Chapter 3
Etiology and Triggers in the Development of Fibromyalgia

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Introduction

Fibromyalgia (FM) is an intriguing cryptic disorder, categorized as a chronic pain syndrome which affects a considerable amount of the population worldwide, with prevalence between 2% and 6% [1]. FM syndrome constitutes a significant healthcare issue causing great disability, loss of employment, and psychological hardship [2].

Major manifestations of FM are chronic widespread pain, accompanied by fatigue and mood and sleep disorders which impose grave effect on quality of life. The widely accepted explanation for chronic pain in FM focuses on aberrant perception of nociceptive stimuli through a process of central sensitization resulting in erroneous interpretation and amplification of pain [2, 3].

Autonomic dysfunction is inherent to FM with descriptions of alternations in function and hypo-reactivity of the autonomic nervous system [4]. Additionally, FM causes a dysfunction of the endocrine system which manifests with alterations in the hypothalamic–pituitary–adrenal functioning which simultaneously contribute to the flawed perception and amplification of the nociceptive system [5].

However, the biological mechanism driving the stimulation of this adverse process continues to elude researchers, and some suggest rather an emotional basis that encompasses the syndrome manifestations [6].

FM is a multisystemic syndrome with a winding path: it is occasionally considered to be at the distant end of the spectrum of psychosomatic syndromes with symptoms and signs frequently misinterpreted as being of psychological or

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psychosocial origin. FM manifests both cognitively and physically, with recent research demonstrating evidence of changes in endocrine, sympathetic, and immune dysregulation [4, 6, 7]. Our understanding of FM has made significant advances over the past decade although to this day, despite extensive research, the etiology and pathogenesis of FM still remains enigmatic [8]. Thus, this syndrome of chronic widespread pain which encompasses clustering of somatic symptoms without definitive etiology gives rise to overlapping syndromes such as chronic fatigue syndrome, somatoform disorders, and chronic regional pain.

Understanding the interrelated physiological, psychological, and social processes is important in any rheumatic disease, though even more in FM due to the inherent invisibility of its symptoms combined with the absence of observable deformity and multiple overlapping psychological symptoms and history [3, 5].

FM is considered as a multifactorial disease with abundant potential triggers and a multifarious pathophysiology process. There is no evidence for a single event that "causes" FM; rather, many physical and/or emotional stressors may trigger or aggravate symptoms [9, 10]. Notable triggers include physical trauma, emotional trauma, and stress, as well as external stimuli contributors such as infections and vaccinations. In a systemic review conducted by Yavne et al., which inquired for precipitating physical and psychological traumatic events in the development of FM, a significant association was established through retrospective data between prior physical or psychological trauma and the subsequent development of chronic widespread pain and FM [3]. Greenfield et al.'s research augments this stance by depicting a high incidence of reactive FM among individuals who reported a precipitating event as trauma, surgery, or a medical illness before the onset of FM [11].

The role of these negative events in the initiation of the FM symptomology has been the center of debate and research as a means of understanding FM pathophysiology with major implications on prediction of disease development and exacerbations [2, 8, 12]. More importantly, understanding the mechanisms underlying altered pain processing characteristic of FM is crucially important in progression toward tailoring of specific treatment and production of novel strategies for therapeutic management and alleviation of care [3, 8].

Genetics

FM is generally regarded as a noninflammatory and nonautoimmune disease with a polygenic inheritance and environmental contributors. Although it is perceived as nonautoimmune, the high proportion of female patients, a trend reflected in many autoimmune diseases, has spurred the search for an immune-mediated basis for FM. FM is common in patients with autoimmune disease, for instance SLE, with overlapping symptomatology [13, 14], while some FM patients showed evidence of autoimmunity, without meeting the criteria for a specific diagnosis.

