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PERSPECTIVES IN RHEUMATOLOGY

Hypothetical framework for post-COVID 19 condition based on a fibromyalgia pathogenetic model

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Abstract
There is a clear clinical overlap between fibromyalgia, myalgic encephalomyelitis, and post-COVID 19 condition. Chronic fatigue, cognitive impairment, and widespread pain characterize these 3 syndromes. A steady line of investigation posits fibromyalgia as stress-evoked sympathetically maintained neuropathic pain syndrome and places dorsal root ganglia dysregulation with the ensuing small fiber neuropathy at the epicenter of fibromyalgia pathogenesis. This article discusses emerging evidence suggesting that similar mechanism may operate in post-COVID 19 condition.

Keywords Dorsal root ganglia · Fibromyalgia · Long COVID · Myalgic encephalomyelitis · Post-COVID-19 condition · Small fiber neuropathy

Introduction

A substantial fraction of patients (10 to 20%) recovering from COVID-19 (SARS CoV-2) infection experience chronic vexing symptoms [1]. This complication is known as long-COVID or post-COVID-19 condition. According to the World Health Organization clinical case definition, "Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time" [2].

There is a clear clinical overlap between post-COVID-19 condition, myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), and fibromyalgia. Chronic fatigue, cognitive impairment, and widespread pain characterized these syndromes [3–7]; these three illnesses may also share underlying pathogenetic features. An established mechanistic model suggests fibromyalgia as a stress-evoked, sympathetically maintained neuropathic pain syndrome, and puts dorsal root ganglia dysregulation with the ensuing small fiber neuropathy at the epicenter of fibromyalgia pathogenesis [8]. Unfolding research from different groups of investigators hints that similar mechanism may be also occurring in patients with post-COVID-19 condition [9–16].

The objective of this article is to highlight the clinical overlap between post-COVID-19 condition, ME/CFS, and fibromyalgia, and to focus on the emerging evidence suggesting that dorsal root ganglia phenotypic changes with the resulting small fiber neuropathy may also play a role in the mechanisms leading to post-COVID-19 condition.

Our review strategy included PubMed database search linking the following entry subjects: "COVID-19 and myalgic encephalomyelitis," "COVID-19 and fibromyalgia," "COVID-19 or SARS-Cov2 and small fiber neuropathy," and finally "COVID-19 or SARS-Cov2 and dorsal root ganglia." Original investigations looking for dorsal root ganglia dysregulation and/or small fiber neuropathy in COVID 19 condition are included in this viewpoint article.

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Clinical overlap between post-COVID-19 condition, ME/CFS, and fibromyalgia

ME/CFS is a complex illness typified by profound malaise after mental or physical effort occurring in patients already suffering from constant fatigue [17]. The presence of musculoskeletal pain is implied in ME/CFS name. A systematic review with meta-analysis found that ME/CFS and fibromyalgia diagnoses overlapped in 47% of the reported cases with well-defined classification criteria [18]. This concordance will be likely higher when using the most recent fibromyalgia diagnostic criteria that incorporate chronic fatigue and cognitive symptoms as key diagnostic features [19]. Post-COVID 19 condition is characterized by similar symptoms; in a cross-sectional study of 178 patients with post-COVID 19 condition, the most frequent reported complaints were difficulty concentrating (81%), dyspnea (75%), arthralgia (71%), fatigue (68%), and hair loss (60%) [6]. A web-based survey found that after 3 months from the acute COVID-19 illness, 30% of the affected patients fulfilled the fibromyalgia diagnostic criteria [3]. The long-term consequences of post-COVID-19 condition are not known at the present time; a cohort of patients suffer chronic symptoms. Compared with uninfected individuals, a group of 1276 hospitalized patients with COVID-19 had more problems with mobility, pain, anxiety, or depression 12 months after hospital discharge [20].

