

Fibromyalgia

Introduction

Fibromyalgia was initially described in France and England in the mid-nineteenth century, and is now thought to be the most common cause of chronic generalized musculoskeletal pain in females between 20 and 55 years old. Fibromyalgia patients tend to look well, without any significant or obvious abnormalities on physical exam. Diagnostic studies such as lab tests and imaging studies are also often unremarkable. Fibromyalgia can occur along with other rheumatic or connective tissue diseases, such as rheumatoid arthritis, making pain symptoms sometimes difficult to distinguish.

Clinical manifestations and diagnosis

Fibromyalgia occurs 6 times more frequently in women than men, with most patients presenting between the ages of 20 and 55. The primary symptom of fibromyalgia is diffuse musculoskeletal pain, with common sites including the neck, back, chest wall, arms, and legs. The pain is chronic and persistent, but can often vary in severity. Pain is often described as burning, tingling, or numbness. The patient's joints usually do not appear swollen, red, or warm on exam. Pain is sometimes made worse by increased activity, stress, poor sleep, and changes in the weather.

The next most common symptom of fibromyalgia is fatigue, being present in more than 90 percent of cases. Other common symptoms are sleep disturbances, mood alterations (e.g. anxiety and depression), headaches, weight gain/loss, Raynaud phenomena, dry mouth, and dry eyes.

On physical exam, one looks for significant tenderness on palpation at tender points (muscle and tendon insertions). Tender points are typically bilateral. The American College of Rheumatology established a simple set of criteria to diagnose fibromyalgia in 1990, based on a large diagnostic criteria study which included 293 fibromyalgia patients and 265 patients with chronic rheumatic disorders (e.g. rheumatoid arthritis, osteoarthritis, chronic low back pain). The study analyzed over 300 variables, including symptoms, physical exam findings, lab tests, and imaging, and the diagnostic criteria were established:

- diffuse musculoskeletal pain
- significant tenderness in at least 11 out of 18 tender points

The presence of both of the above diagnostic criteria allows for 80 percent sensitivity and specificity in identifying fibromyalgia patients from patients with other chronic rheumatic disorders, and is used most often for clinical trials and for diagnostic classification [1]. It should also be noted that symptoms should be present for at least 3 months.

The tender point exam should be performed in the same manner from patient to patient to help establish consistency in diagnosis. Pressure should be applied to the tender points on both sides of the body at about 4 kg/cm, which can be approximated by palpation with a finger, applying enough pressure to whiten the fingernail bed of the examiner. The examiner should also apply pressure to several “control locations” (e.g. over the mid-forearm or the thumbnail), which should be less tender than the tender points.

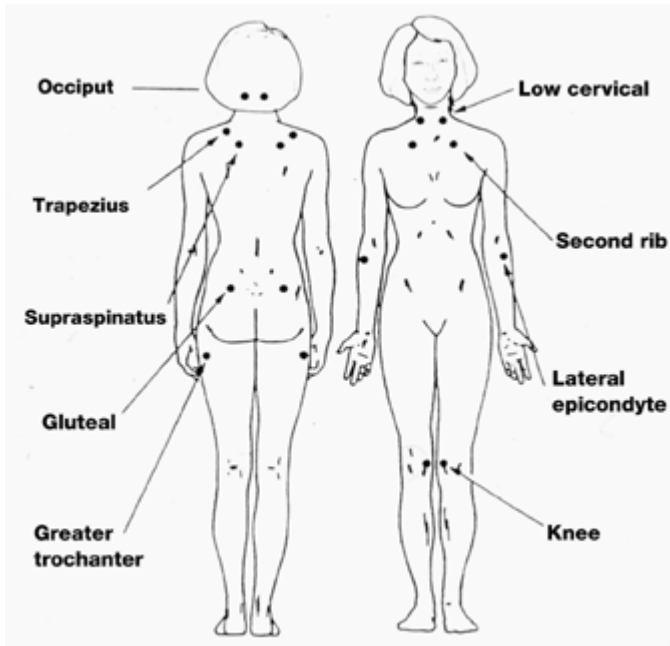


Diagram of tender points from fibromyalgiasupport.com

As stated previously, lab tests in fibromyalgia patients are often unremarkable, but should still be checked initially to rule out other rheumatic or systemic disorders. A good basic background lab evaluation includes CBC, ESR, thyroid function tests, CPK, and aldolase. Pursuing other lab tests is highly dependent on the patient and can sometimes provide confusing results (i.e. false positives), resulting in a patient being diagnosed with another rheumatic disorder that he or she does not truly have. For example, in many cases (5 to 10 percent), patients with fibromyalgia may have a positive ANA, but the same percentage of healthy patients may also have a positive ANA [3]. One should not then say that patients have systemic lupus erythematosus (SLE) if they have a positive ANA, unless they exhibit the other characteristics that typically go along with that disease process. In other words, the positive predictive value of a positive ANA is poor unless the signs and symptoms that typically go along with SLE are present.

