Is Fibromyalgia a Rheumatological Disease?

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Abstract: Fibromyalgia is not an uncommon clinical problem in rheumatology clinics. Widespread pain is the main symptom of fibromyalgia. Pain can help avoiding dangers and saving lives, but it can also destroy lives of people having chronic pain. Pain is a subjective and yet complex feeling. The mechanism of pain amplification in fibromyalgia is discussed. Current evidence suggests that fibromyalgia has neurologic pain processing problem. It cannot be considered a primarily psychological disorder, but as in many chronic conditions, other factors especially psychological factor may play a role in the root cause of the problem.

Keywords: Central sensitization, Fibromyalgia, Peripheral sensitization, Widespread pain

Vignette 1 in Rheumatology Clinic

Forty-two years old secondary school teacher complains of widespread pain over her body for 2 years. The pain intensity has been increasing for recent few months after discovery of her mother's breast cancer. She notices many tender spots in her body. She has history of depression 2 years ago; however she refuses to take anti-depressant. Both her mood and her sleep have been very bad lately. She admits she has tremendous stress in her schoolwork and family issues. She has already seen four doctors and has been given various painkillers without avail.

Vignette 2 in Rheumatology Clinic

Forty-seven years old housewife complains of muscle pain over her neck, upper body, back, arms, legs and buttock for 3 years. Pain is very widespread. The pain wakes her up in the night; therefore, she can hardly sleep through the night. She denies any stress. She has tried many different NSAIDs and opiates without improvement. She has seen four different doctors before she is finally referred to a rheumatologist. She is crippled with this chronic pain.

Introduction

Fibromyalgia (FM) is not an uncommon clinical condition. It mostly affects females in their mid-life. Is it a real disease? Is it merely something in the head? There is no debate as to the validity of fibromyalgia as a disease. WHO has included fibromyalgia into International Classification of Diseases (ICD_10). Why are there still many people skeptical about the existence of such disorder? One of the reasons is fibromyalgia has not been fully understood up to date. Fibromyalgia is a confusing and misunderstood condition. It has been misdiagnosed often. Various misdiagnoses including somatoform pain disorder, myofascial pain syndrome, polymyalgia rheumatica or even malingering has been given to fibromyalgia patient. The classic medical model we are using today cannot explain it. In the classic medical model, there is always pathology to account for the clinical features of a disease. In fibromyalgia, we cannot find a definite "pathology" to account for its clinical features, widespread pain, hypersensitivity, allodynia, and sleep problem. In United States, National Institute of Arthritis and Musculoskeletal and Skin disease estimates there are over 3.7 million of fibromyalgia patients. Most FM patients if not all are referred to rheumatologists. The reason is obvious; the disease is characterized by musculoskeletal pain like many other rheumatological conditions.
Pain, especially widespread pain is the main symptom of all fibromyalgia patients. Pain is considered essential as in avoiding insult and danger to the body, but it also destroys the lives of many people with chronic pain. Pain is only perceived in highly complex neurosensory system in humans, and, it is a subjective and yet complex feeling. For many years, FM has been considered as a disease in muscles. Biopsy of tender points does not reveal any abnormality. In recent years, a number of researches have started to clarify some of the pathophysiology of chronic pain. Persistent activation of nociceptive receptor transmission to the dorsal horn changes central pain processing. This induces pathological changes that lower the threshold for the receptors to transmit pain signals, which is commonly found in FM patients. In addition it may generate non-nociceptive nerve fibers to respond to pain signals.6 These findings suggest fibromyalgia may be in fact, a neurologic disorder in central pain processing.

Most fibromyalgia patients want to be reassured that their symptoms are the product of a "real disease" rather than "imagination" which commonly ascribed to the psychological diagnosis such as somatization, hypochondriasis, or depression. The mysterious part of fibromyalgia is that there is no detectable body damage while sufferers continue to complain of widespread pain in the body. The good news is that contemporary research is hot on the track of unraveling the changes that occur within the central nervous system of fibromyalgia patients. Nonetheless, psychological factors may still play a role if not the most important one in FM.7,8

How is Fibromyalgia Diagnosed?

Currently there are no laboratory tests that can confirm fibromyalgia. A process of elimination makes diagnosis. Before one can be labeled as having fibromyalgia, it must be determined it is not some other causes. Doctors rely on taking a history; patient reported symptomatology and physical examination for correct diagnosis. An accurate manual tender point examination is essential in making the diagnosis of fibromyalgia. This examination is based on the standardized American College of Rheumatology (ACR) criteria.9

American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia:

1. History of Widespread Pain
   Definition: pain is considered widespread when all of the following are present: pain in the left side of the body, pain in the right side of the body, pain above the waist, and pain below the waist. In addition, axial skeletal pain (cervical spine or anterior chest or thoracic spine or low back) must be present. In this definition, shoulder and buttok pain is considered as pain for each involved side. "Low back" pain is considered lower segment pain.