An alternative fibromyalgia mechanistic model

There is an alternative explanation to the orthodox theory proposing fibromyalgia as a centralized "nociplastic" pain syndrome. This different model views fibromyalgia as a stress-evoked sympathetically maintained neuropathic pain syndrome and proposes dorsal root ganglia as the key neural hubs were different infective, autoimmune, and/or psychological stressors could be converted in neuropathic pain [8]. This model has been backed by the following lines of investigation: Dorsal root ganglia contains the small nerve fiber nuclei, each individual nucleus is tightly enveloped by immune-competent glial cells [8]. About half of fibromyalgia patients have skin biopsy–proven small fiber neuropathy [21]. The eye cornea is the most densely innervated part of the body, making it an ideal site to study small nerve fiber pathology. Several groups of investigators have described corneal sub-basal plexus abnormalities consistent with small fiber neuropathy in individuals suffering from fibromyalgia [22]. One study found a tight clinical-pathological correlation between corneal nerve fiber damage and small fiber neuropathy symptoms in fibromyalgia patients, after excluding cases with concomitant severe anxiety/depression [23]. The ion channel (Nav1.7) plays a major role in the pain electric signaling within the dorsal root ganglia. Severe fibromyalgia is associated with a particular Nav1.7 genotype [24]. After exercise, patients with ME/CFS and comorbid fibromyalgia displayed greater increases than controls in gene expression for metabolites detecting dorsal root ganglia sensory receptors including acid-sensing ion channel 3 and P2X purinoreceptors 4 and 5 [25]. Immunoglobulin G derived from fibromyalgia patients induces hyperalgesia and peripheral denervation in mice; such immunoglobulin G is specifically deposited in the mice dorsal root ganglia [26]. Similarly, neutrophils from fibromyalgia patients induce hyperalgesia and dorsal root ganglia inflammation in mice [27].

Small fiber neuropathy may also explain the chronic fatigue and other dysautonomia symptoms seen in fibromyalgia and in ME/CFS. Immunohistochemical studies show that small nerve fibers regulate microvascular tone, primarily by sympathetic and parasympathetic cholinergic synapses on perivascular myocytes. [28]. Peripheral denervation may lead to distal venous blood pooling with decreased cardiac return. This hemodynamic instability could theoretically explain chronic fatigue as well as exercise and orthostatic intolerance [29].

Post-COVID 19 condition, dorsal root ganglia, and small fiber neuropathy

Unfolding evidence advocates that dorsal root ganglia dysregulation with the ensuing small fiber neuropathy may also play a role in post-COVID-19 condition. SARS-CoV-2 enters cells via angiotensin converting enzyme-2 receptor. Shiers et al. demonstrated that this receptor and other coronavirus-associated receptors and factors are expressed in human dorsal root ganglia small nerve fibers. They posit that SARS-CoV-2 could gain entrance to the dorsal root ganglia via the small nerve fibers free ending residing in the skin, in the respiratory tract mucosa, and in the eye cornea [9]. This SARS-CoV-2 infection could induce dorsal root ganglia phenotypic changes with the resulting small fiber neuropathy, thus generating widespread pain.

Alterations in the peripheral immune system induced by COVID-19 infection can theoretically lead to chronic musculoskeletal pain. In a hypothesis-generating study, Lesnak et al. built a ligand-receptor interactome network to identify potential connections between the peripheral blood cells of patients with COVID-19 infection and human dorsal root