Past research suggests genetic factors may play a role in the pathogenesis of FM. Research evolved regarding polymorphisms of genes in the serotoninergic,

dopaminergic, and catecholaminergic systems in light of their cardinal role in pain transferal variation and perception [15, 16]. H. Cohen et al. observed an association between COMT polymorphism, which is involved in the mediation of pain perception, and the number of pressure points reported, an important component of FM severity [17]. Another research performed by Seong-Kyu et al. demonstrated NO enzyme is partially responsible for pain sensitivity in the pathogenesis of FM and GCA1 gene is a potential protective component in FM susceptibility and pain sensitivity [17, 18].

Furthermore, it is presumed that certain environmental factors, especially physiologically or mentally related stress, may trigger the development of FM in already genetically predisposed individuals. Recent publications have documented increased prevalence of FM among family members of patients suffering from FM, likely representing both polygenic inheritance and environmental influence [15]. Another study demonstrated gene polymorphism inheritance in specific family clusters, which make them predisposed to suffering from FM [19]. Deciphering the genetic underpinning for the hyperalgesia in FM would constitute a major advance in understanding FM syndrome pathophysiology. The future is near with new genetic modalities such as the genome-wide association study, which offers the hope of integrating the genetic, the physiological, and ultimately the therapeutic levels for FM [20].

Physical Trauma

Patients often report that a precipitating event, such as physical or emotional trauma, occurred before the onset of FM with a prevalence of 21–47% [21]. The precipitating event may be mechanical, including motor vehicle accidents (MVA), surgery, physical and sexual abuse, or a diagnosis of a medical illness [22–24]. In a study investigating the development of reactive FM following a preceding physical event, the patient-reported prevalence of FM was 23% [11]. These results were later reinforced by Al-Allaf et al. who investigated patient-reported physical trauma during the previous 6 months in FM patients versus controls, demonstrating that physical trauma was significantly associated with the onset of FM, with 36% report rate in FM patients compared to 24% in matched controls [25].

There is a common assumption that a diagnosis of FM occurring after a previous precipitating event carries a graver course and prognosis. Published studies comparing the severity of clinical features of FM between patients with a preceding physical trauma and patients with idiopathic presentation show conflicting results. Findings vary from no significant difference [21] to negative effects and greater disability in patients with traumatic onset compared with those with idiopathic onset [11].

Trauma has been suggested to precipitate the onset of FM by altering normal sleep patterns as well as by turning local injury sites into focuses of regional pain by causing neural plasticity [11]. It is believed that the persistent nociceptive input

from peripheral tissues following a traumatic event may lead to neuroplastic changes resulting in central sensitization and FM [5]. Further research is warranted in order to better understand which types of trauma are more likely to lead to FM and which patient characteristics are most likely associated with the development of FM after precipitating events [12].

FM development after motor vehicle collision was the center of a review which established criteria for determining causality, thus supporting causation between the two [26]. Gareth et al. reinforced their claims by demonstrating a high prevalence (11.3%) of FM development after motor traffic accidents during 4 years of follow-up, compared to the general population. In addition, it was suggested that individuals from a lower socioeconomic background may be more predisposed to develop chronic widespread pain (CWP) syndromes, including FM, following a traumatic stimulus [27, 28]. On the other hand, Wolfe et al. claim in their review that the causative model between the two is poor due to low quality of scientific evidence, depending mostly on studies which rely on patient's recall and attribution [29]. This approach was later refuted in an editorial by Jones who argued that the authors presented a very partisan argument, basing their claim on the analysis of five published studies with no evidence of systematic literature search and without a structured review [30].

Whiplash injury is a common kind of mechanical trauma which may lead to the development of FM. The interpretation of the biological association between mechanical stress, for instance chronic whiplash syndrome in regard to FM, has generated considerable controversy, due to its social and medicolegal implications and consequences, in all jurisdictions where compensation is available [3, 7, 26, 31–34]. Thus, emphasis must be placed on the differentiation between medical and legal approaches and on the need for more research to elucidate the manner of causation [10, 34].