2. Pain in 11 of 18 Tender Point Sites on Digital Palpation
   Definition: pain on digital palpation, must be present in at least 11 of the following 18 tender point sites:
   - Occiput: bilateral, at the suboccipital muscle insertions.
   - Low cervical: bilateral, at the anterior aspects of the intertransverse spaces at C5-C7.
   - Trapezius: bilateral, at the midpoint of the upper border.
   - Supraspinatus: bilateral, at origins, above the scapula spine near the medial border.
   - Second rib: bilateral, at the second costochondral junctions, just lateral to the junctions on upper surfaces.
   - Lateral epicondyle: bilateral, 2 cm distal to the epicondyles.
   - Gluteal: bilateral, in upper outer quadrants of buttocks in anterior fold of muscle.
   - Greater trochanter: bilateral, posterior to the trochanteric prominence.
   - Knee: bilateral, at the medial fat pad proximal to the joint line.
   - Digital palpation should be performed with an approximate force of 4 kg.
   - For a tender point to be considered "positive" the subject must state that the palpation was painful. “Tender” is not to be considered "painful".
   - For classification purposes, patients will be said to have fibromyalgia if both criteria are satisfied. Widespread pain must have been present for at least 3 months. The presence of a second clinical disorder does not exclude the diagnosis of fibromyalgia.

Pathophysiology of Fibromyalgia

Pain in FM patients is significantly amplified. They are sensitive to both painful and non-painful mechanical stimuli, for example, touching and light rubbing. The cause for the heightened sensitivity of FM patients can involve abnormalities in peripheral nervous system (PNS), central nervous system (CNS), as well as peripheral tissue abnormalities.10,11
Functional Anatomy of Pain/Nociceptive System

The anatomy of the pain/nociceptive system can be grossly divided into the peripheral and central nervous system. The peripheral nervous system consists of small myelinated and unmyelinated nerve fibers. These nerve fibers converge into dorsal horn in spinal cord. The dorsal horn is the first relay station in pain signal transmission. The next element of pain transmission includes nerve fibers travel to the thalamus. From the thalamus some of them goes to limbic system and sensory cortex. The limbic system supports a variety of functions including emotions, behaviours and long term memories. Functional magnetic resonance imaging has shown that pain is processed in many parts of the brain. The involvement of limbic system explains why emotion has strong influence on pain.

Peripheral Sensitization and Peripheral Tissue Abnormalities

Acute pain or nociceptive pain occurs everyday in response to simple insult or injury. This helps us to prevent severe injury. Nociceptive receptors convert external stimuli or tissue injury information to electrical stimuli that are transmitted to CNS via spinal cord. When tissue damage is healed, stimuli disappear and there is no more pain. However, the mechanism of simple nociceptive pain cannot explain phenomena, such as pain that persists despite removal or healing of the stimulus, such as in phantom limb pain. In some cases of tissue damage, for example surgical wounds, there is inflammatory response triggered by the damage. Inflammatory response produces a number of cytokines and chemokines, which are to mediate healing and regeneration, may change or irritates the primary sensory neurons/nociceptive receptors surrounding the area of tissue damage. These afferent receptors respond to stimuli that ordinarily do not produce pain, such as a touch, clothing, light pressure, or a hairbrush, as if they are painful (alldynia) now. The pain intensity is also increased in these areas even with same stimuli (hypersensitivity). Both alldynia and hypersensitivity are a result of peripheral sensitization.

More recent evidence suggests there are alterations in skin and muscles in FM patients. Substance P is found to be increased in muscle tissues. DNA fragmentation of muscle fibres is increased in FM patients' muscles. Interleukin-1 is increased in cutaneous tissues and, FM patients have more muscle perfusion deficits. These changes may contribute to increase tonic nociceptive input into spinal cord that results in peripheral sensitization. This means that low intensity stimuli delivered to the skin and muscles results in high output of nociceptive afferent to the brain.

Central Sensitization

Tissue injury activates the PNS, which sends signals through the spinal cord to the brain, where pain perception occurs. But what causes the acute experience of pain to become an unremitting phenomenon? Chronic pain researchers speculate there are neural "memories" of previous pain. In the process of central sensitization, neuroplastic changes occur in the central nervous system through repeated stimuli from PNS. Several events are observed in central sensitization, which include increased excitability of spinal cord neurons, enlargement of receptive fields of these neurons, reduction in pain threshold, or recruitment of novel afferent inputs. Morphologically, there is spreading of hypersensitivity to uninjured sites (alldynia) and generation of pain by low threshold mechano-receptors that are normally silent in pain processing. After central sensitization, low threshold afferents, which normally do not serve to transmit a pain response, are recruited to transmit spontaneous and movement-induced pain.

