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Chronic pain, fibromyalgia, and long COVID

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Abstract

Chronic pain is a common problem in rheumatology. A distinction is made between nociceptive pain and nociplastic pain. Nociceptive pain is, for example, mechanistically explained by persistent inflammation. Neuropathic pain is caused by nerve damage of various possible causes. In contrast, nociplastic pain is not due to tissue damage or a lesion in the somatosensory nervous system—at least not with the currently available techniques. Nociplastic pain is based on an altered perception of pain through modulation of stimulus processing. The concept of central sensitization, together with other neurobiological and psychosocial mechanisms, is considered to be the best explanation for such pain conditions. The syndrome of fibromyalgia (FM), considered to be due to central sensitization, plays a major role in rheumatology—both in terms of differential diagnosis and because the management of inflammatory rheumatic diseases can be made more difficult by the simultaneous presence of FM. During the coronavirus pandemic, persistent pain syndromes with similarities to FM were described following a COVID-19 infection. There is a growing scientific controversy as to whether the so-called long COVID syndrome (LCS) is a separate entity or just a variant of FM.

Keywords

SARS-CoV-2, COVID-19, central sensitization, nociplastic pain, neuropathic pain

Introduction

Acute and chronic pain states play an important role in the care of patients with rheumatic musculoskeletal diseases (RMD)—a daily challenge for rheumatologists, as the former in particular often raise questions that are not always easy to answer. For the understanding, diagnosis, and treatment of chronic pain conditions, those that cannot be explained by objective tissue damage are of particular clinical significance.

In the recently published International Statistical Classification of Diseases and Related Health Problems (ICD-11), chronic pain is referred to as a root code, with chronic primary pain being a subcategory that can occur in one or more anatomical regions—independent of identifiable biological or psychological factors [1]. The parent category of chronic primary pain includes chronic widespread pain

and chronic primary musculoskeletal pain. These primary pain conditions have no identifiable tissue abnormalities, with central sensitization proposed as the mechanistic etiology [2]. In contrast to nociceptive or neuropathic pain, these pain conditions can be categorized as a mechanistic third pain descriptor, also known as nociplastic pain [3, 4]. Accordingly, the International Association for the Study of Pain has now defined 3 mechanistic descriptions of pain: in addition to nociceptive pain, a distinction is made between neuropathic and nociplastic pain [5].

The concept of central sensitization, together with other neurobiological and psycho-social mechanisms, currently best explains chronic primary pain conditions [3–5]. The following article attempts to outline the individual components of the problem of chronic pain conditions and to reflect the current discussion on the various areas—with a focus on fibromyalgia syndrome (FMS) and the long COVID syndrome (LCS).

Rheumatologic research has made important contributions to the development of many immune-based therapeutics that are now considered standard therapy for various inflammatory RMD. In addition, important insights have been gained to better understand the epidemiology, the risk factors, and the natural history of COVID-19 in immune-mediated inflammatory RMD [6, 7]. Now, the next phase of the pandemic requires further research efforts [8], and this is mainly on the long-term consequences of COVID-19 including the not yet sufficiently defined LCS [9, 10].

Nociplastic pain, central sensitization, and fibromyalgia

There is agreement recently coming from the international community of pain researchers that FMS is the classical example of a third identified pain mechanism, called nociplastic pain. The core symptoms among many other underlying features include fatigue, memory, sleep, and mood problems. The pathomechanisms responsible for nociplastic pain, which are not fully understood, are based on altered nociception, and without any evidence of actual or impending tissue damage that may have caused the activation of peripheral nociceptors, nor any lesion of the somatosensory system causing the pain [3–5].

Nociplastic pain differs from nociceptive pain, caused by persistent inflammation, and from neuropathic pain, caused by nerve damage, primarily mechanistically. While nociceptive pain is caused by damage to peripheral tissue and neuropathic pain is due to nerve injury, nociplastic pain is primarily controlled by the central nervous system (CNS). The primary nociplastic mechanisms in these disorders are probably triggered by the same process in the CNS [3–5].

Although central sensitization is most likely a dominant mechanism in nociplastic pain conditions, the term “nociplastic pain” should not be considered synonymous with the neurophysiological term “central sensitization”, as peripheral sensitization may also play a role. The concept of nociplastic pain is consistent with the current view that certain forms of chronic pain are better understood as conditions or diseases in their own right, rather than as symptoms of another problem [3–5]. As widespread pain is a common symptom in patients with nociplastic pain, the widespread pain index (WPI) is used to quantify the extent of this pain [11], while neuropathic pain is investigated by the PainDETECT questionnaire [12]. The prevalence of chronic widespread pain or FMS is reported in population-based studies to be between 7–11% and 1–5%, respectively [13, 14].

