PATHOGENESIS OF FIBROMYALGIA IN PATIENTS WITH AUTOIMMUNE DISEASES: SCOPING REVIEW FOR HYPOTHESIS GENERATION

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Abstract
Introduction: Fibromyalgia (FM) prevalence is much higher in patients with other rheumatic diseases than in the general population. This leads to increase in the perceived disease activity scores and prevents patients from reaching remission. Elucidating the pathogenesis of such “secondary” FM can help alleviate some unmet needs in these diseases.

Methods: MEDLINE and Scopus databases were searched for a scoping review for hypothesis generation regarding the genesis of secondary FM.

Results: FM has been postulated to be due to cytokine dysfunction, neurogenic neuroinflammation, stress, including social defeat, sleep disturbances, sympathetic overactivity, and small fibre neuropathy. These factors increase in most autoimmune and autoinflammatory diseases. Further the evidence for the role of these factors in the pathogenesis of FM is seems strong. Metabolic syndrome and mitochondrial dysfunction are also associated with FM, but it is difficult to distinguish between cause and effect.

Conclusion: FM is the common phenotype arising from the amalgamation of various aetiologies. Recruitment or amplification of the above 6 factors by various rheumatic diseases may thus lead precipitation of secondary FM in susceptible individuals.
INTRODUCTION
Fibromyalgia (FM) is a syndrome of widespread pain with other overlapping somatic symptoms. It is a frequent comorbidity in several rheumatic diseases. The prevalence of FM in the general population ranges from 1.5 to 2% (3-6% in women) [1]. However, it is much higher in rheumatoid arthritis (9-30%) [2], axial spondyloarthritis (4-25%) [3], lupus (6.2%) [4], and Sjögren syndrome (15%) [5]. Prevalence of FM was higher even in non-rheumatic diseases like primary immunodeficiency (19%) [6] and thyroid disease [7]. Though the prevalence figures based on different classification criteria may differ [8], the proportions of “primary” to “secondary” FM remain the same. The presence of concomitant FM leads to increased pain, fatigue and physical limitations [9] besides inflating disease activity scores and preventing attainment of remission [10].

With the advent of various targeted therapies in various inflammatory rheumatological conditions, remission or low disease activity is a viable target. However, there are concerns about unmet needs in these diseases [11]. Despite the resolution of inflammation, patients still perceive pain and have poor quality of life. A large proportion of this may be due to the presence of concomitant FM [12]. Therefore, dealing effectively with fibromyalgia can potentially improve the outcomes.

The high prevalence of secondary FM, that is FM comorbid with other rheumatic diseases, seem to suggest that chronic inflammation might be a factor that precipitate or unmask FM in susceptible individuals. In this article we attempt to understand various theories underpinning the pathogenesis of FM, and then attempt to apply these concepts to explain how various rheumatic diseases can lead to the genesis of secondary FM. We also go beyond conventional ideas to propose an alternative hypothesis that FM itself may predispose to other rheumatic diseases.

SEARCH STRATEGY
Scopus and MEDLINE databases were queried with search strings “Fibromyalgia”, “aetiology OR pathogenesis OR aetiopathogenesis” and “rheumatic diseases” as per standard practices for biomedical reviews [13]. Original articles were predominantly analyzed along with highly relevant hypotheses and reviews. The two authors independently searched through the articles and made the lists of causes that they felt can contribute to the pathogenesis of secondary FM. The two lists were then amalgamated.

BASIC HYPOTHESIS
FM is the common phenotypic expression of a number of different mechanisms leading to chronic persistent and widespread pain. However, these mechanisms can have overlapping aetiologies further complicating the picture. We attempt to demonstrate how different mechanisms can contribute to a FM phenotype in autoimmune and other inflammatory diseases.
A. Cytokine dysregulation model of FM

Dysregulated cytokines processing has long been viewed a basis for FM [14]. Early candidates were interleukin-2 and soluble glycoprotein-130 [15,16]. Some studies showed no difference in serum cytokines: there is plenty of controversy on the topic [17]. It has been suggested that a subset of patients have the so-called inflammatory FM with increased levels of acute-phase reactants [18]. Other cytokine abnormalities have been described in cerebrospinal fluid (CSF). Randomized controlled trials have supported this hypothesis by demonstrating changes in cytokine profiles in FM patients [19,20]. Also exome sequencing of patients with FM has shown multiple polymorphisms in immune related genes (CCL11, CCL4 and MEFV) [21]. If this hypothesis is true, it is possible to explain secondary FM in patients with autoimmune and autoinflammatory diseases: the primary disease changes the cytokine profile that leads to manifestations of FM in genetically susceptible individuals.