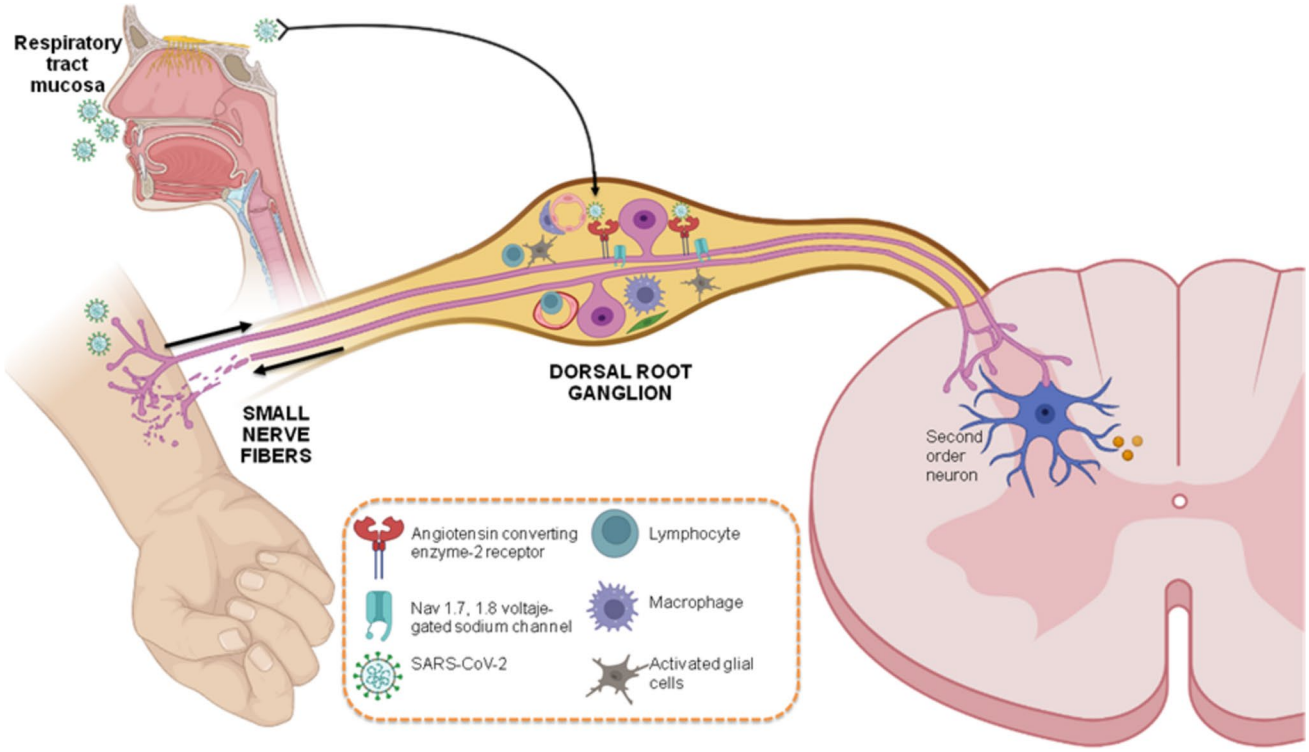

Fig. 1 Hypothetical framework for post-COVID-19 condition. SARS-CoV-2 invades the body through the skin or through the respiratory tract. SARS-CoV-2 enters dorsal root ganglion (DRG) using angiotensin converting enzyme-2 receptor. The local immune response to the invading virus provokes DRG inflammation and small nerve fiber nuclear degeneration. Small fiber neuropathy induces fatigue and widespread pain (image created with BioRender.com)

ganglia sensory neurons. The ligands most consistently upregulated in COVID-19 patients involved the alarmins S100A8/9 and MHC-I signaling [30].

Serafini et al. studied the effects of infection with SARS-CoV-2 compared with influenza A virus on the sensory nervous system of hamsters. Non-infective SARS-CoV-2 transcripts were present in dorsal root ganglia within 24 h after intranasal virus infection. Thirty-one days after infection, a neuropathic transcriptome emerged in thoracic dorsal root ganglia from SARS-CoV-2-infected animals, which coincided with SARS-CoV-2 mechanical hypersensitivity that was not seen after influenza A virus infection. These data suggest that the host response to SARS-CoV-2 infection elicits a unique transcriptional output capable of inducing lasting dorsal root ganglia plasticity [10].

Dorsal root ganglia inflammation may lead to small fiber pathology and chronic pain [8]. Several studies have described small nerve fiber neuropathy in post-COVID-19 condition. Abrams et al. described 6 patients with new-onset paresthesias during or soon after COVID-19 infection; skin biopsy disclosed small fiber neuropathy [11]. Oaklander et al. described 10 patients with World Health Organization-defined post-COVID condition and biopsy-proven small fiber pathology [16].

Corneal nerves express neuroleptin receptors 1 and 2 as well as angiotensin converting enzyme-2 receptor making them vulnerable to SARS-Cov-2 infection. Barros et al. studied 23 mildly symptomatic or asymptomatic patients recovering from COVID-19 infection using corneal confocal microscopy. Ninety-one percent of patients displayed corneal subbasal plexus alterations consistent with small fiber neuropathy. None of the 46 uninfected control volunteers had corneal nerve damage [12]. Midena et al. used corneal confocal microscopy to assess small nerve fiber structural abnormalities in 151 patients recovering from acute COVID-19 infection; this group had significantly thinner corneal nerves when compared to 46 healthy individuals with no history of COVID-19 infection [14]. Bitirgen et al. found significant negative correlation between total score on the NICE long COVID questionnaire and corneal nerve fiber density in 40 patients recovering from COVID-19 infection [13].

Final remarks

Post-COVID-19 condition, ME/CFS, and fibromyalgia share clinical features and may also have similar underlying pathogenetic mechanisms. A consistent line of investigation places dorsal root ganglia at the epicenter of

fibromyalgia pathogenesis. Unfolding evidence suggests that dorsal root ganglia phenotypic changes with resulting small nerve fiber neuropathy may also play a role in post- COVID-19 condition. Figure 1 graphically summarizes our hypothesis: SARS-CoV-2 may invade the body through the respiratory tract or through the skin. The coronavirus could gain access to the dorsal root ganglia using the angiotensin converting enzyme-2 receptor. Once in the dorsal root ganglia, SARS-Cov-2 or its transcripts may induce an immune-mediated inflammation; the mounted response could affect small nerve fibers nuclei with the resulting small fiber neuropathy manifested as chronic pain and dysautonomia. This different model is a hypothesis-generating construct that should be tested with the appropriate animal and clinical studies.

Compliance with ethical standards

Disclosures None.

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