The question of pathogenesis

Fibromyalgia is thought to be a disorder of pain regulation. “Central sensitization” is a term commonly used to label this concept of altered pain processing. Fibromyalgia patients tend to perceive pain at lower levels of stimulation when compared to healthy patients.

A research group in Mexico in 2002 looked at the presence of norepinephrine-evoked pain in fibromyalgia, using a prospective double-blind placebo-controlled study [12]. The study involved 20 patients with fibromyalgia and two age and sex matched control groups (20 rheumatoid arthritis patients and 20 healthy controls). Ten micrograms of norepinephrine diluted in 0.1 ml of saline solution were injected in a patient's forearm. Then 0.1 ml of saline solution alone was injected in the opposite forearm. Maximum local pain experienced in the 5 minutes after injection was graded on a visual analog scale. Norepinephrine-evoked pain was diagnosed when norepinephrine injection induced greater pain than placebo injection. Intensity of the evoked pain was calculated as the difference between norepinephrine-induced minus placebo-induced visual analog scale scores. The results of the study showed that norepinephrine-evoked pain was observed in 80 percent of patients with fibromyalgia (95 percent confidence interval 56.3 to 94.3), compared to 30 percent of rheumatoid arthritis patients and in 30 percent of healthy controls (95 percent confidence interval 11.9 to 54.3, $p < 0.05$). Intensity of norepinephrine-evoked pain was greater in patients with fibromyalgia (mean 2.5 +/- SD 2.5) when compared to rheumatoid arthritis patients (0.3 +/- 0.7), and healthy controls (0.3 +/- 0.8) ($p < 0.0001$). It could therefore be concluded that norepinephrine-evoked pain is present in patients with fibromyalgia, supporting the theory that certain neurotransmitters are involved in maintaining the pain response in fibromyalgia. However, the exact mechanism of action is still unclear, and there is still no widely accepted explanation for the pathogenesis of fibromyalgia.

Additionally, patients with fibromyalgia may have increased regional blood flow to pain-sensitive areas of the brain that are associated with affective pain processing (e.g. amygdala and anterior insula) and have increased magnitude of neuronal activations in these regions on functional MRI [13]. These findings support the concept that depressed mood may exert influence on pain processing in patients with fibromyalgia.

Possible genetic predisposition?

Fibromyalgia has been shown in several studies to have a possible genetic basis. The fact that some antidepressant medications are successful in improving symptoms in fibromyalgia patients suggests that genes involved in serotonin or catecholamine signaling pathways may be responsible for some of the observed effects. One study showed that patients with fibromyalgia have an increased likelihood of having inherited deletions in the serotonin transporter gene, possibly resulting in a lower threshold for pain sensation [4]. Catechol-O-methyltransferase gene polymorphisms have also been suggested as being involved in fibromyalgia [5], however much research still needs to be done to further elucidate possible genetic relationships.

Differential diagnosis

As one can imagine, there are many diseases and conditions that have symptoms that sound similar to those of fibromyalgia. For example, a patient with fibromyalgia complaining of chest wall pain may prompt evaluation for cardiac disease. Complaints of

myalgias and subjective muscle weakness may cause concern for an inflammatory muscle disorder. A good point of distinction, however, is that myositis and myopathies are often associated with observed significant muscle weakness on exam, whereas fibromyalgia patients typically do not exhibit significant weakness. In addition, fibromyalgia patients have unremarkable muscle enzyme tests, whereas in myositis, these tests are usually abnormal.

There is also an overlap of symptoms between fibromyalgia and psychiatric disorders, especially depression and anxiety. Since symptoms of depression can also include many somatic symptoms, this can make the tender points exam particularly useful in distinguishing fibromyalgia from psychiatric illnesses like depression. However, it is important to note also that fibromyalgia often coexists with psychiatric disorders. Studies have shown that about 30 percent of patients with fibromyalgia meet criteria for major depression at the time of diagnosis. In addition, the lifetime prevalence of depression in patients with fibromyalgia is 74 percent, and of an anxiety disorder is 60 percent [2]. Since depression is fairly common in patients with fibromyalgia, an assessment of mood should be performed in these patients, such as with questionnaires. If significant impairment is detected, patients can then be referred to a mental health professional.

Since sleep disturbances and fatigue are common features in both fibromyalgia and in obstructive sleep apnea (OSA), it is important to evaluate for the possibility of OSA with a sleep study or referral to a sleep clinic if the clinical history is suggestive.

