Review Article

Fibromyalgia progression and association with other diseases and inheritance with management practices in humans

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Abstract

Fibromyalgia is a widespread pain disorder characterized by chronic, diffuse pain, about 1 to 5% around world. While more prevalent in women and adults, it can also manifest in children and adolescents. The specific pathophysiology of fibromyalgia remains unclear, but it is associated with neuronal over sensitization, reduced conditioned pain modulation, cognitive dysfunction, memory loss, and impaired information processing. It has now been categorized as a somatic symptom disorder. This study aimed to investigate fibromyalgia, focusing on its potential hereditary connections and management practices. A key pathophysiological aspect of fibromyalgia is central sensitization, marked by increased functional connectivity with pre-receptive brain areas, decreased connectivity with antinociceptive areas, and alterations in central nervous system neurotransmitters, also in size and shape of specific brain areas. Fibromyalgia is not directly inherited from parents to offspring, it does exhibit a tendency to cluster within families. The serotonin transporter gene, characterized by single nucleotide polymorphism with "S" (short) allele, is more prevalent in individuals with fibromyalgia and psychological distress. In conclusion, fibromyalgia is a widespread pain disorder with a substantial impact on the central nervous system, resulting in significant disability and an elevated risk of chronic diseases. Early diagnosis and intervention can minimize the impact of fibromyalgia. Physical therapy and non-drug therapies should be customized for each patient. The FDA has approved three drugs including pregabalin, duloxetine, and milnacipran for fibromyalgia treatment.

Keywords: Fibromyalgia, Single nucleotide polymorphism, Gene, Physical therapies, Drugs, Pregabalin, Duloxetine, Milnacipran.

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Introduction

Since the 1800s, fibromyalgia (FM) has undergone various denominations, with William Richard Gowers coining the term "fibrositis" in 1904 to describe the condition. Predominantly affecting women in adulthood, FM can also manifest in

children and adolescents, with a prevalence ranging from 5-12 percent depending on the studied population [1]. In research not utilizing tender points as a criterion, the female-to-male ratio is approximately 3:1. The American College of Rheumatology (ACR) classification criteria for fibromyalgia, established in the 10th revision of the International Classification of Diseases (ICD) in 1994, required the presence of multiple tender points through physical examinations and continuous generalized pain. In 2010, the ACR introduced initial diagnostic criteria that deviated from tender points, allowing for less pain, and incorporating patient-reported cognitive impairments and somatic symptoms [2-5]. The etiology and underlying pathologies influencing the development of fibromyalgia remain unknown, making it a prominent subject in pain analysis. The condition is associated with a spectrum of related and overlapping issues, often referred to as severe overlapping pain conditions or functional pain illnesses, depending on the healthcare practitioner consulted

Fibromyalgia, a prevalent pain disorder characterized by chronic widespread pain, is estimated to impact 1 to 5% of the population [6]. Physical and psychological symptoms associated with the condition include difficulties in sleep, fatigue, stiffness, anxiety, cognitive dysfunction, and memory loss [7]. While the specific pathophysiology remains unknown, fibromyalgia is believed to be linked to neuronal over sensitization and diminished conditioned pain modulation (CPM), exacerbating cognitive dysfunction and impaired information processing. The syndrome results in heightened connectivity across brain regions involved in pain cognition and alertness, posing challenges for medicinal treatment. Fibromyalgia often coexists with other chronic disorders, and untreated cases can lead to adverse outcomes [8]. Fibromyalgia is a prevalent chronic pain condition affecting approximately 2% of the general population. Unlike autoimmune or inflammation-based disorders, fibromyalgia is intricately connected to the nervous system, as indicated by research findings. As defined by the American College of Rheumatology (ACR), fibromyalgia involves widespread pain lasting at least three months, and individuals with this condition typically exhibit 11 to 18 tender points across various body parts, such as the legs, shoulders, neck, arms, hips, and back. Pressing these tender points elicits severe pain in fibromyalgia patients. While the complete pathophysiological mechanism of fibromyalgia remains elusive, earlier studies have highlighted a familial tendency, emphasizing the role of genetic factors in the ailment's etiology [9] Intriguingly, a subgroup of severe fibromyalgia has been identified, characterized by physiological distress, which, in certain studies, appears independent of pain severity. A potential biomarker for fibromyalgia, deficits in diffused noxious inhibitory control (DNIC), has been utilized to explore the influence of depression on the condition. Researchers found that fibromyalgia patients with concurrent depressive symptoms were more likely to experience heightened pain severity compared to those without such symptoms.