Some studies have demonstrated a positive correlation between whiplash injury and higher prevalence of FM, the most well known by Buskila et al. which demonstrated that FM development following neck injury was 13 times more frequent than following lower extremity injury, with the same rates of insurance claims [35]. Other studies have demonstrated a negative correlation, with the same 1-year follow-up incidence of FM post-whiplash injury as in the general population. The difference may lie in the referral bias of non-recovered patients or due to malingering and personal gain [36]. In such cases, the decision regarding a diagnosis of FM and the degree of work-related disability require a systematic approach. A precaution is warranted to maintain a "divide-and-conquer" approach, on one hand, from a medical standpoint to establish a strong diagnosis and determine disability level, and on the other hand from a legal standpoint to determine the causative relation between the disease and disability [7].

Physical trauma and emotional trauma in many cases are entwined. Buskila et al. conducted a research following the course of survivors of a train crash who were exposed to the combination of physical injury and extreme stress, with a diagnosis of FM found at a high prevalence (15%) among 53 survivors in a follow-up time of

3 years. This finding is in accordance with previous data regarding the association of FM with both physical and emotional stress [35].

Stress and Emotional Trauma

There is a long-standing debate regarding psychology versus biology for FM, one espousing psychology as the more important component and the other claiming that biology plays the greater role [37]. Nevertheless, there is no doubt that the psychological perspective is of major importance in FM. The pathophysiology mechanism linking between precipitating stress-related events and the physical manifestations of FM is yet to be understood. The deviations of the neuroendocrine stress systems in FM are the same as in healthy individuals pre-exposed to an acute stressor. This observation strengthens the assumption that FM is a stress-associated syndrome and enhances the mind–body connection narrative. However, strong evidence in favor of the arguments is lacking [5, 38, 39].

Another potential trigger for FM is emotional turmoil which can be derived from many possible circumstances, from negative experiences in early childhood, such as neglect or abuse, to traumatic adult experiences involving PTSD and sexual abuse [22]. Patients suffering from mental health issues have a higher risk of suffering from FM symptomology and being diagnosed with FM, and vice versa. The reported rate of depression among FM patients is significantly increased, at the somewhat alarming rate of up to 50–70% of patients [38, 40, 41].

There are many studies investigating the association between physical and sexual abuse and FM, with the assumption that abuse may affect the expression and perpetuation of FM syndrome in adult life [42]. Häuser et al. concluded in a meta-analysis that the association of FM with prior physical and sexual abuse could be confirmed, but that the overall low quality of evidence was a confounding factor [23]. These results were augmented by a comprehensive meta-analysis conducted by Afari et al., which demonstrated that individuals had a 2.52-fold likelihood of developing FM following exposure to trauma [43]. Edwards et al. found higher rates of traumatizing events such as sexual and emotional abuse in FM patients in comparison with rheumatologic controls, in association with disability severity, and a more treatment-refractory illness [44]. Another study performed by Haviland et al. reinforced these results, with a significant association between self-reported sexual assault and physical abuse in women and a physician-given FM diagnosis [28]. Childhood trauma was more commonly reported than adult trauma, as supported by Hellou et al.'s observation of significantly higher levels of emotional abuse and neglect in FM patients [45]. In a cross-sectional study by Häuser et al. only emotional and sexual abuse in childhood remained significantly associated with FM in comparison with healthy controls after removing the confounding factor of depression [46]. In a similar study by Yeung et al., childhood neglect was correlated with a flattened cortisol profile in FM patients [47], which is associated with pain, as

supported by previous research depicting endocrine changes related to FM syndrome [5].

Previous studies have described a high prevalence of PTSD among FM patients, which can be up to 56%, with concurrent occurrence increasing the severity of both disorders [48–51]. There is evidence that even re-traumatization of a previous traumatic event can lead to development of both PTSD and FM. When attempting to evaluate the temporal relationship of stressful events to PTSD and FM, their connection seems to be interwoven. The association between the two syndromes does not appear to be explained by a common familial or genetic vulnerability [52]. Häuser et al. have demonstrated a PTSD prevalence of 45.3% among 395 FM patients and showed that chronic widespread pain and a diagnosis of FM symptoms were antedated by the traumatic event and the diagnosis of PTSD in 66.5% of patients [49]. Another study investigated FM–PTSD comorbidity in a cohort of men following a traumatic event. Of the PTSD patients, 49% fulfilled FM diagnostic criteria, suggesting that PTSD is highly associated with FM and that the degree and impact of these disorders are closely related [53].

