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Is fibromyalgia an autoimmune disorder?

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ABSTRACT

Fibromyalgia (FM) is a multifactorial syndrome which includes not only widespread pain and stiffness, now recognized as major symptoms, but also numerous other somatic, emotional, and neuropsychic manifestation. The lack of specific validated biological and instrumental biomarkers has made FM a condition of unexplained medical significance, and its pathophysiology remains controversial and subject to debate. The current hypothesis regarding the pathogenesis of FM proposes that its development is influenced by various mechanism, including genetic predisposition, stressful life events, inflammatory processes, and cognitive-emotional factors. However, despite the extensive research conducted to date, the available data do not provide a clear understanding of the pathogenesis of FM.

In this article, we report the opposing viewpoints of two leading experts who debate the question of whether FM is an autoimmune disease, based on scientific data regarding this condition. Both perspectives are discussed and the latest evidence on the pathophysiology of FM is reported to provide a comprehensive understanding of this complex syndrome.

1. Introduction

Fibromyalgia (FM) is a multifactorial syndrome characterized by chronic widespread pain (CWP), as defined by the International Association for the Study of Pain (IASP) as "pain in at least 4 of 5 body regions (in at least 3 or 4 body quadrants)" [1,2]. Although pain is the main symptom among patients with FM, patients with FM may also experience functional and cognitive disorders, including fatigue, sleep and mood disorders, and cognitive impairment, for at least 3 months [3,4].

Given its estimated global prevalence of around 2.7%, FM is to be considered a significant medical issue. It primarily affects women during their fifth decade of life, but it can occur at any age and may be associated with various conditions, including chronic fatigue syndrome, anxiety, irritable bowel syndrome, and most of musculoskeletal rheumatic diseases [5].

Certain aspects of FM are still controversial, including pathophysiology, which remain a subject of debate. Specifically, the lack of specific validate biological and instrumental biomarkers has made FM an emblematic condition of unexplained medical significance, and still many physicians, in agreement with Perrot's 2012 statement, continue to express doubts about its entity [6,7].

Nonetheless, due to the high prevalence of the disease and its significant impact on the lives of affected patients, it is essential for the scientific community to make a concerted effort to better define the aspects, especially pathophysiological one, that characterize this condition [8].

In recent years more and more experts have defined FM as a complex phenomenon, considering it as a biopsychosocial model [1,9,10]. Popkirov and collegues advocates this for all diseases characterized by chronic pain, but the concept is particularly relevant when discussing complex and heterogeneous syndromes such as FM [3]. According to Pinto et al., it constitutes an integrated pattern of neuro-inflammatory and psycho-social factors, with a dynamic interaction between them [9]. This is not surprising given the evidence that cognitive and affective processes can modulate the perception and processing of pain [11], both positively and negatively [12]. It is now known that emotions influence the various processes of pain modulation in both a bottom-up and top-down sense, through spinal and supraspinal mechanisms [13]. For example, both placebo and nocebo effects activate the same modulation

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mechanisms that are activated by emotional states, and in both cases, subjects may experience hypoesthesia and hyperesthesia phenomena [14].

This model would be the basis for the current pathogenetic hypothesis, which suggests that FM develops due to the interplay between various mechanisms, including genetic predisposition, stressful life events, inflammatory, and cognitive-emotional factors. This combination can result in neuromorphological changes, included a hyperactivation of brain areas dedicated to pain, as well as a reduction in the endogenous pain inhibitory signal [15,16], that lead to the onset of nociplastic pain and altered pain perception, commonly observed in FM patients. As a result, there exists a reciprocal relationship between the central nervous system and peripheral body events [1,9].

Thus, since the role of the immune system and inflammation in the pathophysiology of FM is still under debate, the hypothesis suggesting the presence of "neuro-inflammation", which causes an activation of the immune system capable of modulating the excitability of nociceptive pathways, has been widely reported [17]. However, the autoimmune origin of this phenomenon remains controversial.

Studies have shown that altered levels of pro-inflammatory cytokines (such as interferon-γ, interleukine (IL)-5, IL-6, IL-8) lead to chronic low-grade inflammation [18], which sensitizes neurons at all levels of the pain transmission chain, making them more excitable. Subsequently, it results in the activation of the innate and adaptive immune systems, leading to the secretion of cytokines, inflammatory and neuro-sensitizing molecules, which can dysregulate the complex nociceptive system.