Current treatment strategies encompass a range of pharmacological and non-pharmacological interventions, yet the absence of a definitive understanding of the etiology of FM hinders the pursuit of effective therapeutic solutions [10, 11]. Studies suggest that fibromyalgia patients with depressive symptoms may exhibit deficiencies in central pain mechanisms. Additionally, disturbances in pain processing in fibromyalgia are believed to be linked to central augmentation, manifested as increased brain processing of both harmful and normal stimuli, interpreted as central sensitization a deficit

in pain inhibitory mechanisms. Given serotonin's well-established role in pain perception, emotional regulation, and attention, hypersensitivity in fibromyalgia has also been associated with serotonergic dysfunction [12]. This study aimed to explore the severity of fibromyalgia and its associations with various disorders, while also examining management practices.

Classification of fibromyalgia

The term "primary pain" was introduced in the latest definition due to the unspecified etiology of various forms of chronic pain. The eleventh International Classification of Diseases revision committee selected this term, recognizing its appropriateness from a non-specific perspective [13]. The presence of allodynia and spontaneous pain elucidates sixteen distinct dysfunctions in pain modulation, indicating that fibromyalgia is a painful condition characterized by heightened pain sensitivity and a reduction in pain inhibitory controls [14].

There is a common misconception that fibromyalgia is an underlying depression or falls within the affective spectrum. The lifetime prevalence of depression in individuals with fibromyalgia varies from 40 to 80 percent, dependent on the diagnostic tools and criteria employed [15]. However, it's crucial to note that not every fibromyalgia patient experiences depression, and conversely, not every individual with a depressive disorder endures persistent widespread pain. The association between fibromyalgia and depressive disorders can be better understood by considering symptom overlap, such as shared biological factors (e.g., genes) and psychological mechanisms (e.g., childhood adversities) According to German criteria, fibromyalgia and (masked) depression are distinct entities and should not be interchangeably considered [16, 17].

The identification of small-nerve-fiber pathology in certain patients led to the assertion that fibromyalgia can be categorized as a neurological disorder, often referred to as 'small fiber neuropathy. However, it's important to note that not every patient meeting the fibromyalgia criteria exhibits small fiber pathology findings [16]. Moreover, in many chronic pain conditions and other unrelated disorders (e.g., amyotrophic lateral sclerosis and postural tachycardia syndrome), minor pathological findings have been noted, such as decreased intraepidermal nerve fiber density (IENFD) [16, 18].

The absence of a distinct pathology and the observed correlation between fibromyalgia symptoms and psychosocial stress have led some psychosomatic medical experts to introduce the term "persistent somatoform pain disorder" (ICD-10 F45.4). Notably, 60-80 percent of fibromyalgia patients align with diagnostic criteria indicating psychosocial stress and emotional conflicts as potential contributors to or exacerbators of fibromyalgia symptoms [19]. However, it is crucial to underline that, according to the German guideline, fibromyalgia and persistent somatoform pain disorder are distinct entities and should not be used interchangeably [16].