Parallels can be drawn from the pathogenesis of depression: mice injected with lipopolysaccharide show clinical signs of depression [22]. Similarly, patients with depression and post-traumatic stress disorder can have elevated levels of interleukin-6 and blunted responses of IL-6 to steroids [23].

Patients with primary fibromyalgia have decreased cytokines production in vitro for reasons that are unclear. This hyporesponsiveness is generalised affecting multiple cytokines and not any one in particular, which is exploited by the patented test for FM [24]. Chronic activation and stress might potentially depress stimulated cytokine production. However, this could be a secondary phenomenon. Experimental studies in non-human primates found immune status to correlate with social hierarchy [25].

B. Neurogenic neuroinflammation

While cytokine abnormalities are usually minor in the serum, some definitive changes have been noted in the CSF [26,27]. In cases of peripheral neuropathic pain, the CSF cytokine profile shows increase in IL-8 and the chemokine fractalkine, changes similar to those observed in FM [28]. Peripheral blood mononuclear cells have been used to induce microglia-like cells. Such induced microglia-like cells obtained from FM patients have been shown to express higher levels of tumour necrosis factor (TNF)-α at mRNA and protein levels as compared to cells obtained from healthy controls. These have led to the concept of neuroinflammation in FM [29]. Neuron-induced inflammation leads to damage of surrounding neurons, perpetuating a vicious cycle of neurogenic neuroinflammation. Evidence for the role of neurogenic neuroinflammation has been reported in depression [30]. Chronic widespread pain is associated with accelerated biological [31] aging and also with increased mortality [12]. Thus accelerated neuronal aging may also contribute further neuroinflammation. Indirect evidence for this can be the higher rates of dementia seen in patients with FM (adjusted hazard ratio of 2.77) [32].

Chronic autoimmune diseases are expected to exhibit similar neuroinflammation that might predispose to FM. For example, in neuropsychiatric lupus, interferon (IFN) has been shown to cause microglial activation leading to synapse pruning. The rodent models used in this elegant paper exhibit various behaviour phenotypes overlapping with features of fibromyalgia [33]. The gut microbiome in FM has been shown to alter glutamate metabolism. Glutamate is an excitatory neurotransmitter that has been implicated in neuropsychiatric lupus [34]. A “brain-fog” similar to “fibrofog” has thus been postulated in lupus [35]. Thus there seems to be good evidence of neuroinflammation in lupus leading to certain FM characteristics.

Another caveat supporting the neuroinflammation theory is the role of macrophages in the resolution of pain. Pain is naturally perceived in the higher neural areas in response to noxious stimulus to nerves (nociceptors) in the periphery. However, the macrophage is a key mediator in the resolution of inflammation as opposed to neurons or microglial cells [36]. This strengthens the relationship between inflammation and pain perception.

C. Stress as a basis for FM

Chronic stress can activate neuroinflammation. A systematic review has shown consistent effect of psychosocial stress in activating microglia in the hippocampus. There is also evidence that it can
activate microglia in other regions of the brain [37].

The chronic stress can both increase central sympathetic outflow and alter the immune response of the individual. It has been shown in animal models that chronic stress in the form of social defeat increases the susceptibility to pain and hyperalgesia [38,39].

Social defeat is the conflict between member of the same species (resident versus intruder) that leads to emotional and psychological stress [40]. The loss of a mental confrontation or physical fight induces suppression of aggression and other behaviour reminiscent of symptoms of various human psychiatric illnesses [41]. Thus, social defeat models in rodents provide good simulations to study depression, anxiety and even fibromyalgia in the laboratory. Most chronic diseases can work in the same way inducing microglial activation and thus decrease pain thresholds. Prolonged social stress can cause microglial activation and monocyte infiltration in the brain leading to behavioural changes ranging from anxiety and depression to violent anti-social behaviour [42]. Social defeat can change the social standing of an individual that determines the individual’s immune responsiveness and regulation [25].

