Etiology, Pathogenesis, Diagnosis, and Treatment of Fibromyalgia Syndrome

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Fibromyalgia is a common syndrome (FM) that is prevalent all over the world with different prevalence rates in each country. The etiology and pathogenesis of fibromyalgia are still unknown, unclear, and with uncertain pathophysiology. Diagnosis of fibromyalgia is not that easy because the disease is described as multifactorial, and very little information is known about the causes of the disease. Treatment of fibromyalgia is not totally curative; treatment aims to improve and alleviate the symptoms as easing pain, improving sleep, develop the physical function. The main problem
with fibromyalgia is not only difficulty of diagnosis or poor prognosis, but also the treatment is not adequate or satisfactory, so it is of great importance to educate the patients about their illness and giving them advice on how to limit the risk factors that aggravate the case, besides educating patients to use non-pharmacological strategies for better management.

Keywords: Fibromyalgia; joints; musculoskeletal; management.

1. INTRODUCTION

Fibromyalgia is a common syndrome (FM) that is prevalent all over the world with different prevalence rates in each country. Fibromyalgia syndrome (FMS) is regarded as chronic widespread musculoskeletal pain at multiple tender points, joint stiffness, and somatic and systemic symptoms (as mood disorders, fatigue, cognitive dysfunction, insomnia, psychiatric, tenderness, muscle stiffness, joint stiffness, anxiety, depression, general sensitivity and the inability to perform normal daily activities.) [1, 2]. Patients also show both hyperalgesia and allodynia; Symptoms severity, risk factors, and occurrence vary from case to another depending on various factors as sex (as females are more susceptible), childhood difficulties, age (middle and older ages are more susceptible), alcohol dependence/dependence, smoking, body mass index (high body mass index increase the risk), and history of past medical disorders. Also there were a great association with headaches, sleeping disorders, different pain, illness behavioral disorders, and depression [3].

The etiology and pathogenesis of fibromyalgia are still unknown, unclear, and with uncertain pathophysiology [4]. Although a new study claimed that autoimmunity may be involved in the pathogenesis of fibromyalgia. Classical autoimmune diseases are characterized by the presence of dual genes: Th-17 and Type I interferon; these genes are also present significantly in fibromyalgia gene expression. It is also noted that high levels of CD4+ T cells produced by circulating IL-17 and of serum cytokines such as TGF-beta, IL-6, IL-21 and IL-23 that promote Th17 differentiation, survival and expansion in fibromyalgic patients, therefore settling the gene expression signature and the presence of a continuing inflammation. This study also found two uncharacterized LncRNAs that aim, and regulate networks of genes that are included in numerous characteristics of fibromyalgia through their miRNA [5].

Diagnosis of fibromyalgia is not that easy because the disease is described as multifactorial, and very little information is known about the causes of the disease. Some physicians rely on diagnosing the major and main symptoms, and then fulfill an updating diagnostic criterion. Others do not align with a specific diagnostic criterion. Diagnosis until 2010 depended on 1990 ACR criteria, with at least three consecutive months of pain and pain points with digital palpation [6, 7]. Then 2010 ACR criteria were used with 2 new different parameters, the diffuse pain index, and the score measured on symptom severity scale [8].

The incidence of fibromyalgia in the world was estimated to be around 1%-2% (3.4% for women and 0.5% for men) [9, 10].

Treatment of fibromyalgia is not totally curative; treatment aims to improve and alleviate the symptoms as easing pain, improving sleep, develop the physical function [11]. A multi-approach treatment is needed to achieve the goal of treatment, including pharmacological medications, non-pharmacological strategies, and also through increasing knowledge and awareness of patients and their families about the disease and its management [12]. The main problem with fibromyalgia is not only difficulty of diagnosis or poor prognosis, but also the treatment is not adequate or satisfactory, so it is of great importance to educate the patients about their illness and giving them advice on how to limit the risk factors that aggravate the case, besides educating patients to use non-pharmacological strategies for better management.

2. EPIDEMIOLOGY OF FIBROMYALGIA WORLDWIDE

Studying epidemiology of fibromyalgia is an important measure to evaluate the effect of the disease on patients and their families, and also to measure the efforts to be exerted by the healthcare organizations to control and manage the disease. The prevalence of fibromyalgia has been assessed in some studies in different regions, and countries, and on four continents: Africa, Asia, the Americas, and Europe.
Unfortunately, there was only single study in Africa, in Tunisia [13].