It has been reported that patients with FM in some cases showed a small fibers neuropathy (SFN). It is a condition that affects the small nerve fibers in the skin and other organs. These fibers are responsible for transmitting sensory information such as pain, temperature and touch [19]. Moreover, this condition has been induced in mouse models by the transfer of sera rich in anti-GPCR antibodies [20,21]. When SFN occurs, the affected nerve fibers are damaged or destroyed, resulting in a wide range of symptoms [22]. This includes symptoms such as dysesthesia, burning pain, and autonomic dysfunction [23,24], which are commonly observed in patients with FM. However, while the presence of SFN may explain these symptoms, it may not constitute the etiological determinant of a condition as heterogeneous as FM. Indeed, although the premises and studies regarding the possible presence of autoantibodies among patients with FM are intriguing [25–27], in particular those recently published from Krock et al. about the role of anti–satellite glia cell immunoglobulin G antibodies [25], the available data are still scares, and further studies are needed to determine the exact role of these autoantibodies.

Some papers have reported that individuals with FM have alteration in gut microbiota composition and function, which may contribute to the development of chronic pain and other symptoms [28,29]. These changes in gut microbiota may results in increased intestinal permeability (also known as "leaky gut"), which allows harmful substances to enter the bloodstream and trigger an immune response [29]. In addition, alterations in the gut-brain axis may also affect the production of neurotrasmitters such as serotonin and dopamine, which play a role in pain modulation and mood regulation. Dysregulation of these neurotransmitters may contribute to the development of FM symptoms [30].

In this article we report the opposing viewpoints of two leading experts on this condition who debate the question "is fibromyalgia an autoimmune disease?". In both cases, reflections based on scientific data regarding this pathology are reported.

2. FM is an autoimmune disease by Professor Yehuda Shoenfeld

FM is a clinical condition characterized by a panoply of symptoms such as CWS, fatigue, paresthesia, cognitive impairment, sleep disturbances, memory loss, as well as dryness of mouth and eyes, hearing loss, tachycardia, and many others [24,31–33].

Despite extensive testing, there is currently no conceivable pathophysiological explanation for all these subjective complaints [23,31]. FM shares many clinical features, sometimes designing overlapping diseases, with other conditions, including, chronic fatigue syndrome (CFS) [34], sick building syndrome (SBS) [35], post-COVID syndrome [36,37], and many others [23,24,31,32,38]. Patients complaining of these overlapping clinical conditions get subjected to many instrumental examinations, and extensive blood work, which are often result in clinical pictures in the normal range. Patients are consequently considered healthy and are prescribed anti-depressant or anti-anxiolytic drugs, considering the symptoms merely functional [24,31,39].

Among the most supportive evidence that FM may be an autoimmune disorder are anti- G protein-coupled receptor (GPCR) antibodies (Ab) and the Small Fiber Neuropathy (SFN).

Anti-GPCR, autoantibodies directed against the autonomic nervous system receptors [23,32,33,40], have been detected in the serum of patients with FM, and their titers correlated with clinical symptoms [39]. The autoantibodies have also been found in patients with the other clinical conditions that overlap with FM [24,31,33]. According to the Ernst Witebsky and Noel Rose's criteria for autoimmune disease diagnosis, a passive transfer of these autoantobodies should induce all the clinical symptoms in experimental models [41,42]. The transfer of FM patients's Immunoglobuline G had led to all the clinical findings in mice, including the development of a SFN [20,21]. In addition, sera of subjects with FM in which anti-GPCR autoantibodies were extracted, transferred to mice, did not result in the development of clinical manifestation [32,43].

SFN was also found in all the clinical overlapping conditions, including fibromyalgia; and may explain several additional many of the clinical manifestations reported by the patients, i.e. paresthesiae, widespread pain, severe fatigue [37,44,45].

The fact that fibromyalgia is an autoimmune disease induced by anti-GPCR autoantibodies also has clinical therapeutical implications – plasmapheresis with IVIG (intravenous high dose gammaglobulin) infusion may have beneficial effects on the subjects. These beneficial effects are supplementary to therapy with progressive exercise. The positive results were described in all the clinical overlapping conditions in which dysautonomia can be detected [20,34,46,47]. The improvement effects of exercise in these conditions stems from stabilizing of the para-sympathetic arm of the autonomous nervous system [48,49].

3. Fibromyalgia is not an autoimmune disease by Professor Daniel Clauw

Asserting that FM is an autoimmune disease is incorrect.