There has been a shift towards categorizing fibromyalgia under the umbrella of Somatic Symptom Disorder (SSD). The American Psychiatric Association updated the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), replacing the category of "pain disorder" with SSD. According to the revised criteria, when individuals experience chronic (i.e., lasting more than 6 months) somatic symptoms that are distressing or significantly disrupt daily life (criteria A and C), and exhibit excessive or disproportionate symptom-related feelings, thoughts, and behaviors (criteria B), a diagnosis of SSD may be considered.

Recent literature has classified fibromyalgia as an SSD in various publications [20].

Fibromyalgia (FM) is a complex condition marked by chronic pain, fatigue, sleep disturbances, and a range of diagnostically and therapeutically challenging symptoms, emphasizes the necessity for a holistic and integrated approach that considers psychological factors affecting patient responses. They highlighted the significant impact of environmental factors such as climatic variations, air pollution, electromagnetic field exposure, physical and emotional traumas, dietary patterns, and infections on the manifestation and severity of symptoms. They advocate for personalized, holistic treatment that addresses patients' psychological and environmental sensitivities through tailored dietary and stress management strategies. Additionally, they call for further research into the intricate interplay of environmental, biological, and psychological factors influencing FM to develop more effective individualized treatments, ultimately improving patient care and outcomes [21].

Fibromyalgia physiology and heredity

The predominant pathophysiological characteristic of fibromyalgia is deemed to be central sensitization, which involves an augmented functional connection with pre-receptive brain areas, reduced connectivity with the antinociceptive area, and concurrent alterations in central nervous system (CNS) neurotransmitters, as well as changes in the size and structure of certain brain areas. Notably, a subset of individuals exhibited amelioration in the cardinal symptoms of fibromyalgia when these CNS abnormalities were addressed through pharmacologic or nonpharmacologic interventions known to modulate CNS function. This notion of fibromyalgia as a brain disorder gained support through the observed correlation between these interventions and improvements in functional, chemical, and structural neuroimaging outcomes [14].

Fibromyalgia may manifest independently, but it is often perceived as a stereotyped, maladaptive biological response of the body to the cumulative impact of physical or mental stress, particularly in individuals genetically predisposed to the condition [22, 23]. This syndrome is associated with both psychological and musculoskeletal issues, which can contribute to unfavorable outcomes. Additionally, fibromyalgia can be triggered by infections. Furthermore, its occurrence tends to be higher in individuals with chronic health conditions in general [24].

Multiple familial studies suggest that genetic susceptibility is likely to be a contributing factor, and the mode of transmission is estimated to be polygenic. Among the genes studied, those associated with neurotransmitters are particularly noteworthy. For instance, the serotonin transporter gene exhibits a single nucleotide polymorphism, with the allele "S" (short) being more prevalent in individuals with fibromyalgia and psychological distress. Other genes implicated in this context include the catechol-O-methyltransferase gene, the dopamine D4 receptor gene, and the HLA-region [25-31].

Fibromyalgia (FM) is not directly inherited from parents to offspring. Nevertheless, it does seem to cluster within families. The likelihood of developing FM is significantly higher in families where individuals have FM compared to families with no prior cases of FM. DNA studies involving FM patients and those with a family history of chronic pain syndrome suggest that the genetic basis of FM involves several genes crucial in central nervous system pain response, depression, and anxiety. This sheds light on why certain

antidepressants can be effective in alleviating FM pain.

Fibromyalgia related disorders and management

The pathophysiology of fibromyalgia is underpinned by changes in the Central Nervous System (CNS) [32, 33] altering the processing of afferent sensory information, collectively termed as 'Central Sensitization. Long-term psychological or physical distress is a common trigger for these changes in central sensitization [34]. These alterations result in an amplification of stimulus intensity, transforming stimuli that are typically painless into perceived painful experiences. Additional effects include disruptions in sleep cycles, characterized by an inability to achieve deep, restorative stage IV non-REM sleep, and disturbances in the hypothalamic-pituitary axis, manifesting as altered serum cortisol levels, reduced 24-hour urinary free cortisol, and blunted cortisol responses to dynamic testing [35]. Ongoing research is investigating the impact of genetic polymorphisms on CNS serotonergic and catecholaminergic processes, revealing a potential enhancement in the likelihood of developing fibromyalgia [36]. Clinical fibromyalgia is often triggered, irrespective of any genetic predisposition. A survey of 2,596 fibromyalgia patients in North America showed that 79 percent reported plausible triggering events at the onset of their disease [37] Similarly, in an Australian public hospital fibromyalgia clinic, 88.7 percent of patients indicated recognized triggers [38]. In susceptible individuals, a physical or psychological stressor can activate a persistent, maladaptive stress response, which then mediates the central alterations observed in fibromyalgia [39].