The mean prevalence of fibromyalgia worldwide is 2.7 %, ranging from 0.4 % in Greece [14] to 9.3 % in Tunisia [13]. The mean rate of fibromyalgia is 3.1 % in the Americas, 2.5 % in Europe, and 1.7 % in Asia. In women, the mean prevalence of fibromyalgia is 4.2 % and in men 1.4 %, with a female-male ratio of 3:1.

Fibromyalgia is found to be more common in females as mentioned above, the reason for high incidence in females is that females experience more elevated levels of anxiety, elevated levels of depression, utilizing maladaptive coping strategies, changed and different behavior responding to pain, different input to the CNS and hormonal effects of the menstrual cycle; fibromyalgia prevalence in women ranges from 2 to 3% in the United States and other countries [15, 16]. The prevalence in adolescents was same as those in adults in many studies. Among the patients referred to a pain clinic, more than 40% met the criteria settled for fibromyalgia [17].

3. ETIOLOGY AND PATHOGENESIS OF FIBROMYALGIA SYNDROME

Fibromyalgic patients appear to have a problem in the brain with processing of pain. Patients frequently become hypersensitive to the perceiving of pain. The constant increasing stength of pain is also associated with various psychological problems. The dysfunctions noted in fibromyalgia consist of high levels of the excitatory neurotransmitters as glutamate and substance P, lower levels of serotonin (5-HT) and norepinephrine (NEP), dysregulation of dopamine, prolonged development of pain sensations, and changes in the activity of brain opioids.

Even in present times, the etiology and pathogenesis of fibromyalgia is not clearly and fully understood, a lot of ambiguity is still surrounding this disease and the definite causes are still under study for further investigations.

There are some major factors that are thought to be the main causes of fibromyalgia (FM) like dysfunction of central nervous system, autonomic nervous system, neuroendocrine system, immune system, hormones, chemical neurotransmitters, psychiatric factors, genetic predisposition, stress, and other factors. Patients identify noxious stimuli as painful at low levels of physical stimulation compared to healthy controls. And promptly repetitive short noxious stimuli to fibromyalgia patients, they experience higher than normal increases in the perceived strength of pain. There is a deficiency in the endogenous analgesic chemicals in patients affected with fibromyalgia. Also differences in activation of areas of the brain which are pain-sensitive areas by functional neuroimaging techniques were observed [18].

Central nervous system: central sensitization is the main and only biopsychosocial explanation for chronic widespread pain in patients with fibromyalgia and chronic fatigue syndrome [19]. Central sensitization is the increased response to stimulation mediated by CNS. Nerve activity, enlarged receptive fields, and increased stimulus transmitted by afferent fibers are the causes of central sensitization [20]. The “windup” is a significant phenomenon included which reveals the increased excitability of spinal cord neurons. After painful stimuli, consequent stimuli with the same strength are perceived as stronger stimuli and it happens excessively in fibromyalgic patients [21]. This phenomenon expresses the neuroplasticity and is mediated by N-methyl-D-aspartate (NMDA) receptors which are located in the postsynaptic membrane in the dorsal horn of the spinal cord [22, 23].

Autonomic Nervous System: fibromyalgia is recognized as stress-related disorder; it is easy to realize that the hypothalamic-pituitary-adrenal (HPA) axis is involved. Diverse studies showed increased cortisol levels, mainly in the evening, associated with a disrupted circadian rhythm. Also these patients showed increased values of adrenocorticotropic hormone (ACTH) both basally and as a reaction to stress, most likely as a result of a chronic insufficient secretion of corticotropin-releasing hormone (CRH). Those changes are probably related to low levels of 5-HT seen in patients with fibromyalgia, because serotoninergic fibers control the HPA axis function [24-26].

4. DIAGNOSIS AND SYMPTOMATOLOGY OF FIBROMYALGIA SYNDROME

Basically, diagnosis has been achieved by relying on 1990 ACR criteria of widespread pain with at least three consecutive months of pain and pain points with digital palpation. Now we use 2010 ACR criteria, with 2 new different
parameters, the diffuse pain index, and the score measured on symptom severity scale [6].