In addition, there is significant overlap of features of fibromyalgia and of chronic fatigue syndrome (CFS). The most notable symptom of CFS is chronic, debilitating fatigue, with other associated symptoms being similar to those of fibromyalgia discussed earlier. It is important to note that patients can have both fibromyalgia and CFS. CFS predominantly occurs in otherwise healthy young and middle-aged females. Physical exam often reveals no signs of any systemic illness.

As mentioned above, fibromyalgia often coexists with other rheumatic or connective tissue diseases, such as rheumatoid arthritis, SLE, Sjögren's syndrome, or osteoarthritis, thus making it difficult to determine if a patient's symptoms are due to fibromyalgia or due to another one of these disorders. However, the usual synovitis seen in connective tissue disorders is absent in fibromyalgia, again making the physical exam a key component in determining the disease process that is at the root of the patient's symptoms.

Polymyalgia rheumatica (PMR) and fibromyalgia may also have similar musculoskeletal pain complaints, but there are several key differences that have been noted between the two disorders: tender point exam is not usually positive in patients with PMR; patients with PMR complain more commonly of stiffness than of pain; patients with fibromyalgia have unremarkable labs, while PMR patients will likely have an elevated ESR; and PMR patients usually respond well to treatment with corticosteroids.

Another condition that may be difficult to distinguish from fibromyalgia based on symptoms alone is hypothyroidism. This is due to the fact that patients with

hypothyroidism may also have diffuse aches, sleep disturbances, and fatigue. As a result, in the initial workup for possible fibromyalgia, thyroid function tests should always be obtained to rule out thyroid disease.

Peripheral neuropathies and certain neurological diseases, such as myasthenia gravis and multiple sclerosis, can also be confused with fibromyalgia secondary to patients often describing their pain as a tingling or numbness, and due to the common complaint of fatigue. However, a few features that separate myasthenia gravis and multiple sclerosis from fibromyalgia are post-exercise muscle fatigue and the lack of diffuse musculoskeletal pain with tender points.

Treatment

General principles

Fibromyalgia is very difficult to treat, but patients usually respond best when treated with a multidisciplinary program. Patient education is vitally important as the initial step in treatment. Providing the actual diagnosis of fibromyalgia to patients, along with a thorough explanation of what is known and what is not known about the syndrome, can help ameliorate some patients' fears that a more serious condition is the cause of their symptoms. In some patients, it has been observed that they have fewer symptoms and have an overall improvement in their health status once the diagnosis has been established. The likely basis of this observation is that giving patients an official diagnosis helps to reassure them that their symptoms are due to a real illness, and not just secondary to psychological or mental distress.

One study published by a group in Switzerland in 2004 looked at the efficacy of a treatment program based on self management using exercise and education [14]. The trial involved 164 patients that were randomized to either an immediate 6 week program (n=84) or to a waiting list control group (n=80). The trial had a 6 month follow up to evaluate the program, and the main outcomes were changes in quality of life, functional consequences of fibromyalgia, patient satisfaction, and pain. These outcomes were graded using a combination of patient questionnaires and clinical exams. 61 patients in the treatment group and 68 controls completed the program and 6 month follow up examinations. Results showed significant improvements in quality of life, functional consequences of fibromyalgia, and patient satisfaction in the treatment group as compared with the control group. However, no change in pain was seen between the two groups.

Another study published in 2003 showed that a day and a half of intensive educational intervention from a multidisciplinary team led to patients having significantly less pain and subjective improvement in functioning, fatigue, and mood disturbances [6]. Ideally, a multidisciplinary treatment program should involve rheumatologists, psychiatrists, physical therapists, pain management specialists, and mental health professionals.

Medications

Typically, anti-inflammatory medications, such as non-steroidal anti-inflammatory drugs and steroids (e.g. prednisone), have not been shown to be effective when compared to placebo in the treatment of fibromyalgia. This observation is not particularly surprising since tissue inflammation is not thought to be an underlying mechanism of disease in patients with fibromyalgia.

Other analgesics, on the other hand, such as tramadol and acetaminophen, have been shown to be helpful in reducing pain in patients with fibromyalgia. A study in 2003 randomly assigned 315 female patients to receive therapy with 75mg tramadol plus 650 mg acetaminophen four times daily versus placebo. The results showed that a greater proportion of the patients treated with tramadol and acetaminophen had a 50 percent or greater decrease in pain (35 percent versus 18 percent in placebo group). However, the patients involved in this study were enrolled with the exclusion criteria that they could not have used tricyclic antidepressants, cyclobenzaprine, and analgesics (including acetaminophen) prior to enrollment. As a result, it is not clear if this tramadol and acetaminophen combination is as effective for patients who have tried and failed other treatments, or for patients who are also on treatment with neuropsychiatric medications [7].

