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Unclear etiology and current hypotheses of the pathogenesis of fibromyalgia

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Abstract:

Introduction and purpose: Fibromyalgia is a chronic condition affecting almost 2% of the general population, mostly women. The main symptoms are chronic diffuse musculoskeletal pain or stiffness, tiredness, nonrestorative sleep, anxiety, depression and cognitive dysfunction. The etiology of fibromyalgia remains unclear and has been the subject of debate and scientific investigation. The aim of this article was to collect and analyse current and new information on the etiology of fibromyalgia and present the most popular hypotheses.

Brief description of the state of knowledge: Pathogenesis of fibromyalgia is multifactorial. Genetic factors, in addition to environmental factors, such as psychical stress and various types of infection, are considered to be the triggers of the disease. Central sensitization became a commonly accepted hypothesis of the fibromyalgia's pathogenesis. However, the newest finding of small fiber neuropathy in patients with fibromyalgia supports another hypothesis, in which the disease is presented as stress-related dysautonomia with neuropathic pain features.

Conclusions: Understanding the pathogenesis of fibromyalgia is essential to provide the best care to the patients with fibromyalgia. Although there are multiple evidence for central sensitization hypothesis, new findings continue to emerge and question commonly accepted paradigm. Despite numerous findings on etiology of fibromyalgia, more studies are needed.

Key words: fibromyalgia; etiology; physiopathology; central sensitization; dysautonomia; small fiber neuropathy

1. Introduction and purpose:

Fibromyalgia (FM) is a disease, characterized by chronic widespread pain with a low pain threshold. The main symptoms of fibromyalgia are chronic diffuse musculoskeletal pain or stiffness, typically accompanied by tiredness, sleep disturbances, anxiety, depression and memory problems [1,2]. Fibromyalgia is diagnosed when the symptoms meet ACR criteria (2016) and a somatic disease explaining the symptoms is excluded [3]. The diagnosis is established on the basis of patients' reports (Fibromyalgia Survey Questionnaire) and clinical assessment. There are no objective tests for fibromyalgia [3,4]. For the treatment current guidelines recommend a multimodal approach – education, physical therapy, aerobic exercise, hydrotherapy or acupuncture. If the effect is insufficient, individualized treatment should be applied, such as cognitive behavioral therapy, pharmacotherapy (for pain, sleep problems, severe depression or anxiety) or multimodal rehabilitation programs [5].

Fibromyalgia is a common chronic pain condition affecting mainly females, aged 25-40 years old. The prevalence of fibromyalgia is 1,78% in the general population [1,6]. However, there are number of reasons why this data may be understated, such as potential physicians' poor knowledge about FM, absence of objective tests to confirm the diagnosis, stigmatization of patients with FM, under diagnosis of comorbid FM in patients with some other primary disease blurring the classical clinical presentation or diagnosing as psychiatric disease [7,8]. The prevalence of FM is substantially higher in patients with particular diseases, such as irritable bowel syndrome (IBS), hemodialysis patients and those with type 2 diabetes mellitus [6].

The prevalence of fibromyalgia emphasizes the importance of the disease. Patients should be provided with optimal care. In order to achieve the best therapeutic and diagnostic standards it is crucial to understand the processes leading to fibromyalgia. The aim of this review was to collect and analyze current and new information on the etiology of fibromyalgia and to present the most popular hypotheses.

2. State of knowledge:

The development of fibromyalgia is still a matter of debate [4]. At present, it is almost commonly accepted that the main cause of fibromyalgia is augmented sensory and pain processing in the brain [9]. The pathogenesis involves some components of the peripheral, central and autonomic nervous system. There are a lot of reliable findings of biochemical studies and functional imaging studies (fMRI) [9,10]. Various hypotheses of fibromyalgia's pathogenesis were formulated based on these data. The most accepted is the concept of central sensitization proposed by *Yunus et. al.* and supported by *Häuser et. al.* [9]. In recent years researchers have paid a lot of attention to the new finding of small fiber neuropathy's high prevalence in FM patients, which supports the other popular hypothesis of stress-related dysautonomia-neuropathy and argues with central sensitization hypothesis [11].