Two unique studies by Ablin et al. have been published regarding traumatized population that sustains the strong correlation between PTSD and FM: Firstly, a population-based survey which demonstrated a significantly elevated proportion of CWP, FM-like somatic symptoms, and depression among residents of a city targeted by missile attacks, in comparison with residents of a city which was beyond the line of fire [52]. Secondly, a research which examined holocaust survivors and documented an increased rate of FM and PTSD among this unimaginably traumatized population, in comparison with controls [54]. These works were noteworthy due to their design, which focused on uniquely traumatized populations and were able to extend previous data by demonstrating the ability of stress to induce chronic pain and FM symptoms up to decades after the initial exposure.

To conclude, stress and emotional trauma appear to have a crucial effect on the development of FM. A study conducted by Bennet et al. reinforces this claim by demonstrating a vast association between the two. In this study, emotional distress was the most common exacerbating factor, with 83% report rate and the most common triggering event with over 73% of FM patients with a prior triggering event attributing it to emotional trauma or chronic stress [55]. These findings are in accordance with other studies presented in this review, emphasizing the relationship between physical and psychological trauma to FM. As aptly noted by Yavne et al. in their review, while the misgivings may remain regarding the strength of the evidence linking FM to physical and psychological trauma, it is worth keeping in mind that by its very nature this association remains elusive due to the impossibility of conducting randomized controlled trials, the gold standard of medical research. Nevertheless, the substantial cumulative retrospective data gathered throughout the years and presented here establish the presence of a significant association between prior physical or psychological trauma and the subsequent development of chronic widespread pain and FM [3].

Fibromyalgia in the Workplace

An increasing number of patients attribute their illness to faulty workplace ergonomics or demands, often involving sustained poor posture, repetitive movements, and stress induced by environment. Workplace-related regional pain syndromes are common, and such clinical entities as acute cervical strain or mechanical lower back pain may evolve into generalized diffuse pain and tenderness characteristic of FM [36, 56, 57]. Past studies suggest that the majority of FM cases develop as a result of a peripheral insult and associated long-standing nociceptive input, which finally results in central sensitization and pain. Indeed, it is well demonstrated in research that localized or regional pain in most patients with FM precedes widespread pain, thus supporting the notion that FM can develop from localized pain [58].

Gallinaro et al. reported that among 34 workers diagnosed with repetitive strain injuries (RSIs), 58.8% fulfilled the American College of Rheumatology criteria for FM, while only 10.4% of the controls meeting the same criteria [57]. In a study performed among professional athletes, subgroup of a population which is young, healthy, and as such not prone to FM, the frequency of FM observed was 2.2% [59], a rate which is surprisingly similar to the rate presented in normal population-based studies, potentially due to different repetitive strain injuries.

Several interesting studies have been conducted regarding FM development in stressful unbalanced workplace environments. Firstly, a study conducted among nurses, who work long stressful shifts, demonstrated an increased prevalence of FM, especially in female nurses, with a strong correlation to concurrent symptoms of PTSD [60]. Secondly, in a study which investigated FM prevalence among Israeli kindergarden teachers, FM symptoms were found to be highly prevalent, with a 25% rate that greatly exceeds the ~2% prevalence in the general Israeli population. FM symptoms were associated with an increased rate of days of leave and poorer work performance [61]. Last but not least, a similar study conducted among Israeli school teachers demonstrated an increased prevalence of FM, with concomitant PTSD symptoms and lower motivation [62].

We conclude that stressful work-related events appear to be positively associated with the occurrence of FM symptoms and may serve as triggers for their development. Healthcare professionals treating individuals engaged in such occupations should be vigilant for the occurrence of symptoms that are clinically associated with FM syndrome and overlapping functional disorders.