The main three symptoms for detecting fibromyalgia are the widespread musculoskeletal pain, debilitating fatigue, cognitive behavior, and other symptoms. The main complaint of fibromyalgic patient is widespread bilateral musculoskeletal pain, including both the lower and upper parts of the body; the pain maybe localized in the neck and shoulders. The complaint can extend to be of joint pain also not only muscle pain. Another major symptom and frequent complaint of fibromyalgia is fatigue, especially early in the morning. Even small normal daily activities worsen the pain and fatigue, although inactivity for long time also aggravates the symptoms, so it is difficult for the patient to carry out the daily life. Patients also suffer from light sleeping, waking up a lot in the night, and waking up with stiffness in the body. They hardly feel refreshment after sleeping even if they sleep 8 or 10 hours per day. Patients also suffer from “fibro fog” which is the cognitive dysfunction; patients have problems with tasks that need rapid changes in thoughts and they also endure low attention.

Some patients often endure paresthesias in both arms and both legs, and also exhibiting gastrointestinal manifestations (as irritable bowel syndrome (IBS)), and gastroesophageal reflux disease (GERD)). Patients also complain of some minor symptoms as dyspnea, dysphagia, dry eyes, and palpitations. At diagnosis, thirty to fifty percent of fibromyalgic patients suffer from anxiety and/or depression, and over than half of the patients have migraine and different types of headaches.

The 1990 ACR criteria included two main classifications, symptoms of pain, exist on both sides of the body and above and below the waist, and Physical discoveries of minimum 11 of 18 defined and clear tender points: Suboccipital muscle insertion bilaterally, anterior aspect of C5 to C7 intertransverse spaces bilaterally, mid upper border of trapezius bilaterally, origin of supraspinatus muscle bilaterally, second costochondral junctions bilaterally, 2cm distal to the lateral epicondyles bilaterally, upper outer quadrants of buttocks bilaterally, greater trochanteric prominence bilaterally, and medial fatpad of the knees bilaterally. The pressure suitable for detecting those tender points must be equal to 4 kg/cm². If both criteria of the classifications are met the patient is said to have fibromyalgia.

The 1990 ACR criteria had many limitations as difficulty to know how to examine tender points, performing the exam incorrectly, limited validity of clinical pain, and difficulties of applying pressure algometry in primary health care; a number of symptoms which were not considered in the past were increasingly appreciated as key symptoms for fibromyalgia, and lastly little room was left for variation among fibromyalgia patients. So 2010 ACR criteria was developed where nonrestorative sleep (NRS), fatigue, and cognitive dysfunction have almost equal weight for diagnosis and including depression, anxiety, irritable bowel syndrome (IBS), fatigue, muscle weakness, Raynaud’s, ringing in ears, and other secondary fibromyalgia symptoms; as it also the first to introduce the idea of widespread pain, then 2011 modified ACR criteria followed by 2016 ACR criteria. Besides, some authors think that the role of pain in fibromyalgia has grew from the peripheral allodynia of 1990 ACR until the central pain perception of 2016 ACR [27-29].

Until now there is no accurate diagnostic tool to measure any biomarker that helps in identifying the disease, but some new approaches is studied in order to find out new parameters and biomarkers for diagnosing fibromyalgia. One of these approaches is made through a cross-sectional study which worked on exploring if Mu opioid receptors on lymphocyte membranes can be considered as a fibromyalgic biomarker or whether it should be a common marker for different pain syndromes [30]. This approach is based on the role of opioids and the immune system, as the use of opioids can interact with the endogenous antinoceptive systems [31]. Studies have shown that morphine induces T cells to release T-lymphocytes cytokines, through improving the differentiation of B-lymphocytes [32]. Also, Mu agonists increase production of IgM and IgG by B cells. Morphine activates Mu and this aid in regulating macrophage functions, including production of nitric oxide and phagocytosis [33].

As diagnosis of FM is still difficult and frequently missed due to ambiguity of symptoms, the American College of Rheumatology preliminary diagnostic criteria are used nowadays for good prognosis, the criteria are: widespread pain index (WPI) is 7 and symptom severity (SS) scale score is 5, or WPI equals 3 to 6 and SS scale score of 9, symptoms have been present at a
constant level for three consecutive months, and the patient does not show any other disorder that would otherwise explain the pain [16].