As it stands now, primary chronic musculoskeletal pain belongs to the category of chronic primary pain strains being mechanistically described as nociplastic pain. Possibly, many patients previously diagnosed with myofascial pain are in fact suffering from chronic primary musculoskeletal pain, requiring a paradigm shift to more centrally focused treatment strategies. However, many questions remain, such as the validation of proposed examination techniques, their prevalence, ideal treatment approaches, and the acceptance of the medical community. Anyhow, this new classification is likely to be accepted as an explanation for regional pain conditions that had previously shown poor responses to physical treatments [5].

The complex clinical picture of fibromyalgia [13, 14] is a chronic pain disorder that primarily manifests itself in soft tissue [15, 16]. As this common disease is usually polysymptomatic, it is also referred to as

FMS. It is characterized by deep muscle and joint pain in the right and left side of the upper and lower body; other symptoms include sleep disorders, daytime tiredness, concentration problems, and fatigue.

Accompanying symptoms such as depression and anxiety are also common. More women than men are affected by the neurological symptoms with pain perception and processing. There are diagnostic criteria for FMS, which have been changed several times in the last decades. While the initial focus was on the examination of certain tender points with pressure pain, the focus is now on the WPI for which a minimum number of defined pain locations and a certain number of points on the symptom severity score (SSS) must be present [11].

It is particularly important for rheumatology that FMS also occurs secondarily in inflammatory rheumatic diseases, and this is not exactly rare [17, 18]. This makes it sometimes considerably more difficult to assess the therapeutic success of anti-inflammatory drugs such as biologic disease-modifying anti-rheumatic drugs [19].

Fatigue is a frequent problem in many rheumatic diseases, and it is often chronic [20]. However, there is also a disease called chronic fatigue syndrome (CFS)/myalgic encephalomyelitis which has been recognized as a neuro-immunological disease by the World Health Organization (WHO) since 1969 [21, 22].

Chronic fatigue syndrome

CFS is primarily characterized by chronic fatigue which restricts activity levels, lasts for at least 6 months, and women are more frequently affected than men. The disease compromises the ability to perform daily activities, patients report feeling unwell after exertion and not sleeping restfully, they show either cognitive impairment or orthostatic intolerance, and physical disability may occur [21, 22].

In addition to fatigue, people affected by CFS suffer from neurocognitive, autonomic, and immunological symptoms. Post-exertional malaise (PEM), a pronounced and persistent intensification of all symptoms after minor physical or mental exertion, is particularly characteristic of the disease. This leads to pronounced weakness, diffuse muscle pain, flu-like symptoms, and a worsening of the general condition [21, 22].

CFS, FMS, LCS, silicone breast implant syndrome (SBI), sick building syndrome (SBS), post-orthostatic tachycardia syndrome (POTS), and adjuvant-induced autoimmune inflammatory syndrome (ASIA) are often associated with clinical symptoms characteristic of dysautonomia: severe fatigue, dizziness, fogginess, memory loss, dry mouth and eyes, hearing impairment, tachycardia [23].

Long COVID

The term LCS has recently been used as a diagnostic label for individuals who have persistent health problems in the form of an inadequately understood state of incomplete recovery following infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or who develop a variety of medically unexplained symptoms that have arisen following COVID-19 infection, which are ultimately controversial. Several features of these most common clinical manifestations of LCS are also found in a disease that is well known to rheumatologists and has been the subject of extensive epidemiologic, clinical, and basic science research in recent decades—FMS [13, 14]. Recently, it has been suggested that long COVID is simply a new name for FMS [10] and that this diagnosis is in fact the condition that many or most people suffer from as a result of just any preceding infection [24].

Rheumatologists have much to contribute to LCS research due to their existing rheumatologic and immunologic expertise in chronic inflammation and autoimmunity. Nonetheless, LCS has now already long become part of everyday medical practice and occupies rehabilitation physicians and several other professional groups [25], and psychosomatic aspects are thought to play an important role here [26].

LCS is a condition that often severely debilitates the affected patients and occurs in at least 10% of infections with SARS-CoV-2 in COVID-19 [27]. However, the nomenclature has not yet been standardized and there is still no international consensus. More than 200 potentially LCS-associated symptoms have now

been identified, which can affect various organ systems. Approximately 65 million people worldwide are thought to suffer from these often-protracted illnesses [28]. There is currently no consensus on a single pathogenic mechanism in LCS, although there are indications of autoimmune disease, effects of persistent viral infections or latent viral reactivation, microvascular disease, dysbiosis, and tissue damage, see below.

