheral pain generators that are thought to serve as triggers for the more widespread pain attributed

to central nervous system factors. Potential pain generators such as arthritis, bursitis, tendinitis, neuropathies, and other inflammatory or degenerative conditions should be identified by history and physical examination. More subtle pain generators may include joint hypermo bility and scoliosis. In addition, patients may have chronic myalgias triggered by infectious, metabolic, or psychiatric conditions that can serve as triggers for the development of FM. These conditions are often identified in the differential diagnosis of patients with FM, and a major challenge is to distinguish the ongoing pain of a triggering condition from FM pain that is occurring as a consequence of a comorbid condi tion and that should itself be treated.

CHAPTER 385 Fibromyalgia Neuropsychological Symptoms In addition to widespread pain, FM patients typically report fatigue, stiffness, sleep disturbance, cogni tive dysfunction, anxiety, and depression. These symptoms are present to varying degrees in most FM patients but are not present in every patient or at all times in a given patient. Relative to pain, such symp toms may, however, have an equal or even greater impact on function and quality of life. Fatigue is highly prevalent in patients in primary care who ultimately are diagnosed with FM. Pain, stiffness, and fatigue often are worsened by exercise or unaccustomed activity. The sleep complaints include difficulty falling asleep, difficulty staying asleep, and early-morning awakening. Regardless of the specific complaint, patients awake feeling unrefreshed. Patients with FM may meet criteria for restless legs syndrome and sleep-disordered breathing; frank sleep apnea can also be documented. Cognitive issues are characterized as difficulties with attention or concentration, problems with word retrieval, and short-term memory loss. Studies have demonstrated altered cognitive function in these domains in patients with FM, although speed of processing is age appropriate. Symptoms of anxiety and depression are common, and the lifetime prevalence of mood disorders in patients with FM approaches 80%. Although depression is neither necessary nor sufficient for the diagnosis of FM, it is important to screen for major depressive disorders by querying for depressed mood and anhedonia. Analysis of genetic factors that are likely to pre dispose to FM reveals shared neurobiologic pathways with mood dis orders, providing the basis for comorbidity (see later in this chapter). Overlapping Syndromes FM is considered as part of a group of conditions called chronic overlapping pain syndromes because of the propensity to coexist with other syndromes that may share underlying mechanisms. Review of systems often reveals headaches, facial/jaw pain, regional myofascial pain particularly involving the neck or back, and arthritis. Visceral pain involving the gastrointestinal tract, bladder, and pelvic or perineal region is often present as well. It is important for patients to understand that shared pathways may mediate symptoms and treatment strategies effective for one condition may help with global symptom management. Comorbid Conditions FM is often comorbid with chronic mus culoskeletal, infectious, metabolic, or psychiatric conditions. Whereas FM affects only ~2% of the general population, it occurs in ~10–30% of patients with degenerative or inflammatory rheumatic disorders, likely because these conditions serve as peripheral pain generators to alter central pain-processing

pathways. The proposition that there may be an inflammatory or autoimmune etiology for FM in some patients has not been rigorously tested to date. It is particularly important for clinicians to be sensitive to pain management of these comorbid con ditions so that when FM emerges—characterized by pain outside the boundaries of what could reasonably be explained by the triggering condition, development of neuropsychological symptoms, or tender ness on physical examination—treatment of central pain processes will be undertaken as opposed to a continued focus on treatment of peripheral or inflammatory causes of pain. Psychosocial Considerations Symptoms of FM often have their onset and are exacerbated during periods of perceived stress. This pattern may reflect an interaction among central stress physiol ogy, vigilance or anxiety, and central pain-processing pathways. An understanding of current psychosocial stressors will aid in patient

Generalized pain - do not count jaws, chest, or abdomen

Widespread Pain Index (WPI score 0-19) Pain and tenderness during the past week Neck Region 5 Right jaw PART 11 Immune-Mediated, Inflammatory, and Rheumatologic Disorders Left jaw Right shoulder Left shoulder Upper back Chest or breast Right upper arm Left upper arm Lower back Abdomen Right lower arm Left lower arm

Left hip or buttocks Right hip or buttocks Right upper leg Left upper leg Left lower leg Right lower leg Widespread Pain Index (WPI) Total (maximum 19) All of the following criteria must be met to make a diagnosis of fibromyalgia = 3 = 3 = 3 No No = 0