There are several studies showing a high prevalence of post-traumatic stress disorder and childhood adverse conditions in patients with fibromyalgia. This has been validated in a systematic review that past traumatic events can precipitate chronic widespread pain [43].

D. Sleep disorders and FM

Some of the first subjective evidence of existence of FM as a distinct entity was provided by polysomnography studies including increasing alpha to delta ratio in successive sleep cycles [44]. Even epidemiological studies have shown that sleep disturbances predispose to chronic widespread pain. Similarly, even sleep deprivation in healthy individuals can induce symptoms of FM [45]. The relationship between FM and obstructive sleep apnoea (OSA) is known, but often FM patients are not evaluated for OSA [46]. Most rheumatic diseases cause sleep disruption [47]. Inflammatory polyarthritis like spondylarthropathies are linked to night pains. Thus rheumatic diseases can lead to poor quality of sleep that will also predispose to FM.

E. Sympathetic nervous system in various rheumatic diseases, including fibromyalgia

The cross-talk between the immune and the nervous systems has been long recognised [48]. Before the advent of methotrexate, high dose propranolol had been tried for rheumatoid arthritis [49]. The role of the nervous system in determining chronicity of arthritis has been well recognised. Vagal nerve stimulation or activation of the alpha7 subunit of nicotinic acetylcholine receptors (α7nAChR) has been shown to alleviate inflammatory arthritis [50,51].

Sympathetic overactivity has been reported in FM in two-thirds of studies in a review [52]. Sympathetic sudomotor response of skin in FM patients has longer latency compared to that in healthy controls [53]. The arteriole-venule shunts in skin have increased peptidergic innervation in FM [54]. Thus, there is ample evidence of involvement of the peripheral sympathetic system in FM. It can be a common pathway for both inflammation and pain. The catechol-O-methyltransferase (COMT) Val158Met polymorphism has been shown to be associated with severity of FM in a meta-analysis [55]. Chronic inflammatory arthritis may lead to sympathetic dysfunction that predisposes the nervous system to sustained widespread pain perception.

Peripheral arthritis or even a photosensitive dermatitis will cause minimal tissue damage, including damage to free nerve endings. Such damage can potentiate neurotransmitter release upstream, leading to central sensitization of the spinal cord and brain. Repetitive activation of unmyelinated type C fibres leads to temporal summation. Similarly, non-nociceptive Aβ fibres activation can add to dynamic mechanical alldynia while nociceptive Aδfibres can add to hyperalgesia [56].

F. Peripheral small fibre neuropathy model of FM

Both functional and structural studies have demonstrated small fibre neuropathy in patients with FM [57]. Punch biopsies have demonstrated
damage to unmyelinated nerve fibres in up to 50% of FM patients; and some authors are recommending routine skin biopsy in FM patients [58]. Alternatively, even confocal microscopy of the cornea can pick up decreased nerve fibre thickness [59].

Genetic polymorphism studies have supported this concept. Polymorphisms in transient receptor potential vanilloid (TRPV) channel 2 and 3 genes have been shown to be associated with FM diagnosis and with severity of symptoms respectively in Korean patients [60]. Similarly, the SCN9A gene encoding a sodium channel in dorsal root ganglia has been shown to be associated with severe FM in Mexican patients [61].

Neuropathy is a known feature of rheumatic diseases. Studies have shown biopsy proof of small fibre neuropathy in Sjögren syndrome [62]. All types of peripheral neuropathies have been reported in the context of rheumatic diseases. Thus, a question arises whether autoimmune disease can unmask neuropathy leading to FM.

Complex regional pain syndrome (CRPS) has characteristics and mechanisms similar to sympathetic activation in FM, but is limited to one limb. FM may be considered a forme fruste of CRPS. Quantitative electroencephalography studies have demonstrated similarities between the two [63], and neuroinflammation has also been implicated in both [29].

