European Journal of Neurodegenerative Diseases
ISSN 2974-6345 / 2023 vol. 12, ISSUE N. 3, September-December

FIBROMYALGIA: AN INFLAMMATORY DISEASE CHARACTERIZED BY WIDESPREAD PAIN, SLEEP DISTURBANCES, FATIGUE, AND MEMORY PROBLEMS

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ABSTRACT

Fibromyalgia affects 2–7% of the population and 12 million people in the United States and has a higher incidence in females. The disease is likely caused by interactions between the sympathetic nervous system, neurotransmitters, external stressors, and hormones. Increased levels of immunologic signaling molecules have been documented in fibromyalgia, implicating immune dysfunction in this disorder. The most common symptoms that occur are skin sensitivity, abdominal pain (the most common), chronic fatigue, headache, disrupted sleep, cough, upper airway obstruction, hypoxia, breathing dysfunction, depression, epidemic neuro-myasthenia, diffuse idiopathic multifocal pain syndrome, cognitive dysfunction, and lowered quality of life. In addition, fibromyalgia may occur together with other diseases such as autoimmune disorders and cerebral diseases. In this article, we discuss the roles of the immune system and inflammation in the widespread pain, sleep disturbances, fatigue, and memory problems that occur in fibromyalgia.

KEYWORDS: *fibromyalgia, inflammation, immune system, cytokine, chemokine*

INTRODUCTION

Fibromyalgia is an inflammatory disease present in 2-7% of the population that is characterized by chronic and widespread musculoskeletal pain and neurological problems such as fatigue, sleep disturbances, memory problems, and depression (1). The first published paper on fibromyalgia appeared in 1990 with the American College of Rheumatology classification criteria (2). The disease mostly affects women (3), can occur at any age, and is characterized by trigger points where multifocal pain can be activated. The symptoms of this complex and heterogeneous disorder can be debilitating for the patient. However, not all fibromyalgia patients are depressed and not all depressed people suffer from chronic bodily pain.

The exact causes of fibromyalgia are not known, although it is thought that multiple genetic and environmental factors may contribute to the development of the disease (4,5). It seems that subjects with a healthy lifestyle, practicing regular physical activity, healthy sleep habits, and correct nutrition, can counteract the onset of the disease. The most accredited hypothesis for the onset of fibromyalgia is chronic pain correlated with an impairment in the processing of the pain stimulus. It is classified as a central sensitivity syndrome, with amplified pain mediation in the central nervous system (CNS) (6,7). The guidelines dictated by the International Association for the Study of Pain (IASP) and the Canadian Pain

Received: 26 August, 2023
Accepted: 28 September, 2023

2974-6345 (2023)

Society help to formulate adequate diagnosis and therapy indications for this complex and heterogeneous inflammation-based disorder (8,9).

In recent decades, there has been much progress in understanding the epidemiology, diagnosis, and therapy of fibromyalgia, although many points remain controversial. Given that the incidence of the disease is rising, fibromyalgia should no longer be a mysterious disease that is unknown to the population. Moreover, it is now known that it is an inflammatory pathology with a therapeutic strategy aimed at reducing symptoms and restoring the physiological state. Symptoms of the disease can persist for years, often debilitating the patient and reducing their quality of life. The diagnosis can remain difficult, but today, guidelines are in place to distinguish fibromyalgia from other pathologies which present with similar symptoms.

DISCUSSION

Psychiatric comorbidities have a high level of prevalence in fibromyalgia and are linked to a poorer clinical profile, with psychosocial distress and negative emotional states aggravating the disease (10). Additionally, population-based studies have shown an association between trauma, abuse, or the loss of a parent sustained in early life, with the development of chronic pain and fibromyalgia in later life (11,12). Fibromyalgia can be triggered by psychological stress factors, chronic fatigue, or even viral infections. Symptoms of the disease may be similar or overlap with other chronic pain disorders, such as systemic lupus erythematosus, osteoarthritis, and rheumatoid arthritis (13) (Table I). Dysregulated neurotransmitter levels with the involvement of the hypothalamic-pituitary axis may be responsible for chronic pain with fatigue, memory problems, and mood and sleep disturbances (14). Therefore, psychological and/or psychiatric disorders may aggravate the disease, causing chronic pain. The pain can improve with physical exercise while avoiding taking drugs. Aerobic and muscle strengthening exercises have been seen to lower pain levels and increase well-being in fibromyalgia patients, with stretching also providing beneficial results to overall quality of life (15). Together, these forms of physical activity are beneficial for reducing symptoms of depression as well (16,17).