1. WPI ≥ 7 and SSS ≥ 5 OR WPI 4 to 6 and SSS ≥ 9 Yes
2. Generalized pain: at least 4/5 regions Yes
3. Have the symptoms in section 3 and pain been present at a similar clinical level for at least 3 months? No Yes Fulfills all diagnostic criteria for FM No Yes FIGURE 385-1 Fibromyalgia (FM) 2016 diagnostic criteria. (Figure created using data from F Wolfe et al: Semin Arthritis Rheum 46:319, 2016.) management, as many factors that exacerbate symptoms cannot be addressed by pharmacologic approaches. Furthermore, there is a high prevalence of exposure to previous interpersonal and other forms of violence in patients with FM and related conditions. If posttraumatic stress disorder is an issue, the clinician should be aware of it and con sider treatment options. Functional Impairment It is crucial to evaluate the impact of FM symptoms on function and role fulfillment. In defining the success of a management strategy, improved function is a key measure. Functional assessment should include physical, mental, and social domains. Rec ognition of the ways in which role functioning falls short will be helpful in establishing treatment goals. ■ ■DIFFERENTIAL DIAGNOSIS Because musculoskeletal pain is such a common complaint, the dif ferential diagnosis of FM is broad. Table 385-1 lists some of the more common conditions that should be considered. Patients with inflam matory causes for widespread pain should be identifiable on the basis of specific history, physical findings, and laboratory or radiographic tests. ■ ■LABORATORY OR RADIOGRAPHIC TESTING Routine laboratory and radiographic tests yield normal results in FM without comorbidities. Thus, diagnostic testing is focused on iden tification of other diagnoses and evaluation for pain generators or comorbid conditions (Table 385-2). Most patients with new chronic widespread pain should be assessed for the most common entities in the differential

diagnosis. Radiographic testing should be used very sparingly and only for diagnosis of inflammatory arthritis. After the patient has been evaluated thoroughly, repeat testing is discouraged

Region 1 Region 2 Region 4 Region 3 Generalized Pain Total (maximum 5)

Sympton Severity Score (SSS range 0-12) Over the past week: No problem Slight or mild problem: generally mild or intermittent Moderate problem: considerable problems; often present and/or at a moderate level Severe problem: continuous, life-disturbing No problem Slight/mild Moderate Severe • Fatigue • Trouble thinking or remembering • Waking up tired (unrefreshed) = 1 = 1 = 1 = 2 = 2 = 2 = 0 = 0 During the past 6 months: • Pain or cramps in the abdomen • Depression • Headache No = 0 No = 0 No = 0 Yes = 1 Yes = 1 Yes = 1 Symptom Severity Score Total (maximum 12) unless the symptom complex changes. Particularly to be discouraged is magnetic resonance imaging (MRI) of the spine unless there are fea tures suggesting inflammatory spine disease or neurologic symptoms. ■ ■GENETICS AND PHYSIOLOGY As in most complex diseases, it is likely that a number of genes contribute to vulnerability to the development of FM. To date, these genes appear to be in pathways controlling pain and stress responses. Some of the genetic underpinnings of FM are shared across other chronic pain conditions. Genes associated with metabolism, transport, and receptors of serotonin and other monoamines have been implicated in FM and overlapping conditions. Genes associated with other pathways involved in pain transmission have also been described as vulnerability factors for FM. Taken together, the pathways in which polymorphisms have been identified in FM patients further implicate central factors in mediation of the physiology that leads to the clinical manifestations of FM. Psychophysical testing of patients with FM has demonstrated altered sensory afferent pain processing and impaired descending noxious inhibitory control leading to hyperalgesia and allodynia. Functional MRI and other research imaging procedures clearly demonstrate activation of the brain regions involved in the experience of pain in response to stimuli that are innocuous in study participants without FM. Pain perception in FM patients is influenced by the emotional and cognitive dimensions, such as catastrophizing and perceptions of control, providing a solid basis for recommendations for cognitive and behavioral treatment strategies. Studies have indicated that some patients meeting criteria for FM may have a small fiber neuropathy. There have also been early reports of a possible autoimmune etiology for changes in the