G. Linkage with metabolic syndrome: confounder or causal relationship?
FM is linked to metabolic syndrome [64]. Most rheumatic diseases have been shown to increase cardiovascular risk. This can be viewed in two ways. First, presence of FM and other rheumatic diseases induce lifestyle changes, leading to reduced physical activity and increased body mass index. The second alternate view is that there may be common genes or environmental factors that predispose to both metabolic syndrome and FM. This second line of thought seems to imply that there might be common pathways in pathogenesis of both. There are studies of metabolomics demonstrating altered levels of various metabolites in FM [65].

Patients with FM have mitochondrial dysfunction that can be reversed by caloric restriction or by metformin [66]. Mitochondrial dysfunction, oxidative stress and neuroinflammation go hand in hand in the FM, and this inflammation correlates with perceived pain [67]. The relationship between innate immune activation and mitochondrial dysfunction has been demonstrated for major depressive disorder [68]. There might be similar mechanisms active in FM; with the underlying metabolic syndrome causing mitochondrial dysfunction and altered cellular energetics predisposing to chronic fatigue and widespread pain.

H. Opioid induced lowered pain thresholds
Opioid-induced hyperalgesia has been compared to the central sensitization in FM [69]. Morphine induced hyperalgesia in mice has been shown to be dependent on the spinal microglia [70]. This would suggest that opioids can lead to microglial activation.

In chronic rheumatological diseases there might be chronic endogenous opioid secretion leading to receptor fatigue. It has been shown that one abnormality in primary FM is the low prevalence of opioid mu-receptor and reduced sensitivity of this receptor to endorphins. The altered endogenous opioid/receptor functioning can lead to widespread pain and other manifestations of FM.

I. Reverse causality: Fibromyalgia increasing risk of autoimmune diseases
Scientific rigor also entails that we explore the possibility of reverse causality. The strong association of FM with autoimmune rheumatic diseases can be explained even if FM predisposes to increased risk of rheumatic disease. A person with FM who develops rheumatoid arthritis is likely to be detected earlier. Such a person would already be in contact with healthcare, and more often than not, have certain investigations (like rheumatoid factor or anti-citrullinated peptide antibody positivity) that can make diagnosis of early RA easier. It is difficult to state whether FM increases the risk of rheumatoid arthritis or FM simply unMASKS RA earlier.
There are hypotheses related to FM predisposing to chronic inflammatory arthritis. The stimulation due to small fibre neuropathy or sympathetic activation in FM might be the same signal that triggers inflammatory arthritis. The neurogenic neuroinflammation may provide a basis for viral arthritis, and arthritis may not resolve with the resolution of viremia, proceeding to chronic disease indistinguishable from rheumatoid arthritis. Such hypotheses will be difficult to prove, but should be considered in exploring the relationship between FM and rheumatic diseases.

POTENTIAL IMPLICATIONS OF THE UNIFYING HYPOTHESIS
The hypothesis presented (Fig. 1) is that FM is the phenotypic expression of a number of different pathological processes that may or may not overlap in the susceptible individual. Since many of these changes also take place during chronic inflammatory illnesses, such illness will increase the chances of developing secondary FM.

In Central Asia, South Asia and Asia Pacific countries, the prevalence of FM has been reported to range from 0.6 to 4%, which is comparatively less than in the United States and Canada [71,72]. But the prevalence of inflammatory rheumatic diseases is high in these regions. And in many of these countries, the disease burden is high with a large proportion of patients having moderate to high disease activity. Thus, it is imperative for these countries to consider secondary FM as an important clinical condition increasing disease activity scores and a potential factor of poor quality of life in these patients. To test the reverse causality hypothesis, there should be a powered cohort of primary FM matched with a control. Both should be followed up for adequate time to collect the incidence of rheumatic disease in each.

This scoping review focussed on fibromyalgia in inflammatory rheumatic diseases. However, FM is also prevalent in many other chronic conditions such as hypothyroidism, diabetes mellitus, haemodialysis, etc. We have not dwelt on hypotheses linking such non-inflammation diseases with FM. But the basic concept will remain the same, viewed in association with cytokine disbalance, neurogenic neuroinflammation, autonomic neuropathy, and altered sleep.

