Overlap of Fibromyalgia with Other Medical Conditions

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Fibromyalgia is a multisystem illness. One of its defining features, generalized pain, may also be present in other rheumatic entities. The diagnosis of fibromyalgia is not easy by any means, it requires a profound knowledge of internal medicine. This article discusses the different rheumatic and nonrheumatic diseases that overlap or are prone to be confused with fibromyalgia. It emphasizes the key points in the differential diagnosis.

Fibromyalgia (FM) is a pure clinical diagnosis. It has no characteristic laboratory tests or radiographic abnormalities. Its recognition is based on the presence of chronic widespread pain associated with tenderness at palpation on well defined anatomic points. These two defining features are invariably accompanied by an array of multisystem symptoms. According to the seminal study by the Ad Hoc Committee of the American College of Rheumatology, other distinctive features of FM are fatigue, sleep disturbances, morning stiffness, paresthesias, headache, anxiety, sicca symptoms, irritable bowel, and Raynaud's phenomenon. These symptoms are more prevalent in patients with FM when compared to patients with other rheumatic diagnoses (Table 1) [1].

Fibromyalgia is a common syndrome; prevalence studies have shown that near 2% of the general population suffer this illness. FM is also common in clinical practice. It has been estimated that up to 20% of patients who go to a rheumatology clinic have this diagnosis [2]. Its clinical identification is not easy by any means; chronic widespread pain is frequently found in other rheumatic illnesses. Furthermore, the dramatic multisystem features of FM are prone to be confused with the organ damage seen in other rheumatic conditions. This issue is further confounded by the fact that there is a true overlap of fibromyalgia with other musculoskeletal pathologies.

In this article, we consider the diverse rheumatic and nonrheumatic syndromes that are prone to be confused with fibromyalgia, discussing important points in the differential diagnosis (Table 2). Lastly, we mention those syndromes in which there is a true overlap with FM.

Rheumatic Pathologies That Overlap and/or May Be Confused with Fibromyalgia

Osteoarthritis

Taken together with fibromyalgia, osteoarthritis (OA) is one of the most prevalent rheumatic syndromes in clinical practice. Thus, there is no surprise that this disease may overlap with FM just by chance alone. Systematic studies have shown that around 7% of patients with OA have concomitant FM [2].

Osteoarthritis is present in the majority of persons older than 50 years, most of whom are asymptomatic. Therefore, a good proportion of patients with FM will have underlying osteoarthritic changes when radiographs are taken. This fact frequently induces the following clinical sophism:

A patient complains of neck pain, then radiographs of the area show osteoarthritic changes; therefore, neck pain is due to OA. To avoid this clinical sophism, it is important to determine if a patient with complaints in the neck area also has pain elsewhere, and most important if such a patient has the "FM profile"—widespread pain, hypersensitivity at palpation (allodynia) in specific anatomic points accompanied by the multisystem features of FM (particularly by constant fatigue, sleep problems, and paresthesias). Similar consideration is in order in the cases of patients with chronic low back pain.

Rheumatoid arthritis

Patients with FM frequently have diffuse arthralgias and perceive their hand as being "swollen." So it is fundamental to perform a careful physical examination to determine if true synovitis is present. Other important points in the differential diagnosis are the presence (in cases of rheumatoid arthritis) of increased erythrocyte sedimentation rate, high titers of rheumatoid factor, and also the improvement of pain with the use of anti-inflammatory medications.

Ankylosing spondylitis

Females with ankylosing spondylitis often have an atypical and benign course. They may complain of vertebral pain and morning stiffness. Sacroiliitis may not be evident in the early course of the illness [3]. These peculiarities

Table 1. Defining and associated features of fibromyalgia

Defining features
Chronic widespread pain
Tenderness at palpation in 11 of 18 specific anatomic points
Associated features
Sleep disturbance
Fatigue
Morning stiffness
Paresthesias
Anxiety
Headache
Irritable bowel
Sicca symptoms
Raynaud's phenomenon

should be taken into consideration in the differential diagnosis. Key points in favor of the diagnosis of ankylosing spondylitis are decreased range of motion of cervical and lumbar spine, the presence of enthesopathy, positive family history for spondyloarthropathies, and a response to anti-inflammatory medications.

Polymyalgia rheumatica

Similar to FM, polymyalgia rheumatica is characterized by widespread pain and profound morning stiffness. A distinctive feature of polymyalgia is the marked increase in erythrocyte sedimentation rate. Nevertheless, it should be noted that several groups of investigators have reported patients with this illness who have either normal or slightly increased erythrocyte sedimentation rate [4]. Therefore, in some persons with recent onset of the above-mentioned symptoms, a therapeutic trial with a short course of prednisone therapy (20 to 30 mg/d) is in order. The responses to this type of treatment are divergent; in polymyalgia rheumatica there is a dramatic response with disappearance of all symptoms in 24 to 48 hours, whereas in FM there is little or no response.