Table I. *Fibromyalgia symptoms.*

Central nervous system (CNS):	anxiety, depression, headache, insomnia, dizziness, cognitive deterioration, memory impairment.
Muscles:	muscle pain, fatigue, contractions
Joints:	stiffness, mandibular joint dysfunction
Kidneys:	urinary problems and/or interstitial cystitis
Eyes:	tiredness, vision problems
Skin:	tingling, hypersensitivity
Chest:	pain
Stomach:	nausea
Female reproductive system:	accentuated menstrual pain, dysmenorrhea

It seems that fibromyalgia involves the expansion of nociceptors and the hyperexcitability of central neurons, leading to chronic pain and inflammation (18). Pain can occur throughout the body, but there are nine pairs of common trigger points for pain which are hypersensitive to the touch and can be determined by a thorough medical examination (19) (Table II). Patients may present with diffuse or multifocal neuropathic pain accompanied by widespread pain, sleep disturbances, fatigue, and memory problems that characterize fibromyalgia. In addition, the disease presents inflammation, hyperalgesia, cognitive dysfunction, allodynia, and pain at specific points accompanied by stiffness, and fatigue.

Table II. *Some classic trigger points that are present in fibromyalgia.*

- Occiput: lower point of the skull where the trapezius muscle inserts.
- Lower cervical: anterior part of the cervical vertebrae (C5-C7).
- Trapezoid muscle: midpoint of the upper border.
- Supraspinatus: above the medial border of the spine of the scapula.
- Lateral epicondyle: two centimeters below the lateral part of the elbows.
- Gluteus: extreme upper part of the muscle.
- Knees: fat body anterior to the joint.
- Greater trochanter: below and behind the union of the femur with the hip.

Cytokines are modulators of the immunological response that can also mediate the inflammatory state, pain, and tissue dysfunction. In fibromyalgia, both cytokines and chemokines, cellular chemoattraction proteins, appear to be involved in the inflammatory process of the disease (20) (Fig.1). It has been reported that patients with renal cell carcinoma treated with T cell growth factor (IL-2) immunotherapy presented classic signs of fibromyalgia with pain, cognitive dysfunction, and sleep disturbances which were also caused by increased IL-1 induced by IL-2 (21).

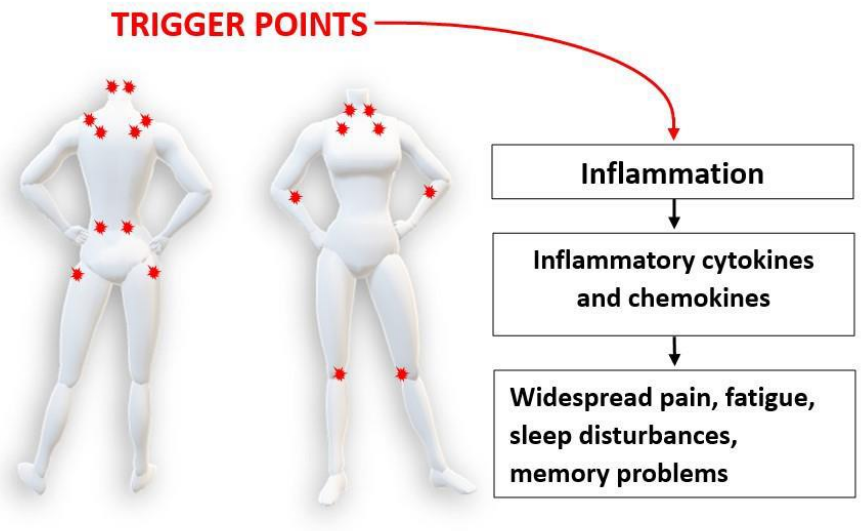

Fig. 1. *Trigger points in fibromyalgia cause hyperexcitability of the central nervous system (CNS), leading to chronic pain and inflammation, which are mediated by inflammatory cytokines and chemokines. Widespread pain, sleep disturbances, fatigue, and memory problems are symptoms that characterize fibromyalgia.*

Chemokines can attract inflammatory cells, and these chemotactic proteins can participate in synaptic transmission and the pain-inflammatory process. Pro-inflammatory cytokines such as IL-1, TNF, IL-2, IL-6, IL-8, IL-12, and IFN, could play an important role in the pathogenesis of fibromyalgia, as in neuropathic pain, where there is a dysregulation of these proteins and a disrupted balance between pro-inflammatory and anti-inflammatory cytokines such as IL-10, IL-4, IL-13, and TGF-β (22). IL-1 is an inducer of other pro-inflammatory cytokines such as TNF and stimulates the arachidonic acid cascade in the brain with an increase in prostaglandin E2 (PGE2), a prostaglandin involved in inflammation and pain (23).