Of particular relevance to the link between LCS and FMS is the common evidence of CNS dysfunction, including glial activation and central sensitization, which are well-documented for both conditions [28]. Previous studies on both conditions have focused on the assumption that psychological factors play a causative role, as most people with nociplastic pain have some form of psychological problem. However, more recent studies show that many people with chronic pain who have high levels of depression or marked tendencies towards catastrophizing show rapid improvement in these areas when their pain is successfully treated, suggesting a not insignificant bidirectional relationship [29, 30].

In an assessment from the Mayo Clinic published during the pandemic [28], there are 4 main points to consider when it comes to the consequences of COVID-19 in patients with FMS and CFS. First, this cohort is just as affected by SARS-CoV-2 infection and possible consequences as the rest of the population. Secondly, stress factors (physical, mental, emotional, or financial) can directly and negatively affect the underlying process of the presenting health problems, which in turn can exacerbate symptoms. Thirdly, given the high comorbidity of mood disorders in patients with FMS and CFS, it is likely that the pandemic will have a negative impact on mood. Additional dysregulation of the limbic system in centrally sensitized patients can acutely exacerbate symptoms of depression and anxiety. Fourthly, it is widely recognized that the financial and social impact of these conditions is significant [28]. The worsening of symptoms will result in higher utilization of health care services and entail direct medical costs, indirect societal costs, and further productivity losses.

The discussion about the nomenclature is currently ongoing. There are experts who feel that we should just call the condition post COVID-19 FMS [10], while others stress that research has not provided enough evidence for a final decision and that more studies are needed [9, 29]. Indeed, already many studies have been performed and they are in large part controversial.

The frequency of LCS is about 10% of all COVID-19 infections [27], depending on the cohort studied. In the biggest study performed to date, an increased risk of anosmia, dysgeusia, cognitive impairment, dyspnea, weakness, and palpitations was found [31]. SARS-CoV-2-RNA doesn't persist in plasma-, stool-, urine-, and probes from the nasopharynx of 57 COVID-19 survivors with symptoms suggestive of LCS [32]. In a randomized controlled trial with 155 LCS patients, antiviral treatment with nirmatrelvir-ritonavir failed to show a significant difference between patients whether treated or not [33]. However, there are studies suggesting a pathophysiological immunologic basis for LCS [34–37], while others failed to show a clear deficit [38–40]. Nevertheless, there is evidence that the body-brain axis acts as a principal conductor of organ-related physiology [41], since it controls organ functions, metabolism, and nutritional states. Indeed, a peripheral immune insult was shown to activate the body-brain axis via cytokines communicating with vagal neurons to regulate immune responses [41].

Several studies support the influence of psychological factors on the outcome of COVID-19 infections [42–45]. For example, the incidence of a psychiatric diagnosis following COVID-19 was 18% in one study, 5.8% of which were a first-time diagnosis [29]. In another study, the majority of patients (64%) with unexplained long-lasting neurological symptoms after COVID-19 met the diagnostic criteria for a somatic symptom disorder, and CFS [42]. However, in other studies, much lower frequencies were reported [45]. In a large Norwegian prospective cohort study, it was shown that the presence of psychological abnormalities prior to infection was the most important predictor of LCS [43]. This result strongly supports the fact that this syndrome is largely favored by pre-existing psychological factors. In addition, patients with a prior diagnosis of FMS reported a significant self-perceived worsening of pain, depressive mood, anxiety as well as reduced physical activity due to the pandemic [46]. The important link between psyche and soma has been convincingly illustrated by a recent study showing that pretreatment emotional distress was

associated with a reduced response (46% vs. 65%) and reduced progression-free survival (74% vs. 91%) to neoadjuvant immune checkpoint blockade response in patients with melanoma [47].

The heterogeneous appearance of LCS indicates involvement of the autonomic nervous system which has numerous tasks in maintaining homeostasis and coordinating responses to various stress factors [48]. The definition of cardiovascular autonomic dysfunction (CVAD) severely affected patients with LCS fulfill the diagnostic criteria for two common manifestations of CVAD [49]: POTS and inappropriate sinus tachycardia. Other possible disorders include orthostatic or postprandial hypotension and recurrent reflex syncope [49]. Of interest, muscle abnormalities have been shown to worsen after PEM in LCS [50].

Two studies have challenged the specificity of COVID-19-related long-term outcomes [51, 52]. Thus, in the COVIDENCE study prospectively performed in the UK, the prevalence of post-COVID symptoms was similar to other types of respiratory infections [51]. In another more recent study, patients presenting to an emergency department who developed symptoms consistent with the clinical case definition of LCS by the WHO were followed up, and those who had tested positive for SARS-CoV-2 were compared to time-matched patients with negative tests [52]. About one-third of patients with a proven acute COVID infection met the WHO criteria 3 months after the index visit. However, about 20% of test-negative patients who reported not to have been infected also reported LCS symptoms. However, whether this is due to a lack of specificity in the clinical case definition has remained unclear.