Systemic lupus erythematosus

The multisystem features of FM may be dramatic. Not infrequently, young females with this diagnosis communicate an array of severe complaints in diverse organs that may suggest lupus. Some of these complaints may be secondary to the relentless sympathetic hyperactivity that has been recently recognized in FM [5]. Adding confusion to this issue is the fact that with the current oversensitive methods, positive antinuclear antibodies are found in 30% of otherwise healthy individuals. Thus, it is no surprise that some of these young females with multisystem complaints and low titer antinuclear antibodies are being misdiagnosed as suffering from lupus. The source of confusion is that such patients with FM frequently have arthralgias and also have swollen hands. This may be misinterpreted as true arthritis. Relentless sympathetic hyperactivity may induce "pseudo-Raynaud's phenomenon" and malar rash, as well as neurocardiogenic syncope (this latter syndrome is difficult to set apart from epilepsy).

Therefore, in the presence of a patient with lupus-like symptoms who also fulfills the diagnosis of FM, it seems wise not to make the diagnosis of lupus unless there is evidence of organ damage or there are antinuclear antibodies with lupus specificity (anti-Sm, anti-DNA, anti-SSA[Ro] or SSB[La]) [5]. On the other hand, there is no doubt that a true overlap exists between FM and lupus; such patients generally have low quality of life and their complaints are usually unresponsive to anti-inflammatory medications.

Sjögren's syndrome

The cardinal clinical feature of Sjögren's syndrome is the so-called "sicca complex," manifested by dry eyes and dry mouth. Fatigue and generalized arthralgias are frequent associated symptoms. Patients with FM have similar complaints. The mucosal dryness in FM is most likely secondary to relentless sympathetic hyperactivity [6•]. What distinguishes Sjögren's syndrome is the heavy lymphocytic infiltration of the salivary glands. Typically, there are more than two clusters of 50 lymphocytes per 4 mm^2 of salivary gland area. It should be noted that scattered lymphocytic salivary gland infiltration is a nonspecific finding. Additionally, in Sjögren's syndrome there is damage to the eye epithelium, which is evident when rose bengal or fluorescein dyes are used. Laboratory tests demonstrate clear evidence of autoimmunity manifested by the presence of high titers of rheumatoid factor and/or antinuclear antibodies, particularly anti-SSA(Ro) and SSB(La) [7]. Thus, capital in the differential diagnosis is the mucosal damage and autoimmunity seen in patients with Sjögren's syndrome.

Chronic Lyme disease

Months or years after *Borrelia burgdorferi* infection a chronic encephalopathy may develop, manifested by memory impairment, sensory polyneuropathy with spinal pain, and distal paresthesias. This syndrome is similar to FM. On the other hand, clear-cut FM is a recognized late complication of Lyme disease. A further source of confusion is the lack of standardization of the serologic test for *B. burgdorferi* infection, which yields both false-positive and false-negative results. Thus, clinicians in endemic areas for Lyme disease report patients with well-sustained diagnoses of neuroborreliosis who later develop FM and also patients with FM who are misdiagnosed with chronic Lyme disease. Experts agree in the opinion that the symptoms of post-Lyme FM do not respond to antibiotics [8].

Osteomalacia

Clinical manifestations of osteomalacia are widespread bone pain and tenderness of the bones at palpation. These peculiarities may be confused with FM. What distinguishes osteomalacia from FM are the presence of hypophosphatemia and radiographic evidence of osteopenia with pseudofractures [9].

Table 2. Rheumatic and nonrheumatic illnesses that may be confused with fibromyalgia

Name of the disease	Key differential points
Rheumatic diseases	
Osteoarthritis	Lack of widespread pain and allodynia, response to analgesic/anti-inflammatory drugs
Rheumatoid arthritis	Synovial effusion, increased sedimentation rate, rheumatoid factor
Ankylosing spondylitis	Enthesopathy, decreased range of motion of the spine, response to anti-inflammatory drugs
Polymyalgia rheumatica	Increased sedimentation rate, response to corticosteroids
Systemic lupus erythematosus	Organ damage, Lupus-specific antibodies
Sjögren's syndrome	Heavy lymphocytic infiltrate of the salivary glands, Sjögren's-specific antibodies
Chronic Lyme disease	Clear-cut history of arthritis and Lyme's rash
Osteomalacia	Hypophosphatemia, osteopenia
Polymyositis	Proximal muscle weakness, increased muscle enzymes, lymphocytic infiltrate in muscles
Nonrheumatic diseases	
Chronic fatigue syndrome	Slight ongoing inflammatory process, normal cerebrospinal fluid substance P levels
Thyroid dysfunction	Thyroid function tests
Hepatitis C infection	Hepatitis C serology
Chiari malformation	Lower cranial nerves and spinal cord signs, cerebellar herniation (magnetic resonance imaging)
Anxiety/depression	Lack of generalized pain and allodynia

Polymyositis

For a beginner on musculoskeletal pathology, there may be room for confusion between FM and polymyositis. The differences are clear-cut in most instances. In polymyositis there is often profound proximal muscle weakness with mild pain. There is also increased serum levels of creatine kinase, and muscle biopsy shows degeneration and regeneration of muscle fibers with chronic inflammatory cell infiltration.