Therapy for fibromyalgia may include neurotransmitter depressants, such as serotonin and norepinephrine reuptake inhibitors, anti-inflammatory drugs, the use of cannabinoid compounds, or a combination of these drugs. In our experience, cannabinoid therapy has proved to be effective in alleviating diverse symptoms in many cases of fibromyalgia (unpublished data). Therapy can be either pharmacological or non-pharmacological, or a combination of both, and can be executed by a rheumatologist, neurologist, immunologist, or by a team that includes all three specialists (Table III).

Table III. *Treatments to improve fibromyalgia.*

- Stress management: reduce stress, a potential cause of pain
- Patient education to improve coping skills
- Use of medications to improve sleep
- Use of medications to relieve pain
- Meditation and deep breathing exercises
- Ensure a regular, sufficient sleep cycle
- Aerobic exercises
- Routine physical exercise
- Improve physical fitness
- Cognitive therapy
- Thermotherapy and massage therapy

Fibromyalgia has numerous comorbidities, but inflammation, pain, and fatigue play a predominant role in this pathology. Recent studies report that the disease is also mediated by immune factors such as cytokines, chemokines, lipid mediators, and oxidative stress (24,25). However, further research is necessary to establish the precise immunological, pain, and inflammatory mechanisms that mediate the pathological state of the patient with fibromyalgia.

CONCLUSIONS

Fibromyalgia, a disease with various symptoms such as widespread musculoskeletal pain, sleep disturbances, fatigue, and memory problems, is an immune disorder mediated by inflammatory molecules released by cells of the innate and acquired immune systems. The disease is characterized by chronic inflammation, where the immune system is disrupted by elevated levels of pro-inflammatory proteins. In conclusion, inflammatory cytokines and chemokines may play an important role in the pathophysiology of fibromyalgia, and further research is needed to focus on the specific inhibitors of these mediators.

Conflict of interest

The author declares that they have no conflict of interest.

REFERENCES

1. Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis & Rheumatism*. 1995;38(1):19-28. doi:https://doi.org/10.1002/art.1780380104
2. Wolfe F, Smythe HA, Yunus MB, et al. The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis and rheumatism*. 1990;33(2):160-172. doi:https://doi.org/10.1002/art.1780330203
3. Cooksey R, Choy E. Exploring gender differences, medical history, and treatments used in patients with fibromyalgia in the UK using primary-care data: a retrospective, population-based, cohort study. *The Lancet Rheumatology*. 2022;4:S20. doi:https://doi.org/10.1016/s2665-9913(22)00296-x
4. Bradley LA. Pathophysiology of Fibromyalgia. *The American Journal of Medicine*. 2009;122(12):S22-S30. doi:https://doi.org/10.1016/j.amjmed.2009.09.008
5. Jones KD, Gelbart T, Whisenant T, et al. Genome-wide expression profiling in the peripheral blood of patients with fibromyalgia. *Clinical and experimental rheumatology*. 2016;34(2 Suppl 96):S89-98.
6. Staud R. Abnormal Pain Modulation in Patients with Spatially Distributed Chronic Pain: Fibromyalgia. *Rheumatic Disease Clinics of North America*. 2009;35(2):263-274. doi:https://doi.org/10.1016/j.rdc.2009.05.006
7. Mezhov V, Guymer E, Littlejohn G. Central Sensitivity and Fibromyalgia. *Internal Medicine Journal*. 2021;51(12):1990-1998. doi:https://doi.org/10.1111/imj.15430
8. Treede RD, Rief W, Barke A, et al. Chronic pain as a symptom or a disease. *Pain*. 2019;160(1):19-27. doi:https://doi.org/10.1097/j.pain.0000000000001384

9. Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. *Pain research & management*. 2013;18(3):119-126. doi:https://doi.org/10.1155/2013/918216
10. Raphael KG, Janal MN, Nayak S, Schwartz JE, Gallagher RM. Psychiatric comorbidities in a community sample of women with fibromyalgia. *Pain*. 2006;124(1):117-125. doi:https://doi.org/10.1016/j.pain.2006.04.004
11. Low LA, Schweinhardt P. Early Life Adversity as a Risk Factor for Fibromyalgia in Later Life. *Pain Research and Treatment*. 2012;2012:1-15. doi:https://doi.org/10.1155/2012/140832
12. Aaron LA, Bradley LA, Alarcón GS, et al. Perceived physical and emotional trauma as precipitating events in fibromyalgia. Associations with health care seeking and disability status but not pain severity. *Arthritis and Rheumatism*. 1997;40(3):453-460. doi:https://doi.org/10.1002/art.1780400311
13. White KP, Harth M, Speechley M, Østbye T. Testing an instrument to screen for fibromyalgia syndrome in general population studies: the London Fibromyalgia Epidemiology Study Screening Questionnaire. *PubMed*. 1999;26(4):880-884.
14. Tanriverdi F, Karaca Z, Unluhizarci K, Kelestimur F. The hypothalamo–pituitary–adrenal axis in chronic fatigue syndrome and fibromyalgia syndrome. *Stress*. 2007;10(1):13-25. doi:https://doi.org/10.1080/10253890601130823
15. Sosa-Reina MD, Nunez-Nagy S, Gallego-Izquierdo T, Pecos-Martín D, Monserrat J, Álvarez-Mon M. Effectiveness of Therapeutic Exercise in Fibromyalgia Syndrome: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *BioMed Research International*. 2017;2017:1-14. doi:https://doi.org/10.1155/2017/2356346
16. Trivedi MH, Greer TL, Grannemann BD, Chambliss HO, Jordan AN. Exercise as an Augmentation Strategy for Treatment of Major Depression. *Journal of Psychiatric Practice*. 2006;12(4):205-213. doi:https://doi.org/10.1097/00131746-200607000-00002
17. Rimer J, Dwan K, Lawlor DA, et al. Exercise for depression. *The Cochrane Database of Systematic Reviews*. 2012;(7):CD004366. doi:https://doi.org/10.1002/14651858.CD004366.pub5
18. Serra J, Collado A, Solà R, et al. Hyperexcitable C nociceptors in fibromyalgia. *Annals of Neurology*. 2014;75(2):196-208. doi:https://doi.org/10.1002/ana.24065
19. Chandola HC, Chakraborty A. Fibromyalgia and myofascial pain syndrome-a dilemma. *Indian Journal of Anaesthesia.* 2009;53(5):575-581.
20. O'Mahony LF, Srivastava A, Mehta PK, Ciurtin C. Is fibromyalgia associated with a unique cytokine profile? A systematic review and meta-analysis. *Rheumatology (Oxford)*. 2021;60(6):2602-2614. doi:https://doi.org/10.1093/rheumatology/keab146
21. Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. *Rheumatology*. 2001;40(7):743-749. doi:https://doi.org/10.1093/rheumatology/40.7.743
22. Hung AL, Lim M, Doshi TL. Targeting cytokines for treatment of neuropathic pain. *Scandinavian Journal of Pain*. 2017;17(1):287-293. doi:https://doi.org/10.1016/j.sjpain.2017.08.002
23. Molina-Holgado E, Ortiz S, Molina-Holgado F, Guaza C. Induction of COX-2 and PGE2 biosynthesis by IL-1β is mediated by PKC and mitogen-activated protein kinases in murine astrocytes. *British Journal of Pharmacology*. 2000;131(1):152-159. doi:https://doi.org/10.1038/sj.bjp.0703557
24. Peck MM, Maram R, Mohamed A, et al. The Influence of Pro-inflammatory Cytokines and Genetic Variants in the Development of Fibromyalgia: A Traditional Review. *Cureus*. 2020;12(9). doi:https://doi.org/10.7759/cureus.10276
25. Theoharides TC, Tsilioni I, Bawazeer M. Mast Cells, Neuroinflammation and Pain in Fibromyalgia Syndrome. *Frontiers in Cellular Neuroscience*. 2019;13. doi:https://doi.org/10.3389/fncel.2019.00353