Genetic and environmental factors:

Some studies have shown a genetic and epigenetic predisposition for fibromyalgia. Genetic polymorphisms in the serotoninergic, dopaminergic and catecholaminergic systems of pain transmission and processing has been found [12]. These data demonstrate a role of sympathetic nervous system in the development of fibromyalgia. Nevertheless, there is no definite candidate gene and additional genes continue to emerge [9].

Environmental stressors have been associated with the development of fibromyalgia and considered as triggers of FM symptoms. Patients with fibromyalgia often experience more stressful, negative life events than healthy controls [13]. They have higher prevalence of childhood maltreatment and adult victimization [14]. The concept of resilience, defined as a protective factor that makes people less vulnerable to future adverse life events, has been applied to fibromyalgia. Resilience is related to reaction to acute or chronic stress, has genetic basis and involves the hypothalamic-pituitary-adrenal (HPA) axis, central nervous system and sympathetic system. Environmental factors may play a major role in developing a more or less resilient personality [15].

The development of fibromyalgia is likely to be triggered by certain types of infections, as well. An infectious cause for FM, including EBV, HIV, HCV, Q fever and Lyme disease, has been suggested. [16]

Patients with FM have disturbances in two major interacting stress-response systems - autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis. Although the role of HPA axis is still debated, some studies suggest impaired ability to activate the HPA axis response to stress through decrease in corticotrophin-releasing hormone (CRH) secretion, the key active peptide of HPA axis. Normally CRH decreases pain perception through opioid peptide secretion, therefore CRH deficiency explains occurrence of pain in symptomatology of fibromyalgia.

Chronically decreased CRH levels and relative glucosteroids deficiency may also explain symptoms of fibromyalgia, such as lethargy and fatigue or depression [17].

Central sensitization:

Fibromyalgia is considered to be a classic centralized pain condition and a member of the group of central sensitivity syndromes (CSS). The hypothesis of central sensitization in fibromyalgia, proposed by *Yunus et. al.* and supported by *Häuser et. al*., has been commonly accepted by medical world. This hypothesis assumes that the changes in central nervous system distort or amplify pain, which in addition to genetic and environmental factors, causes hypersensitivity to pain and sympathetic over-activity [18,19].

The phenomenon of central sensitization manifests as pain hypersensitivity, allodynia, hyperalgesia, altersensations and enhanced temporal summation [20]. Patients with fibromyalgia or other diseases of the CSS group, such as chronic fatigue syndrome, irritable bowel syndrome, interstitial cystitis and myofascial pain syndrome, demonstrate accentuated nociceptive flexion reflex or decreased stimulus threshold, which is indicative of central sensitization [18,21,22]. Painful stimuli may initiate the processes that leads to central sensitization in susceptible individuals by neuroplasticity. The etiology of central sensitization appears to be multifactorial. Genetic factors in addition to environmental stressors, including trauma and infections, may induce immune response in the central nervous system, which leads to production of proinflammatory cytokines that have been implicated in the generation of chronic pain states [17]. Fibromyalgia is also known to overlap or to be associated with the other CSS [23].

Central sensitization occurs when there is pain amplification in addition to reduced pain inhibition throughout the central nervous system [24]. Studies on peptide levels in the cerebrospinal fluid provide objective evidence supporting this hypothesis. Neurotransmission mediated by SP, calcitonin gene-related peptide, vasoactive intestinal peptide are increased. On the other hand, neurotransmintters and neuromodulators of pain inhibition pathways, such as serotonin, norepinephrine, ekephalines and dopamines levels are decreased. These alterations result in amplified pain [18].