Until recently most research into FM had been performed by rheumatologists, who are clinically trained to diagnose and treat autoimmune disorders. The rheumatologists studying this condition, as well as their peers in practice, agreed that FM was much different clinically than the autoimmune disorders that they were seeing in practice. In light of the fact that there was no inflammation identifiable in these individuals, either on examination or in laboratory testing, the name of the condition was even formally changed from fibro*sitis* to fibro*myalgia* in the 1970's [50]. At this point in time, even though many rheumatologists were not certain FM was a real disease, they were quite certain what it was not – an autoimmune disease [7]. This remains the case today. Even though the past few decades have seen tremendous advances in our ability to treat the inflammation in autoimmune disorders with newer DMARDs and biologics, our patients overall are not faring much better in that the majority still have residual pain, fatigue, sleep and cognitive problems from the co-morbid FM that is present in many [51].

But over the past 50 years, there have been tremendous advances in our understanding of FM, and now it is widely studied by many groups of investigators and pain researchers worldwide. In fact, several years ago the most prestigious pain research organization worldwide, the International Association for the Study of Pain (IASP), formally voted to

acknowledge that enough evidence had accumulated that FM is a very real disease, and coined the term nociplastic pain to describe the pain mechanism that is best exemplified by FM. The current understanding of nociplastic pain is that the central nervous system is the driving force behind this pain mechanism, and the key phenotypic features include widespread pain, fatigue, and sleep, memory, and mood disturbances [50,52]. On both quantitative sensory testing and functional neuroimaging there is evidence of amplification of painful stimuli as well as non-painful sensory stimuli (e.g. bright lights, odors, noises), and fairly consistently identified changes in functional connectivity that can even be noted in adolescents who are pain-free but go on to develop new widespread pain the following year [53]. There is now acknowledgement that there is sub-clinical inflammation that is identifiable under ex-vivo provocation in nociplastic pain states, but it is much different in intensity and characteristics than the inflammation seen in autoimmune diseases. And most importantly, this type of inflammation is apparently not successfully treated by the most powerful anti-inflammatories and immunosuppressive we commonly give our patients with autoimmune diseases and co-morbid FM [54].

And perhaps most importantly, in FM classic inflammatory indices are normal (one suspects something other than FM when they are not), there is no objective evidence of inflammation on examination (e.g., synovitis), there is no identifiable tissue damage, and no evidence of tissue inflammation or damage. FM has none of the classic signs of an autoimmune diseases [1].

In contrast, FM is very similar to a large number of highly prevalent Chronic Overlapping Pain Conditions (COPCs). In addition to FM these include headaches, irritable bowel syndrome, temporomandibular disorder, low back pain, and many other common pain conditions [51]. There is a strong familial predisposition to developing these conditions, and individuals who have one of these conditions often meet criteria for many. These same conditions referred to as COPCs are generally those pain conditions considered by the most recent ICD criteria as “primary pain”. This new designation means that the pain is considered the primary problem rather than being due to some other disease, e.g., a real autoimmune disease [55].

There are several recent rodent studies that have purported to show that sera from individuals with FM can cause hyperalgesia or dorsal horn changes in rodents, but these studies are not likely to be helpful in determining whether FM is an autoimmune disease [32]. Very few acknowledged autoimmune disorders can be reproduced in animals simply by giving rodents sera or plasma from humans with that disease, and there are no valid animal models of FM [56]. In light of this it is difficult to see how animal studies are going to counter the overwhelming clinical/human evidence that FM is not an autoimmune disease.

But for the sake of a vibrant debate, let us imagine for a moment that FM is an autoimmune disease. Then so is headache, irritable bowel, TMD, and low back pain – because it is widely acknowledged that the pathophysiology of these pain syndromes is similar. And coronary artery disease, psychiatric disorders, Type II diabetes, and most common medical problems are increasing acknowledged to have a mildly inflammatory component, but these are not considered autoimmune diseases. Aren't we bastardizing the term “autoimmune” if we use it carelessly or flippantly to describe anyone with any inflammation anywhere?

4. Conclusion

FM is a complex condition characterized by heterogeneous symptomatology, which includes not only widespread pain and stiffness, now recognized as major symptoms, but also numerous other somatic, emotional, and neuropsychic manifestation [57].

Despite notable advancements in the understanding of FM [1,58], there are still significant discrepancies in the perspectives regarding its pathophysiology, particularly between the neurophysiological and psychosocial viewpoints, as evidenced by the debate above.

In conclusion, the available data to date do not provide a clear understanding of the pathogenesis of FM. Due to the complexity of the condition, it may not be possible to identify a single etiological factor, whether autoimmune or non-autoimmune. However, it is hoped that in the near future, different subgroups of FM patients can be identified, in which one or more specific elements may predominate.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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