Long COVID: clues about causes

Felicity Liew, Claudia Efstathiou and Peter J.M. Openshaw

National Heart and Lung Institute, Imperial College London, London, UK.

Corresponding author: Peter J.M. Openshaw (p.openshaw@imperial.ac.uk)

Shareable abstract (@ERSpublications)
Scott *et al.* examined monocyte and inflammatory profiles in patients previously hospitalised with COVID-19. They propose localised lung injury causes post-COVID breathlessness, with inflammation affecting monocytes and tissue macrophages driving fatigue. https://bit.ly/40jXs2d

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Many patients report persistent symptoms after resolution of acute COVID-19, regardless of SARS-CoV-2 variant and even if the initial illness is mild [1, 2]. A multitude of symptoms have been described under the umbrella term "long COVID", otherwise known as "post-COVID syndrome" or "post-acute sequelae of SARS-CoV-2 (PASC)"; for simplicity we will use the term long COVID. Symptoms are diverse but include breathlessness, fatigue and brain fog, reported to affect up to 69% of cases [3]. Long COVID can be debilitating, with 45.2% of patients requiring a reduced work schedule [4]. The World Health Organization estimates that 17 million people in Europe experienced long COVID during the first 2 years of the pandemic [5]. SARS-CoV-2 variants continue to circulate and the risk of post-acute complications remains; a recent study of 56 003 UK patients found that even after Omicron infection, 4.5% suffered persistent symptoms [6]. It is therefore likely that long COVID will provide a substantial medical and economic burden for the foreseeable future. There is an urgent need to understand the mechanisms of the disease and develop effective treatments based on this understanding.

Given the heterogeneity of clinical presentations it seems likely that different long COVID phenotypes are driven by distinct mechanisms, yet few studies have focussed on carefully selected patients defined by mechanisms and affected organs (figure 1) [7, 8]. In this issue of the *European Respiratory Journal*, Scott *et al.* [9] studied 75 patients hospitalised with acute COVID-19 alongside 142 convalescent patients, followed-up between 63 and 246 days after discharge. The authors describe severity-related monocyte signatures during acute COVID-19, finding distinct inflammatory profiles in convalescent patients with symptoms. These profiles differed between patients with symptoms of fatigue compared to those with breathlessness, unrelated to the severity of the initial illness. This work provides an important step towards understanding the complexity of long COVID syndromes.

Coming from a collaborative team with expertise in monocyte biology, Scott *et al.* [9] demonstrate enhanced monocyte expression of chemokine receptor CXCR6 and adhesion molecule PSGL1 in patients with post-COVID-19 breathlessness. Both can promote migration into lung tissue [10, 11], and the changes were most pronounced in those with abnormal radiology. The authors suggest that monocyte-driven lung injury might cause breathlessness after COVID-19. Importantly, Scott *et al.* [9] included a post-respiratory syncytial virus/influenza cohort of which five out of 10 remained breathless after hospital admission, but did not show the changes in monocyte phenotype seen after COVID-19. Additionally, they found that PSGL1 expression was not elevated in patients with progressive fibrosing interstitial lung disease, again supporting the specificity of these findings to post-COVID-19 lung injury. These findings provide an exciting insight into the potential causes of post-COVID-19 symptoms.

With respect to the diversity of long COVID syndromes, Scott *et al.* [9] distinguish patients presenting with fatigue from those suffering from breathlessness. They demonstrated that individuals with fatigue exhibited persistently low monocyte expression of COX-2 and CXCR2 up to 9 months after COVID-19. COX-2 is a prostaglandin-producing enzyme involved in the eicosanoid pathway which is known to be