TABLE 385-1 Common Conditions in the Differential Diagnosis of Fibromyalgia Inflammatory Polymyalgia rheumatica Inflammatory arthritis: rheumatoid arthritis, spondyloarthritides Connective tissue diseases: systemic lupus erythematosus, Sjögren’s syndrome Infectious Hepatitis C HIV infection Lyme disease Parvovirus B19 infection Epstein-Barr virus infection Noninflammatory Degenerative joint/spine/disk disease Myofascial pain syndromes Bursitis, tendinitis, repetitive strain injuries Endocrine Hypo- or hyperthyroidism Hyperparathyroidism Neurologic Diseases Multiple sclerosis Neuropathic pain syndromes Psychiatric Disease Major depressive disorder Drugs Statins Aromatase inhibitors peripheral nervous system in patients with FM. Other studies have identified alterations in expressed gene or metabolic signatures in peripheral blood. These studies raise the possibility that confirma tory diagnostic testing could be developed in the future to assist in the diagnosis of FM. APPROACH TO THE PATIENT Fibromyalgia FM is common and has an extraordinary impact on the patient’s function and health-related quality of life. Optimal management requires prompt diagnosis and assessment of pain, function, and psychosocial

context. Physicians and other health professionals can be helpful in managing some of the symptoms and impact TABLE 385-2 Laboratory and Radiographic Testing in Patients with Fibromyalgia Symptoms Routine Erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) Complete blood count (CBC) Thyroid-stimulating hormone (TSH) Guided by History and Physical Examination Complete metabolic panel Antinuclear antibody (ANA) Anti-SSA (anti–Sjögren's syndrome A) and anti-SSB Rheumatoid factor and anti–cyclic citrullinated peptide (anti-CCP) Creatine phosphokinase (CPK) Viral (e.g., hepatitis C, HIV) and bacterial (e.g., Lyme) serologies Spine and joint radiographs Source: LM Arnold et al: J Women's Health 21:231, 2012; MA Fitzcharles et al: J Rheumatol 40:1388, 2013.

of FM. Developing a partnership with patients is essential for improving the outcome of FM, with a goal of understanding the factors involved, implementing a treatment strategy, and choosing appropriate nonpharmacologic and pharmacologic treatments. CHAPTER 385 TREATMENT Fibromyalgia Fibromyalgia NONPHARMACOLOGIC TREATMENT Patients with chronic pain, fatigue, and other neuropsychological symptoms require a framework for understanding the symptoms that have such an important impact on their function and qual ity of life. Explaining the genetics, triggers, and physiology of FM can be an important adjunct in relieving associated anxiety and in reducing the overall cost of health care resources. In addition, patients must be educated regarding expectations for treatment. The physician should focus on improved function and quality of life rather than elimination of pain. Illness behaviors, such as frequent physician visits, should be discouraged and behaviors that focus on improved function strongly encouraged. Treatment strategies should include physical conditioning, with encouragement to begin at low levels of aerobic exercise and to proceed with slow but consistent advancement. Physical activity and exercise are consistently found to be the most helpful strategies. Exercise programs are helpful in reducing tenderness and enhanc ing self-efficacy. Patients who have been physically inactive may do best in supervised or water-based programs at the start. Strength training may be recommended after patients reach their aerobic goals. The U.S. Food and Drug Administration has approved devices including a laser therapy device and a transcutaneous electric nerve stimulation (TENS) device. A large randomized, placebo-controlled trial showed that TENS reduces movementevoked pain and fatigue. Meditative movement therapies, such as qigong, yoga, or Tai Chi, may be helpful to manage symptoms. Other defined physical therapies such as acupuncture or hydro therapy may also be considered. Cognitive-behavioral strategies to improve sleep hygiene and reduce illness behaviors can also be helpful in management. PHARMACOLOGIC APPROACHES It is essential for the clinician to treat any comorbid triggering condi tion and to clearly delineate for the patient the treatment goals for each medication. For example, glucocorticoids or nonsteroidal antiinflammatory drugs may be useful for management of inflammatory triggers but are not effective against FM-related symptoms. At present, the treatment approaches that have proved most successful in FM patients target afferent or descending pain pathways. Table 385-3 lists the drugs with demonstrated effectiveness. It should be emphasized that strong opioid analgesics are to be avoided in patients with FM. These agents have no demonstrated efficacy in FM and are associated with adverse effects that can worsen both symptoms and function. Tramadol, an opioid with mild serotonin-noradrenaline reuptake inhibitor activity, has been studied in this population with indication of efficacy, however its use is generally discouraged due to opioid-related adverse effects. Use of single agents to treat multiple symptom domains is strongly encouraged. For example, if a patient's symptom complex is dominated by pain and sleep distur bance, use of an agent that exerts both analgesic and sleep-promoting effects is desirable. These agents include cyclobenzaprine, sedating antidepressants such as amitriptyline, and alpha-2-delta ligands such as

gabapentin and pregabalin. For patients whose pain is associated with fatigue, anxiety, or depression, drugs that have both analgesic and antidepressant/anxiolytic effects, such as duloxetine or milnacipran, may be the best first choice.

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