Infections

The association of infection and FM has been increasingly reported and studied as a possible triggering event, with a survey answered by FM patients showing that 43% of patients perceived infections as a precipitating or exacerbating event of FM symptoms [63]. Still, the understanding of infection-triggered FM remains limited.

No relationship has been demonstrated between persistent infection and FM or CWP, nor has any relationship been established between infection-aimed therapies and an improvement in pain. Thus, evidence of an association between the two remains tentative [64].

Various infectious agents have been linked to the development of FM, the most common bacterial agents being Lyme disease and mycoplasma, due to overlapping symptoms of arthralgia and myalgia. Viral agents such as HCV, HBV, and HIV are more common with stronger evidence of correlations [65], although data are still insufficient. Research is ongoing regarding the role of SARS-CoV-2 virus in FM, in the context of the ongoing COVID-19 pandemic.

Lyme disease, caused by *Bartonella Burgdorferi*, is recognized as an important confounder in the diagnosis of FM, particularly in areas where prevalence is high, since it causes similar symptoms of diffuse arthralgia, cognitive difficulties such as impaired concentration and memory, as well as fatigue, and since serological testing for Lyme disease is complex and not always conclusive [10]. In an observational cohort study, 8% patients with Lyme disease were found to have FM over a 3.5-year period, suggesting that Lyme disease may frequently be confused with FM, trigger FM development, or may even coexist with the syndrome in a chronic form. The scarce response to antibiotics may serve as an exemplary for other infections, as it implies that once a trigger has initiated the chain of events culminating in FM, it will run its course without the necessity of ongoing infection [66, 67].

There is a strong association between rheumatic diseases and clinical manifestations of HCV infection, with FM frequently appearing as a clinical comorbidity in HCV carriers, in up to 57% of patients. FM comorbidity is a negative prognostic factor, with influence on functional impairment and disability, resulting in a decline in quality of life. The underlying pathophysiology is not clear, with assumptions that range from an immunomodulation basis, implying alterations in cytokines that produce hyperalgesia, to other neutrally mediated symptoms as a result of CNS aberrations, all without real evidence to causal relationship [10, 68, 69]. In addition, other studies inquire the connection between HBV and FM, with evidence for an increased risk of FM symptomatology and diagnosis within carriers of chronic hepatitis B virus, again with diverse explanations, ranging from a psychological link, due to diagnosis-related anxiety, to the purely organic hypothesis focusing on an inflammatory response to HBV [70].

HIV infection is also associated with rheumatic symptoms such as arthralgias and myalgias. In a research performed in order to study the association of HIV with FM, 80% of patients had musculoskeletal symptoms while 10% fulfilled criteria for FM, which remained high after adjustment for depression. Patients with higher risk to develop FM were with prolonged disease duration and depressed mood. Symptoms may derive from the chronic viral infection or secondary to medical therapy. Notably, identification of FM is important for appropriate treatment and improvement of quality of life [71]. It is also widely believed that EBV may serve as a trigger for FM, yet there is minimal supporting evidence for this claim. A research conducted in 50 patients of FM whose symptoms had begun suddenly, as an apparent “virus” infection, appeared to refute this claim, with EBV serology

levels similar to those of the general population and no evidence that reactivation of latent EBV infection was associated with the patients' illness [72].

The COVID-19 outbreak has resulted in uncertainty for patients with autoimmune rheumatic diseases. In preliminary studies, it has been shown that rheumatic patients, including FM, are not more prone to contracting COVID-19, but the long-term effects of this novel pathogen are yet to be fully understood. In addition to the direct sequels of this viral infection, possible impact may be related to stressors such as fear, depression, illness, job loss, and social isolation [71]. It is increasingly acknowledged that stressors worsen FM symptoms with a higher risk of developing PTSD and may generate FM in previously predisposed individuals [73, 74]. One research conducted to study psychosocial and pain-related effects among patients with chronic pain during the COVID-19 pandemic has showed that FM was independently associated with greater pain severity during this time [75]. Risk stratification, sleep disturbance, anxiety, and depression, which are common comorbidities of FM, were associated with greater pain severity and interference. This information may aid to estimate the impact of the COVID-19 pandemic social isolation and emotional stress on chronic pain syndromes and guide development of innovative approaches to support this vulnerable population during this ongoing period.