Several studies have demonstrated the presence of pain symptoms associated with Autoimmune Thyroid Diseases (AITD) and Chronic Lymphocytic Thyroiditis (CLT) in patients diagnosed with fibromyalgia syndrome (FMS) based on the American College of Rheumatology (ACR) classification criteria. The occurrence of fibromyalgia in individuals with AITD is reported to be in the range of 30% to 40%. Notably, Suk and colleagues approached the investigation from an endocrinological perspective rather than a rheumatological one, revealing a statistically significant difference with a prevalence of 19% for thyroid autoimmunity in fibromyalgia patients compared to 7% in controls. Research suggests that the chronic widespread pain observed in fibromyalgia has a neurogenic origin. It is proposed that imbalances in neurochemicals and the central nervous system (CNS) contribute to a 'central amplification' of pain perception characterized by allodynia and hyperalgesia. Neuroimaging studies support this notion, indicating that fibromyalgia is associated with abnormal processing of pain stimuli in the CNS. Magnetic Resonance Imaging (MRI) studies of the brain show that fibromyalgia patients exhibit a pain response to a much lower stimulus intensity than that required for healthy controls [40].

Fibromyalgia can lead to significant disability, but early diagnosis and intervention can help minimize its impact. Fibromyalgia patients often present with additional chronic diseases, underscoring the importance of precise clinical assessment and the management of exacerbating factors. A comprehensive, patient-centered, multidisciplinary management approach is crucial. Patients benefit from education and self-management strategies. Tailored physical therapy and other non-drug therapies are essential for individualized care. While medications can help suppress symptoms, active rehabilitative measures should take precedence in treatment [41]. The FDA has approved three drugs for the treatment of fibromyalgia: pregabalin, which is a gabapentinoid acting through the blocking

of calcium channels, and duloxetine and milnacipran, both serotonin-noradrenaline reuptake inhibitors. However, various types of antidepressants are also employed for treating different chronic pain conditions, including fibromyalgia, with varying levels of evidence regarding their effectiveness [42, 43].

Future prospects

Management strategies are urgently needed to completely cure the disease. If left untreated, the disease can affect heart muscles, leading to complications and potentially causing heart attacks. In the future, it is imperative to thoroughly explore the disease and address its root causes to achieve a complete cure.

Conclusion

In conclusion, fibromyalgia represents a prevalent pain disorder worldwide. Timely intervention is imperative, as untreated cases can give rise to severe complications. The condition may manifest spontaneously or be triggered by physical or mental stress. Furthermore, there is a genetic component, with mutations in the serotonin transporter gene playing a role in its propagation. Fibromyalgia impacts the central nervous system, leading to significant disability and an increased risk of developing chronic diseases. Patients should receive non-drug therapies, including physical therapy, while medications can help alleviate symptoms. Recognizing early signs, particularly stress and workload, is crucial. Additional research is essential to gain a comprehensive understanding of fibromyalgia, thereby mitigating potential complications.

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Abbreviations

FM (Fibromyalgia), CNS (Central nervous system), FDA (Food and drug administration), SSD (somatic symptom disorder), CPM (conditioned pain modulation), ACR (American College of Rheumatology)

Authors' contributions

All authors contributed equally to the manuscript.

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