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Rheumatology and Long COVID: lessons from the study of fibromyalgia

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25 May 2023**ABSTRACT**

Rheumatology, such as other subspecialties, has both a unique perspective to offer as well as an evolving role to play in the global COVID-19 pandemic. Our field has already contributed meaningfully to the development and repurposing of many of the immune-based therapeutics which are now standard treatments for severe forms of the disease as well as to the understanding of the epidemiology, risk factors and natural history of COVID-19 in immune-mediated inflammatory diseases. Still in evolution is our potential to contribute to burgeoning research efforts in the next phase of the pandemic: the syndrome of postacute sequelae of COVID-19 or Long COVID. While our field brings many assets to the study of Long COVID including our expertise in the investigation of chronic inflammation and autoimmunity, our Viewpoint focuses on the strong similarities between fibromyalgia (FM) and Long COVID. While one can speculate on how embracing and confident practising rheumatologists already are regarding these interrelationships, we assert that in the emerging field of Long COVID the potential lessons from the field of fibromyalgia care and research have been underappreciated and marginalised and most importantly now deserve a critical appraisal.

LONG COVID AT A GLANCE

As the pandemic has evolved, a growing number of patients infected with SARS-CoV-2 have reported long-lasting and persistent symptoms following the normal duration of COVID-19. In those with severe COVID-19, these long-term sequelae may be attended by clear evidence of underlying tissue pathology (eg, pulmonary scarring, vascular thrombosis, postintensive care psychological trauma) which have a reasonable basis for understanding.¹ Other manifestations of Long COVID appear highly pathogen-specific such as anosmia and ageusia which were quite common with pre-Omicron strains but have since become relatively rare.² Far more common, however, and the focus of this Viewpoint, are those individuals who, following mild-to-moderate COVID-19, develop a heterogeneous and diverse collection of largely unexplained symptoms dominated by fatigue (often with features of postexertional malaise), neurocognitive dysfunction often referred to as ‘brain fog’, sleep disturbances and varying forms of pain including myalgia, arthralgia, headache, chest pain and beyond.^{1,3} As the international research community attempts to unravel Long COVID, much has been written regarding the similarities with myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS),^{1,2} yet relatively little has been discussed regarding the similarly strong parallels to a condition with a rich background of clinical and basic research which is

familiar to many in the rheumatology community: FM.

FM and other closely related pain conditions have been extensively studied and as such have potential to serve as resources for both mechanistic and clinical studies in Long COVID. In fact the international community of pain researchers recently formally voted to acknowledge that FM is the exemplar for a third newly identified mechanism of pain, nociplastic pain, where pain is one of many seminal features that also includes fatigue, memory, sleep and mood issues as the core symptoms.^{4,5} Several of us with experience in FM wrote an editorial just a few months after the pandemic began predicting much of what Long COVID would look like based on previous experience with similar postinfectious, postdeployment and/or post-traumatic exposures that triggered nearly identical conditions.^{6–9} We believe that it is time to critically appraise the relationships between Long COVID and FM and related conditions to draw on this body of data for current research and future therapies.

PARALLELS BETWEEN FM AND LONG COVID

FM and ME/CFS are now considered chronic overlapping pain conditions (COPCs), which include other common pain conditions such as tension headache, irritable bowel syndrome, low back pain, temporomandibular disorders and bladder pain syndrome.¹⁰ In the newest International Classification of Disease (ICD) criteria, these conditions are lumped together as primary pain syndromes, that is, the pain is the primary problem and is not driven by another disease.¹¹ These conditions all have nociplastic pain, a newly recognised third mechanism of pain, as their primary mechanism. Whereas nociceptive pain occurs because of inflammation or damage of peripheral tissues, and neuropathic pain is due to nerve injury, nociplastic pain is largely driven by the central nervous system (CNS). In all of these conditions there are small subsets of individuals whose pain is driven by ongoing nociceptive input (eg, peripheral inflammation or damage) or neuropathic mechanisms but the primary nociplastic mechanisms in all of these conditions are thought to be driven by the same, CNS process. These same nociplastic pain mechanisms are also commonly superimposed on nociceptive pain states such as autoimmune disorders, where up one-third or more are thought to have what used to be called secondary FM and then more recently central sensitisation. The risk factors for these conditions include female sex (which has 1.5–2×OR), SES factors, poor sleep, physical inactivity and cigarette smoking, which overlaps a tremendous amount with what is seen in Long COVID.^{12,13} In the studies that



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have closely examined the postinfectious pain manifestations of both COVID and similar postinfectious syndromes, individuals who have pain preinfection are likely to be left with more chronic pain as one of the sequelae, although many develop de novo pain.^{14–17}