CONCLUSION
It is likely that FM is the final manifestation of heterogenous aetiologies that lead to a similar phenotype of widespread pain and various somatic symptoms. Rheumatic diseases can unmask the susceptibility to FM via cytokine dysregulation, neurogenic neuroinflammation, sleep disturbances, autonomic dysregulation and/or small nerve damage. They will also add to chronic stress and act as peripheral pain generators that might precipitate FM symptoms in such a predisposed individual.

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AUTHOR CONTRIBUTIONS
SA and AL designed the study and SA made the literature searches. SA drafted the initial manuscript and it was critically revised by both. Both authors have approved the final manuscript and take responsibility for the contents of the manuscript.

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CONFLICTS OF INTEREST
SA and AW declare that they have no conflict of interest, including no relationship with pharmaceutical companies.

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REFERENCES


Түйіндеме

Кіріспе. Фибромиалгия (ФМ) басқа ревматикалық ауруларды бар науқастандар жи жікездеседі. Бұл аурулардың белсенділік көсөткіштерінің жоғарылауына өкеледі және пациенттерге ремиссияга қол жеткізу үшін қамтымдық бермейді. Осындай «еңіншілік» ФМ патогенезін білу әсіресе аурулардың ұсақ болуына қайыптары үшін MEDLINE және Scopus мәліметтер базасында шолу жұрғізіледі.

Нәтижелер: ФМ цитокиндерінің дисфункциясы, ықын, стресс, жаңа жұмыс, жасаулық, симпатикалық белсенділікдің жоғарылауы және уақытқаңыздың нейропатиясы болатындығы анықталды. Бұл факторлар аутоиммунды және ауто-қабынуға ауруларының қәсіпшілігінде күшейеді. Оның нәтижесінде, ФМ патогенезіндеғі осы факторлардың рөлі туралы мәліметтер сенімді болып көрінеді. Метаболикалық синдром және митохондриялық дисфункция ФМ-мен де байланысты, бірақ олардың сәбеттері мен салдарларының ажырату қыяң.

Қорытынды: ФМ - бұл жұмыстарға әсер ететін аурулардың үйлесінің азымында және болатының қоңыр таралған және оның жұмыстың қарапайылыған 6 фактордің әрқалай болуы немесе жоғарылауы, сәйімділік аурулардың екіншілік ФМ дәрежеінің тәндедуіне екегі болуы мүмкін.

Түйін сөздер: Фибромиалгия, патогенез, Нейрорас, Аутоиммунитет, Аурысы.
Патогенез фибромиалгии у пациентов с аутоиммунными заболеваниями: обзорное исследование для разработки гипотезы

Резюме

Введение. Распространенность фибромиалгии (ФМ) у пациентов с другими ревматическими заболеваниями выше, чем в общей популяции. Это приводит к увеличению показателей оценки активности заболевания и не позволяет пациентам достичь ремиссии. Выяснение патогенеза таких «вторичных» ФМ может помочь выяснить неизученные вопросы в лечении этих заболеваний.

Методы: На основании материалов таких баз данных как MEDLINE и Scopus было проведено обзорное исследование с целью разработки гипотезы патогенеза вторичной ФМ.

Результаты: Было установлено, что патогенез ФМ обусловлен такими факторами как: дисфункция цитокинов, нейрогенные нейровоспаление, стресс, нарушения сна, повышенная симпатическая активность и невропатия. Негативное воздействие этих факторов увеличивается при большинстве аутоиммунных и ауто-воспалительных заболеваний. Данные о роли этих факторов в патогенезе ФМ кажутся убедительными. Метаболический синдром и митохондриальная дисфункция также связаны с ФМ, но трудно выявить их причину и следствие.

Вывод: ФМ является распространенным фенотипом, возникающим в результате сочетанного воздействия различных этиологий. Таким образом, увеличение силы воздействия рассмотренных в работе 6 факторов при различных ревматических заболеваниях может привести к развитию вторичной ФМ у восприимчивых людей.

Ключевые слова: Фибромиалгия, Патогенез, Нейровоспаление, Аутоиммунитет, Боль.