WPI: note the number of regions in and how many regions the patient had pain during the previous week. The score is between 0 and 19. Shoulder girdle, left hip (buttock, trochanter), left jaw, left upper back shoulder girdle, right hip (buttock, trochanter), right jaw, right lower back upper arm, left upper leg, left chest neck upper arm, right upper leg, right abdomen lower arm, left lower leg, left lower arm, right lower leg, right.

SS scale score: Fatigue, waking tired and cognitive symptoms. For the each of the three symptoms, specify the severity level over the previous week using the subsequent scale: 0 no problem, 1 slight or mild problems, generally mild or intermittent, 2 moderate, significant problems, often present and/or at a moderate level, 3 severe: persistent, continuous, life-disturbing problems. Considering somatic symptoms in general, indicate whether the patient has: 0 for no symptoms, 1 a few or mild symptoms, 2 a moderate number of symptoms; 3 for many symptoms. The SS scale score sums the severity of the 3 symptoms (fatigue, waking tired or unrefreshed, cognitive symptoms) plus the severity of general somatic/physical symptoms. Finally, the score is between 0 and 12.

Poor prognosis of fibromyalgia may also refer to high levels of stress, long time of disease, alcohol or drugs physical dependence, non-treated anxiety/depression, avoidance of work, and functional impairment.

5. TREATMENT OF FIBROMYALGIA SYNDROME

Treatment of fibromyalgia is never curative; treatment approaches aim mainly to improve, alleviate, and control some of the symptoms as easing pain, improving sleep, develop the physical function, educating the patient, and exercise.

Some mild cases can be managed by only non-pharmacological treatment. But in most cases, it is recommended that the patient continue non-pharmacological treatment along with pharmacological medications. Certain antidepressants and anticonvulsants are approved to effectively treat fibromyalgia. Tricyclic antidepressant medications are used as amitriptyline and other selective serotonin reuptake inhibitors (SSRIs), duloxetine and milnacipran and other norepinephrine reuptake inhibitors (SNRIs), and also Cyclobenzaprine are found to be effective in managing the symptoms of fibromyalgia. Examples of effective anticonvulsants are gabapentin and pregabalin. A therapy approved by the US Food and Drug Administration (FDA) include three drugs, pregabalin, duloxetine, and milnacipran.

Exercise regimen is critical as a non-pharmacological treatment in managing the symptoms of fibromyalgia. Cardiovascular exercise is recommended for fibromyalgic patients as it aids the pain and restores sleep. Optimum cardiovascular exercise consists of aerobic exercise with minimum time of 30 minutes, three times a week [34, 35].

Fibromyalgic patients should know well about their disease before taking any medications. Patients’ knowledge should include some key elements as making sure that the patient perceives fibromyalgia as a real disease, to know that there is a role of stress and mood disorders affecting manifestations of the disease and therapy success so patients should learn stress reducing programs and relaxing practices (around 30% of patients affected with fibromyalgia had depression at the time of evaluation and the lifetime occurrence is 74%, so treating depression is of great value in therapy success), and sleep restore as it is an important part of managing of fibromyalgia and obtaining treatment of sleeping disturbances [36]. Also fibromyalgic patients found to produce high levels of free radicals which contribute to their antioxidants deficiency and inability and thus oxidative stress. ROS affects the central nervous system especially is because of its high lipid content. Consequently, using antioxidants and vitamins as a part of the therapy may help in management and regression of the disease [37].

6. CONCLUSION

Fibromyalgia is a syndrome characterized by chronic widespread musculoskeletal pain and the main manifestations are tenderness, muscle stiffness, joint stiffness, insomnia, fatigue, mood disturbances, cognitive dysfunction, anxiety, depression, general sensitivity and the inability to perform normal daily activities. Diagnosis of FMS is difficult to achieve and evaluate by physicians as the etiology and pathogenesis is still ambiguous and indefinite. More studies should be carried on the chemical state of the brain to know the pathogenesis and causes; this will
make the diagnosis easier and will help scientists to set defined criteria for evaluation of the symptoms. In addition, prospective studies will offer more non-pharmacological strategies to help in improving treatment outcomes of the disease.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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