PATHOPHYSIOLOGICAL LINKS BETWEEN FM AND LONG COVID

Further alignment between Long COVID and nociplastic pain is pathophysiologic. At present, there is no agreement of a singular pathogenic mechanism in Long COVID across clinical domains though evidence is emerging for numerous putative pathways including autoimmune, the effects of persistent viral infection or latent viral reactivation, microvascular disease, dysbiosis and tissue damage.¹⁸ Of particular relevance to the connection between Long COVID and FM is shared evidence of CNS dysfunction including glial activation¹⁹ and central sensitisation²⁰ which are well documented across both disorders. Using functional neuroimaging and quantitative testing techniques in nociplastic pain states such as FM, we can identify reproducible neural signatures, some of which even might be present in children who are at risk of subsequently developing this spectrum of illness.^{21 22}

The role of psychological factors in these nociplastic conditions is somewhat contentious but becoming increasingly understood. Many early studies in these conditions focused on these psychological factors being causative, since many or most individuals with a nociplastic pain condition will exhibit some form of psychological distress. But more recent studies show that many individuals with chronic pain who have high levels of depression or catastrophising have rapid improvements in these domains when they are successfully treated for their pain,^{23 24} suggesting a strong bidirectional relationship. When a nociplastic state is triggered by a stressor such as deployment to war, infections or trauma the typical course is that individuals begin sleeping

poorly, become fatigued and less active, and develop distress since they are uncertain of whether or when they will improve. Moldofsky and Scarisbrick have shown the importance of sleep and activity with these conditions. A FM/CFS state can be experimentally induced in healthy individuals with sleep restriction and/or exercise cessation, and was noted in 2011 in individuals with severe acute respiratory distress syndrome.^{25–27} Often when individuals with these nociplastic states seek healthcare for these non-specific symptoms, they are minimised or ignored, since few clinicians have experience treating this spectrum of illness. Thus, it is not surprising that many have psychological comorbidities that should be addressed, just as we should target their issues with sleep, pain and functional decline.

With the understanding that Long COVID appears to be a highly clinically heterogeneous disorder with multiple clinical endotypes we propose that both Long COVID and FM as well as other forms of COPCs should be viewed as a collectively rich network of inter-related disorders for which a shared pathogenic mechanism may account for a significant segment—but clearly not all—of this evolving clinical spectrum. (figure 1).

CLINICAL POTENTIAL OF CROSS-DISCIPLINARY RESEARCH

As rheumatologists, we know that even though there have been major advances in the therapeutics which enable us to much more effectively treat the inflammation and resultant tissue damage in individuals with autoimmune disorders, many or even most of our patients are still left with a constellation of fatigue, multifocal pain, sleep, memory and mood disturbances. So one lesson from the rheumatology community to the broader medical community is that even with established autoimmune disorders that often begin as very inflammatory conditions, the core symptoms of fatigue, sleep, multifocal pain, memory and mood problems seen in these nociplastic disorders often continue once the inflammation is successfully treated. Moreover, the most effective treatments of these nociplastic pain conditions are

Proposed Relationship between Long COVID and Fibromyalgia and related pain conditions

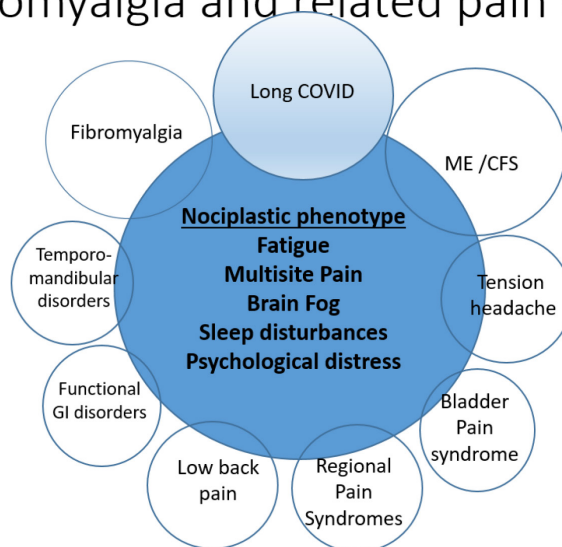


Figure 1 The figure depicts the partial relationships among a number of defined conditions with overlapping symptoms with the most common clinical endotype observed in Long COVID (ie, fatigue, pain, brain fog and sleep disturbances). Fibromyalgia and ME/CFS are displayed most prominently to reflect the centrality of the represented symptoms in these disorders. While each entity is represented by a discreet circle virtually all may have overlap with each either singly or in combination and cannot readily be displayed. ME/CFS, myalgic encephalomyelitis or chronic fatigue syndrome.

non-pharmacological therapies such as various types of cognitive behavioural therapy, having individuals become more active and engaging in the use of a number of integrative therapies such as meditation, yoga, Tai Chi, physical and movement therapies, and acupuncture/acupressure.²⁸ The pain in these conditions is not typically responsive to opioids or NSAIDs. Instead, medications such as tricyclic antidepressants, gabapentinoids and serotonin norepinephrine reuptake inhibitors that act in the CNS can be helpful. While there are many integrative therapies now undergoing clinical trials in Long COVID our past experience in FM and related conditions could and should inform these and future studies in design and interpretation.