To conclude, there seems to be a significant relationship between FM and infections: FM may appear or worsen after infections, probably because the antigens act as the trigger in the presence of a possible genetic predisposition or environmental influence. There is some evidence that FM is partially caused by infections; however, no relationship has been demonstrated between persistent infection and FM, nor any relationship between infection-targeted therapies and improvements in FM symptomology [63].

Vaccinations

Several intriguing lines of evidence suggest that vaccinations may play a role in triggering FM, but the specific effects of antigens and adjuvants or environmental and personal context are still elusive.

The stance of association between vaccinations with FM began with the rubella vaccine. After the rubella vaccination, various conditions were observed including onset of chronic arthropathy and arthritis, arthralgia, and myalgia with a few studies supporting the subsequent development of FM, though the claim was finally contradicted by an RCT which failed to demonstrate a statistically significant increase in FM prevalence [63, 76].

Subsequently attention became directed toward the phenomenon of the Gulf War syndrome, which appeared to be associated with vaccination against various biological agents, with symptomology similar to FM and CWP. This unique clinical entity was first described after the military conflict in the Persian Gulf that took place in the early 1990s, where soldiers received a combination of pre-deployment vaccinations and during deployment for biological agents due to concern regarding

use of unconventional weapons of mass destruction. The Gulf War syndrome was characterized by chronic fatigue, musculoskeletal symptoms, general malaise, irritability, and cognitive disturbances. The syndrome developed with a prevalence of 10–15% and frequently overlapped with PTSD, with both syndromes appearing at a higher rate than observed in servicemen participating in other military conflicts. Thus, the authors conclude that while multiple vaccinations in themselves did not appear to be harmful, the combination between administration of such vaccinations and the concurrent stress associated with deployment in the combat zone and other possible environmental factors may cause an increased risk of developing FM-like syndrome [10, 63, 77].

Of note, a trial performed by Ablin et al., evaluating the efficacy and safety of influenza vaccination in FM patients, demonstrated that influenza vaccination was both safe and effective in FM patients compared to healthy controls [78].

To conclude, the role of vaccination in the pathogenesis of FM is still uncertain. It appears that the mere exposure to one or another specific vaccine is not a trigger for developing FM. Based on the experience of the related Gulf War syndrome, it is believed that the combination between various vaccines and adjuvant and environmental factors may compound the effects of vaccination on the immune system and on the eventual development of chronic FM symptomology [79].

Conclusions

Fibromyalgia is an intriguing clinical syndrome with an elusive path and winding trajectory. Although extensive research has been dedicated to this important entity throughout the years, to this day there is no evidence for single etiologic factor or mechanism. The pathophysiology of FM is unclear and considered to derive partly from aberrant pain perception, presumably involving neurohormonal and endocrine dysregulation. FM, like other chronic pain syndromes, provokes patients and caregivers to grasp the concept that the medical model of specific cause and effect may not apply in this case.

This chapter has covered comprehensive research which has demonstrated a number of substantial triggers to the development of FM. Physical trauma is a major contributor with a spectrum of mechanical trauma on the one hand with examples of MVA and whiplash injuries and physical or sexual abuse on the other hand. Emotional trauma is by itself an independent trigger for FM development and in many cases may be intertwined with physical trauma as in chronic medical illness, sexual abuse, or childhood trauma and neglect, PTSD, or stressogenic workplace environments. Infections and vaccinations also play a role in the development of FM both as precipitating and as exacerbating factors. The course and prognosis of FM patients is directly related to psychosocial factors, including past and current psychological distress and work status or disability issues.

Currently, despite wide-scale research, FM etiology remains elusive, and an effective remedy is yet unknown. This reality emphasizes the importance of

understanding FM's presumed etiology and pathophysiology, in the aspiration of better predicting FM development and anticipating the disease trajectory, for the benefit of improving quality of life and possibly tailoring patient-specific pharmacological and nonpharmacological treatment.

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