FM patients have faulty pain processing, though specific abnormalities in persons with FM have not been identified that produce the prolonged impulse input to initiate the events underlying central sensitization. One of the potential sources of nociceptive input speculated is muscle tissue. Several types of muscle abnormalities have been reported in FM patients, inflammatory infiltrates and moth-eaten fibres. Possible causes of such changes might be repetitive muscle microtrauma, which could contribute to post-exertional pain experienced by patients. In addition, prolonged muscle tension and ischaemia found in FM patients may also be a source of the nociceptive impulses.

From the analysis of phantom limb phenomena, the "normal feeling of ourselves" is subserved by neural processes in the brain. Once this "feeling" is established, the neural/brain processes can occur in the absence of inputs from the body. All the "body feeling" including pain we feel, can be felt in the absence of inputs (e.g. amputation) from the body. The best example of this is phantom limb pain. From this we can speculate that all experience in the body lies in neural (brain)
network. When central sensitization has occurred in chronic pain like FM, little additional nociceptive input is required to maintain the sensitized state. Thus, daily activities, which seem to be effortless, can contribute to the maintenance of the chronic pain state in FM. Microtrauma in muscles is not uncommon. Why some people develop FM and others do not? Other factors like psychological, genetic, and missing nutrients may play a role.

Role of Psychological Factors

Fibromyalgia patients are labeled as having a stress-related sleep problem for a long time; long enough to make a lot of people believe it is not a disease. They are also labeled as a group of people having psychological problems. Referring back to Yunus’s study on relationship between clinical features and psychological status in fibromyalgia, the clinical features of FM are independent of the psychological status and are more likely to be related to FM itself. However, pain severity may be influenced by psychological factors. In a study of rheumatoid arthritis, he studied 77 patients with rheumatoid arthritis compared with 67 healthy controls. He found that anxiety and stress aggravated the pain symptom in rheumatoid arthritis group, similar to the FM group. He concluded that any of the chronic diseases including cancer, will come up with similar results, pain severity is affected by anxiety and stress. Although research suggests FM patients have no different levels of magnesium compared to control group. A double-blind study examined the effectiveness and safety of magnesium (50 mg three times a day) and malic acid (200 mg three times a day) in 24 people with fibromyalgia. Malic acid is a fruit acid present in apples. After 4 weeks, the magnesium/malic acid combination was not more effective than placebo. The participants later received 6 months of the combination in larger doses (up to 300 mg magnesium and 1200 mg malic acid per day) for 6 months. This time, the combination resulted in a significant improvement in pain and tenderness; however, this portion of the study was open label, so the results, while promising, cannot be used as strong evidence that the combination was effective. Further RCT studies are needed.

2. Vitamin D

Vitamin D deficiency has been implicated in musculoskeletal pain and chronic pain. In a recent pilot study, low vitamin D level correlated with more severe pain and poor health. In a German study of over 900 patients, it shows strong inverse correlation between vitamin D level and duration and intensity of musculoskeletal pain. Though it is prudent not to extrapolate these results to FM patients, it does alert researchers that there may be relationship between vitamin D level and widespread pain in FM patients. Further studies are required to delineate the causal relationship.

Conclusions

It may still be too early to conclude fibromyalgia is indeed not a rheumatological disease. However, it also cannot indubitably say that fibromyalgia is a rheumatological disease as it seems to be a disease in the neural/brain network rather than in the musculoskeletal system. The etiology of FM is no doubt multifactorial. Researchers have been focusing at muscles for a long time, which apparently is just not the right tree. The mechanism discussed represents a hallmark of FM and other chronic pain syndromes. Better understanding of pain and the pathophysiology of chronic pain may provide new approaches and new insights for the prevention and treatment of fibromyalgia. The basic message is that fibromyalgia cannot be considered a primarily psychological disorder, but as in many chronic conditions, anxiety and psychological factors may play a role in who becomes disabled, and may even up-regulate the central nervous system changes that are the root cause of the problem.

Genetic Factors

Like other autoimmune diseases, genetic and environmental factors may play a role in FM. There is aggregation of FM in families. The mode of inheritance is unknown but very likely to be polygenic. There is also evidence that polymorphisms of genes in the serotonergic, dopaminergic and catecholaminergic systems may play a role in the etiology of FM.

Nutrients

1. Magnesium

It is affected by a number of hormones, for examples, insulin, and growth hormones. Low levels of magnesium can contribute to PMS, headaches, muscle cramping, and muscle spasms.
References