There are number of changes in the brain in patients with fibromyalgia provided by neuroimaging [25]. Patients with fibromyalgia display less connectivity within the brain's pain inhibitory network during calibrated pressure pain in functional magnetic imaging studies (fMRI) than healthy controls [26]. Moreover. increased cortical activity supports the hypothesis of central sensitization in fibromyalgia [27].

Although the role of central sensitization in inducing pain is well described, it is still discussed whether the other symptoms of FM, fatigue and nonrestorative sleep, can be explained by central amplification, are secondary to pain, or are caused by some other pathophysiological process. Mood dysfunction and memory problems may result from neurotransmitter abnormalities [28].

Dysautonomia-neuropathic hypothesis:

In this hypothesis fibromyalgia is presented as stress-related dysautonomia with neuropathic pain features. Genetic predisposition, leading to a deficient COMT enzyme or defective adrenergic receptors, underlies the persistent hyperadrenergic state. Exogenous stress, physical or emotional trauma or different types of infections are responsible for sympathetic hyperactivity and may act as triggering events. Chronic sympathetic hyperactivity results in alterations in dorsal root ganglia, such as new abnormal connections between the sympathetic and nociceptive system [11].

Chronic sympathetic hyperactivity and neuroplasticity in dorsal root ganglia are the basis of sympathetically maintained pain concept [29]. These phenomena explain not only pain in fibromyalgia, but the other symptoms too, such as anxiety or sleep disturbances. Fatigue is the effect of hyperactivity's "ceiling effect" leading to sympathetic hyporeactivity [30].

This hypothesis has been recently reinforced by researchers revealing the high prevalence of small fiber neuropathy (SFN) in patients with FM. SFN is a disorder of the peripheral nerves, small and autonomic fibers, resulting in sensory changes, such as pain, burning, tingling, numbness. SFN has been associated with many diseases, including diabetes, autoimmune diseases or vitamin B12 deficiency [11]. In 2018, Grayston *et al.* proposed meta-analysis of 935 studies and demonstrated the pooled prevalence of SFN in fibromyalgia is 49%. SFP was diagnosed by a skin biopsy or corneal confocal microscopy [31]. These findings may be useful in understanding the aetiopathogenesis of fibromyalgia and for diagnostic purposes. It is unlikely that SFN is connected to central sensitization [11].

There is possibility that a subgroup of fibromyalgia patients have genetic sodium channelopathy in dorsal root ganglia. Both, in small fiber neuropathy and fibromyalgia reported SCN9A gene-encoded Nav1.7 dorsal root ganglia sodium channel variants [11]. Blockers of these channels are potential therapeutic targets.

Autoimmunity is likely to be the underlying mechanism in a subgroup of young fibromyalgia patients with SFN. These patients present serologic markers of disordered immunity [32]. Adrenergic autoantibodies are associated with young women with an overlap between fibromyalgia and postural orthostatic tachycardia syndrome[11,33]. SFN and adrenergic or muscarinic receptors autoantibodies have been found in young girls after HPV vaccination [34].

3. Conclusions:

Throughout the last years, etiology of fibromyalgia seemed to be well explained by central sensitization theory. This paradigm, supported by evidence from biochemical and neuroimaging studies, has dethroned the other hypotheses. However, the new finding of the high prevalence of small fiber neuropathy in patients with fibromyalgia supports the hypothesis of stress-related dysautonomia with neuropathic pain and secondary changes in the brain, forcing the reevaluation of accepted paradigm. The new findings continue to emerge and force experts to repeatedly confront them with the previous data.

Fibromyalgia appears to be a heterogeneous disease. There are multiple environmental factors involved in pathogenesis of fibromyalgia, such as psychological stress, injury, various types of infection, even HPV vaccination. There are also the subgroups of patients with autoimmune cause of fibromyalgia or specific genetic polymorphisms.

These patients should be identified and provided with individualized therapy. In order to achieve the best results in the individualized management of fibromyalgia, more researches on pathophysiology are needed.

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