Nonrheumatic Syndromes That Overlap and/or May Be Confused with Fibromyalgia

Chronic fatigue syndrome

There is a large overlap between FM and chronic fatigue syndrome (CFS). Chronic pain and constant fatigue are common to both entities and these symptoms are listed among their distinctive features. Some experts suggest that these two syndromes are different perspectives of the same disease process. Nevertheless, there are several differences among these two entities. In CFS there appears to be an ongoing subclinical inflammatory process manifested by low grade fever, lymph gland enlargement, and acute onset of the illness, a phenomenon not seen in FM. Substance P is elevated in the cerebrospinal fluid only in patients with FM. A biochemical marker that segregates patients with CFS from FM has been recently described [10•]; this finding awaits confirmation. In our opinion, the difference between these two syndromes may reside in the ability of the pathogenetic stimulus (purportedly sympathetic hyperactivity) to sensitize primary nociceptors and induce pain (in cases of FM).

Thyroid dysfunction

Hypothyroidism may be manifested by profound fatigue, muscle weakness, and generalized achiness. On the other hand, fatigue and anxiety may be present in the opposite end of the spectrum, hyperthyroidism. Therefore, fundamental in the clinical evaluation of patients with FM is to search for clinical signs of thyroid dysfunction, and to order thyroid function test when clinically indicated.

Hepatitis C virus infection

A study by Rivera *et al.* [11] shows that patients with FM have a higher prevalence (15%) of antibodies against hepatitis C virus when compared to control patients with rheumatoid arthritis (5%). Most of the patients with antibodies also had positive serum hepatitis C virus RNA, demonstrating active viral infection. Of note is that almost half of those patients had normal alanine aminotransferase serum levels. On the other hand, 10% of patients with known hepatitis C virus infection fulfill the diagnosis of FM [11]. Thus, it appears that hepatitis C virus infection is one of the multiple triggers for the development of FM. What remains to be studied is if successful treatment of the viral infection improves FM symptoms.

Chiari malformation

The Chiari malformation is a disorder of the craniovertebral juncture, defined as downward herniation of the cerebellar tonsils through the foramen magnum. This herniation produces a variety of neurologic symptoms. Magnetic resonance imaging has revolutionized its diagnosis and has defined the adult type syndrome, also referred to as Chiari malformation type I.

Milhorat *et al.* [12] described the clinical features of 364 patients with Chiari malformation type I. They found several similarities with FM. The mean age of presentation of such patients was 36 years and most of those affected were female. A total of 24% cited trauma as the precipitating event. The most common symptom was suboccipital headache accentuated by physical exertion or Valsalva

maneuvers. Other frequent features were pseudotumor cerebri-like episodes (blurred vision, visual floaters), Meniere's disease-like syndrome (dizziness, disequilibrium, tinnitus), lower cranial nerve signs (dysphagia, sleep apnea, hoarseness), and spinal cord disturbances (paresthesias, muscle weakness, impaired fine-motor function). Magnetic resonance imaging showed obliteration of the retrocerebellar cerebrospinal fluid spaces in all instances and tonsillar herniation of at least 5 mm in 91% of cases.

Several groups of investigators are currently assessing the overlap between Chiari malformation type I and FM, as well as the response of skull decompression in those cases with hindbrain herniation. In the meantime, it appears sound to include Chiari malformation type I in the differential diagnosis of FM and to perform magnetic resonance studies of the craniovertebral junction in those cases who display lower cranial nerve signs and spinal cord disturbances.

Anxiety/depression

The psychological component of FM is obvious. It could not be any other way in persons who suffer chronic generalized pain and constant fatigue. This psychological component of FM does not diminish the validity of the diagnosis nor make the patients censurable for their suffering [6•]. A sad medical stance has been to label FM patients as "somatizers" or "hypochondriacs"; this obscurant stance has only hampered the understanding of this illness. There is evidence that FM pain is real, as attested by several studies demonstrating raised spinal fluid levels of the prototypic pain transmitter, substance P [13,14]. It should be noted that many patients with FM are not anxious or depressed and many anxious/depressed patients do not have FM. Thus, the key question is how to link anxiety/depression with the pain of FM. In my opinion, a plausible explanation is relentless sympathetic hyperactivity that can either be the cause or the result of anxiety. This sympathetic hyperactivity could, in susceptible cases, sensitize primary nociceptors through the mechanism known as "sympathetically maintained pain," thus inducing chronic pain and allodynia [15].

Conclusions

Fibromyalgia should be considered a multisystem syndrome. Its diagnosis is not easy by any means; it requires a profound knowledge of internal medicine. In patients with widespread pain, it is important to define if they fit the "FM profile" (associated chronic fatigue, sleep disturbances, paresthesias, allodynia). If so, the next step is to establish if FM explains all of the patient's complaints or if there is a true overlap with other diseases.

This approach may have two advantages: 1) to avoid the over-diagnosis of more serious illnesses such as lupus or Sjögren's syndrome, and 2) to realize that a patient with such a profile will not respond to the usual analgesic/anti-inflammatory medications, even if there is a true overlap with other rheumatic diseases.

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