Tricyclic antidepressants are often used as first-line treatment for fibromyalgia, however their use is somewhat limited by the lack of equal effectiveness among patients and by the common occurrence of side effects. Amitriptyline, usually given as a single bedtime dose, and in doses lower than those used to treat depression, still has the common side effects of dry mouth, constipation, fluid retention, weight gain, problems with concentration, and possible cardiotoxicity. Desipramine, another tricyclic antidepressant, is less well-studied in the treatment of fibromyalgia, but may be a potentially useful alternative to amitriptyline due to fewer anticholinergic side effects. With both of these medications, patients with fibromyalgia should be started on very low initial doses (e.g. 5 to 10 mg at bedtime), and gradually titrated up by 5 mg every 2 weeks to a final dose that results in effectiveness for the patient, yet balances side effects.

Cyclobenzaprine has also been shown to be effective in various placebo-controlled trials. A meta-analysis in 2004 of five trials included 312 patients and showed subjective improvement in pain to be more likely in patients receiving cyclobenzaprine than placebo (odds ratio 3.0, 95 percent confidence interval 1.6 to 5.6), with an absolute difference in the rate of improvement of 21 percent [8].

Some serotonin reuptake inhibitors also have some efficacy in the treatment of fibromyalgia. Fluoxetine was found in one study to be more effective in treating pain than placebo when dose escalation was used, from 20 mg daily to a maximum of 80 mg daily [9]. Paroxetine, another serotonin reuptake inhibitor, has also been shown to be effective in improving symptoms. Medications, such as duloxetine and venlafaxine, that involve the inhibition of both norepinephrine and serotonin reuptake have also been shown to be useful in treatment of pain in fibromyalgia.

Certain anticonvulsants, such as gabapentin and pregabalin, have been shown in several studies to be effective. One trial randomly assigned 150 patients to receive gabapentin (1200 to 2400 mg/day) or placebo for 12 weeks. Patients were asked to rate their pain by giving a pain inventory score. A response was defined as a 30 percent or greater decrease in this score. A significantly greater proportion of patients in the gabapentin group had a positive response than in the placebo group (51 and 31 percent, respectively). Common side effects that were observed in the gabapentin group included dizziness, lightheadedness, sedation, and weight gain [10]. Pregabalin's benefits in fibromyalgia were seen in a study that looked at pregabalin versus placebo in 529 patients over 8 weeks. Pregabalin at a dose of 450 mg/day reduced the average severity of pain compared to placebo, i.e. more patients treated with pregabalin had a greater than 50 percent decrease in pain (29 percent in the pregabalin group versus 13 percent in the placebo group). There were also improvements noted in fatigue and sleep disturbances [11].

Some alternatives to medication

As stated previously, pain in fibromyalgia is very difficult to treat. Therefore, many people have looked at alternative methods to address pain, for use in place of, or in conjunction with medications. Pain in fibromyalgia is often made better with heat therapy or massage. Aerobic exercise may also be effective in producing decreased pain and higher pressure thresholds for pain.

A study published in 2002 looked at the effect of cardiovascular fitness exercise in 132 patients with fibromyalgia in a randomized controlled trial [15]. This study had patients take group classes, either in prescribed graded aerobic exercise (active treatment) or relaxation and flexibility (control treatment). The authors measured patients' self assessment of improvement, tender point count, and pain. The active treatment group had more participants rating themselves as "much" or "very much better" at 3 months (35 percent versus 18 percent in the control group, $p=0.03$). Patients in the active treatment group also had greater reductions in tender point counts (4.2 versus 2.0 in control group, $p=0.02$). Pain scores had fallen in both groups at 3 months, but with no significant difference between groups.

With an exercise program, it is important to start patients off slow and to gradually increase their activity over time. Good activities to start with include walking, biking, swimming, or water aerobics. Strength training and flexibility exercises may also help improve pain, decrease the number of tender points, and improve overall muscle strength, especially in patients who have become sedentary as a result of their chronic aches and chronic fatigue.

Tender point injections in the treatment of fibromyalgia have not been studied well enough yet in controlled studies, however there is anecdotal support for their effectiveness. These injections may be performed by injecting 1 percent lidocaine into the tender point, although injections of saline and botulinum toxin have also been used.

Conclusion

Fibromyalgia is a syndrome characterized by chronic diffuse musculoskeletal pain and can cause significant morbidity for patients that are afflicted. There are several concepts and theories regarding its pathogenesis, but there is still much that is unknown. Fibromyalgia may be difficult to distinguish from a wide array of systemic disorders, however, the history, physical exam, and diagnostic studies are all useful in making the distinction. Treatment of fibromyalgia is focused on patient education, pharmacotherapy, such as with antidepressants, anticonvulsants, muscle relaxants, and analgesics, and alternative or complementary therapies.

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