Selected treatment aspects

In a recent review, the most effective treatments for FMS applied in rehabilitation settings have been identified [53]. These cover all treatments incorporating education and exercise programs and including aerobic exercise, stretching, relaxation, muscle strengthening, endurance, including the entire body and biofeedback. Cognitive behavioral therapy for self-management such as occupational therapy, moderation, acceptance, commitment, motivation to change, and forgiveness seems to be also beneficial for the management of FMS [53]. International guidelines have recommended cognitive behavioral therapy, including acceptance and commitment therapy. The effects of a 12-week, self-guided, smartphone-delivered digital program on fibromyalgia management using this approach have just been evaluated with remarkable success [54]. Furthermore, there is some evidence from a prospective, randomized, 52-week, single-blind comparative effectiveness trial on the ancient Chinese traditional exercise Tai Chi [55] which showed beneficial treatment effects using revised FMS impact questionnaire scores at 24 weeks as the primary outcome hereby confirming an extending older data using this technique [56]. In addition, a randomized, controlled clinical trial using Mindfulness-Based Stress Reduction (MBSR) showed positive results in patients with FMS including immune regulatory effects [57]. This was confirmed in another study [58], and also in a systematic review and meta-analysis [59].

Finally, international recommendations on the management of POTS which have some similarities to PEM [60] have been published some time ago, including drug treatment, for example with β-blockers [61–63]. However, this has not been confirmed for LCS to date [64]. I have personally seen several patients who reported to have benefited from treatment with nebivolol (unpublished).

Conclusions

The differential diagnostic and therapeutic assessment of pain conditions is essential for rheumatology care. In addition to the basic assessment of whether the pain patients complain about is caused by inflammation, this includes the differentiation of the three defined forms of pain (nociceptive, neuropathic, and nociplastic) and the diagnostic determination of whether it is FMS. For this purpose, the available criteria (WPI) should always be documented to avoid non-scientific procedures in the diagnostic process of FMS.

Following the COVID-19 pandemic, there is another global public health challenge known as LCS, post-COVID syndrome, or post-acute sequelae of SARS-CoV-2 infection. This post-infection symptomatology occurs in many forms and potentially affects all body organs. Anosmia and ageusia have been identified as

specific symptoms, but these only occur in < 20% of LCS patients. Another potentially specific symptom is inadequate fatigue and malaise after exertion. In addition, there is clear evidence of neurocognitive dysfunction in patients with LCS. Psychological influencing factors have also been identified. While viral persistence does not appear to play a role, there are various studies in which immunological characteristics have been described in LCS patients. However, it is still too early for a summarizing evaluation. There are of course similarities between LCS and FMS [64].

For future research, it will be important to agree on a common definition of LCS [65]. As recently proposed, long COVID may be best explained as an embodied condition with heterogeneous biological, psychological, social, and environmental factors integrated in complex relationships [66].

Following the interesting session including a debate between X. Mariette and L. Calabrese at the EULAR Congress 2024, Landewé [67] and Mariette [68] commented on the current discussion and highlighted the problems of rheumatologic care for patients with FMS and the challenges for rheumatologic research in this regard. They agreed that cooperation with psychologists is important for both.

Given the multitude of symptoms and organ systems, possibly involved collaboration with other specialties is essential for the management of chronic pain syndromes such as LCS. In any case, major therapeutic challenges associated with these complex disorders remain [69].

Rheumatologists had a prominent role in the conceptualisation of nociplastic pain since the prototypical condition of this third type of pain is FMS, and they currently have an important role in the recognition of FMS—not only because it is also present as a secondary phenomenon in many inflammatory rheumatic diseases [70].

Abbreviations

CFS: chronic fatigue syndrome

CNS: central nervous system

CVAD: cardiovascular autonomic dysfunction

FM: fibromyalgia

FMS: fibromyalgia syndrome

LCS: long COVID syndrome

PEM: post-exertional malaise

POTS: post-orthostatic tachycardia syndrome

RMD: rheumatic musculoskeletal diseases

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

WPI: widespread pain index

Declarations

Author contributions

JB: Conceptualization, Investigation, Writing—original draft, Writing—review & editing.

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Jürgen Braun who is the Associate Editor and Guest Editor of Exploration of Musculoskeletal Diseases had no involvement in the journal review process of this manuscript.

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