CONCLUSION

We conclude that the relationship between Long COVID and FM and other COPCs is strong and supported by elements providing both face and content validity based on a large body of clinical and research data. Collectively, we feel these symmetries support the need to advance a research agenda into shared mechanisms across these conditions that might hopefully provide new insights for better understanding and treatments for both.

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REFERENCES

- Davis HE, McCorkell L, Vogel JM, et al. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;21:133–46.
- Choutka J, Jansari V, Hornig M, et al. Author correction: unexplained post-acute infection syndromes. *Nat Med* 2022;28:1723.
- Calabrese C, Kirchner E, Calabrese LH. Long COVID and rheumatology: clinical, diagnostic and therapeutic implications. *Best Pract Res Clin Rheumatol* 2022;101794.
- Fitzcharles M-A, Cohen SP, Clauw DJ, et al. Nociceptive pain: towards an understanding of prevalent pain conditions. *Lancet* 2021;397:2098–110.
- Kosek E, Clauw D, Nijs J, et al. Chronic nociceptive pain affecting the musculoskeletal system: clinical criteria and grading system. *Pain* 2021;162:2629–34.
- Clauw DJ, Engel CC, Aronowitz R, et al. Unexplained symptoms after terrorism and war: an expert consensus statement. *J Occup Environ Med* 2003;45:1040–8.
- Clauw DJ. The health consequences of the first Gulf war. *BMJ* 2003;327:1357–8.
- Clauw DJ, Häuser W, Cohen SP, et al. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *Pain* 2020;161:1694–7.
- Alunno A, Najm A, De Marco G. Immunomodulatory therapies for SARS-CoV-2 infection: a systematic literature review to inform EULAR points to consider. *Ann Rheum Dis* 2021;80:803–15.
- Maixner W, Fillingim RB, Williams DA, et al. Overlapping chronic pain conditions: implications for diagnosis and classification. *J Pain* 2016;17:T93–107.
- Peluso MJ, Kelly JD, Lu S, et al. Persistence, magnitude, and patterns of Postacute symptoms and quality of life following onset of SARS-Cov-2 infection: cohort description and approaches for measurement. *Open Forum Infect Dis* 2022;9.
- McBeth J, Jones K. Epidemiology of chronic musculoskeletal pain. *Best Pract Res Clin Rheumatol* 2007;21:403–25.
- Tsampanian V, Elghazaly H, Chattopadhyay R, et al. Risk factors associated with Post-COVID-19 condition: a systematic review and meta-analysis. *JAMA Intern Med* 2023:e230750.
- Hickie I, Davenport T, Wakefield D, et al. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 2006;333:575.
- Fernández-de-Las-Peñas C, de-la-Llave-Rincón AI, Ortega-Santiago R, et al. Prevalence and risk factors of musculoskeletal pain symptoms as long-term post-COVID sequelae in hospitalized COVID-19 survivors: a multicenter study. *Pain* 2022;163:e989–96.
- Ursini F, Ciuffi J, Mancarella L, et al. Fibromyalgia: a new facet of the post-COVID-19 syndrome spectrum? Results from a web-based survey. *RMD Open* 2021;7:e001735.
- Phillips K, Clauw DJ. Central pain mechanisms in the rheumatic diseases: future directions. *Arthritis Rheum* 2013;65:291–302.
- Peluso MJ, Donatelli J, Henrich TJ. Long-term Immunologic effects of SARS-Cov-2 infection: leveraging translational research methodology to address emerging questions. *Transl Res* 2022;241:1–12.
- Monje M, Iwasaki A. The neurobiology of long COVID. *Neuron* 2022;110:3484–96.
- Goudman L, De Smedt A, Noppen M, et al. Is central sensitisation the missing link of persisting symptoms after COVID-19 infection. *J Clin Med* 2021;10:5594.
- López-Solà M, Woo C-W, Pujol J, et al. Towards a neurophysiological signature for Fibromyalgia. *Pain* 2017;158:34–47.
- Kaplan CM, Schrepf A, Mawla I, et al. Neurobiological antecedents of Multisite pain in children. *Pain* 2022;163:e596–603.
- Lape EC, Selzer F, Collins JE, et al. Stability of measures of pain Catastrophizing and widespread pain following total knee replacement. *Arthritis Care Res (Hoboken)* 2020;72:1096–103.
- Cohen EM, Edwards RR, Bingham CO, et al. Pain and Catastrophizing in patients with rheumatoid arthritis: an observational cohort study. *J Clin Rheumatol* 2019;25:232–6.
- Moldofsky H, Scarisbrick P. Induction of neurasthenic musculoskeletal pain syndrome by selective sleep stage deprivation. *Psychosom Med* 1976;38:35–44.
- Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol* 2011;11:37.
- Ablin JN, Clauw DJ, Lyden AK, et al. Effects of sleep restriction and exercise deprivation on somatic symptoms and mood in healthy adults. *Clin Exp Rheumatol* 2013;31:S53–9.
- Clauw DJ. Fibromyalgia: a clinical review. *JAMA* 2014;311:1547–55.