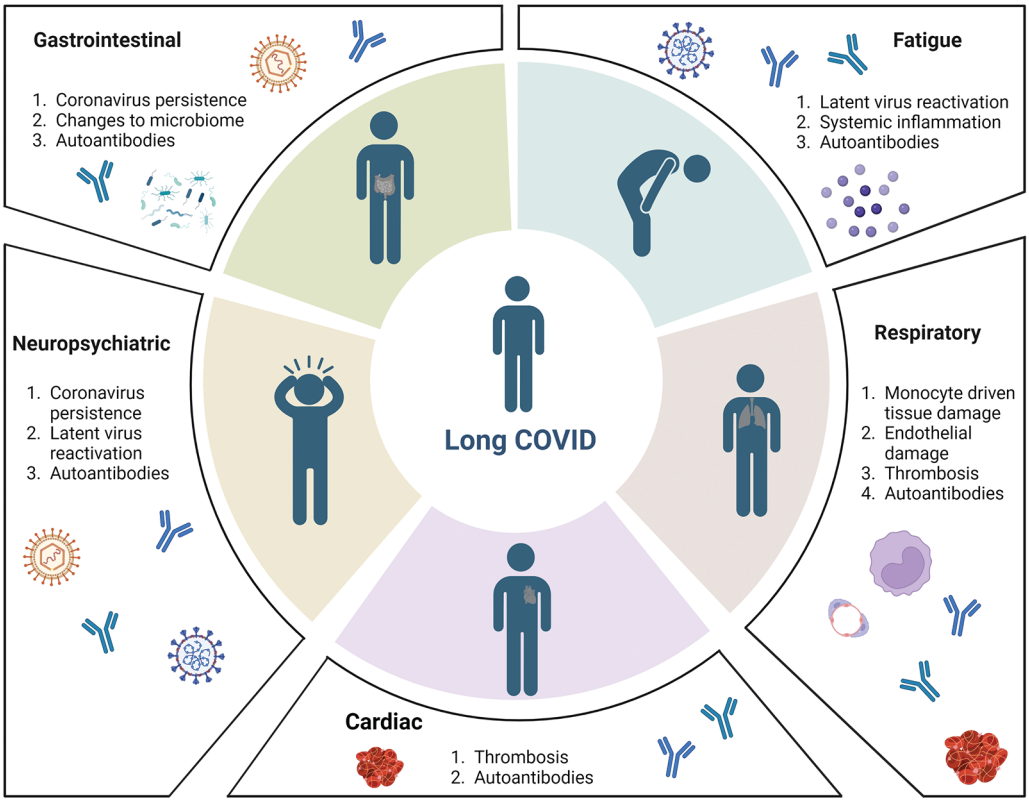

FIGURE 1 Common symptoms associated with long COVID and possible underlying pathophysiology.

important in maintaining tissue integrity, platelet function and innate immune responses against pathogens [12, 13]. Thus, Scott *et al.* [9] make a case for localised lung injury in post-COVID-19 breathlessness, whilst more generalised inflammation involving monocytes and tissue macrophages might drive fatigue.

However, some important questions remain: what causes the persistent inflammation in these patients, and why do some individuals develop abnormal immunological profiles and delayed recovery? Thrombotic events have been described, even many months after acute COVID-19 [14], and the resulting ischaemia and tissue necrosis [15] could explain the monocyte derived lung inflammation described by Scott *et al.* [9]. In fact, the authors cite evidence that some patients with breathlessness after COVD-19 may have extremely subtle changes in the lung that are only evident using advanced imaging techniques, such as hyperpolarised xenon magnetic resonance imaging [16]. In that study, patients with dyspnoea had limitations in diffusion capacity, which is in keeping with thromboembolic disease. To address this, Scott *et al.* [9] used a quantitative lung density analysis to identify lung inflammation in patients who had normal conventional imaging. Using this method, they identified that 37.5% of patients with breathlessness but normal conventional imaging had subtle signs of lung injury. It would be useful for future studies to examine these patient groups specifically, to determine if those with symptoms with and without abnormal conventional imaging exhibit different pathology. Several clinical trials for anticoagulants are ongoing, and careful patient selection for these trials will be integral to their success [8].

Viral persistence has been proposed as a potential mechanism for ongoing immune perturbation in many post-viral syndromes, and demonstrated after Ebola virus infection [17]. One study of 87 individuals found continued evolution of the B-cell response to SARS-CoV-2 up to 6 months after infection when 44% had persistent symptoms [18]. In this study, viral antigen was detected in intestinal biopsies 4 months after infection, providing evidence that persistent virus may stimulate chronic immune disturbance after COVID-19. With this in mind, it is interesting that Scott *et al.* [9] found enhanced monocyte expression of the gut-homing integrin β7 in patients with acute severe COVID-19, highlighting the possibility that an intestinal coronaviral reservoir might be driving persistent inflammation. Persistent virus has also been found in the lung up to 300 days after SARS-CoV-2 infection [19], which might explain ongoing lung inflammation described by Scott *et al.* [9]. Alternatively, reactivation of latent Epstein–Barr virus

(or cytomegalovirus) infection might conceivably result in inflammatory responses in certain patients, as suggested by two studies of patients with persistent fatigue and/or neurological symptoms such as brain fog [20, 21]. Future studies which confirm or refute viral persistence or reactivation as a potential cause could be transformative, should trials of antivirals be shown to clear virus and resolve persistent symptoms.

Finally, anti-interferon autoantibodies have been associated with severe acute COVID-19, leading many to question whether long COVID might sometimes have an autoimmune pathogenesis [22]. Whilst one recent study of 220 patients did not find associations between long COVID and autoantibodies [20], long COVID phenotypes with gastrointestinal and respiratory symptoms have been associated with autoantibodies [23]. The findings of Scott *et al*. [9] support the suggestion that different biological mechanisms underpin different long COVID subtypes.

Scott *et al*. [9] used changes in pulmonary function tests (PFTs) to substantiate their findings that inflammatory damage to lung tissue underlies persistent breathlessness. Whilst PFTs are useful in clinical practice, they must be interpreted carefully with respect to understanding the physiology of a new disease. Scott *et al*. [9] report a reduced forced expiratory volume in 1 s in patients with breathlessness, but the differences were small and the mean percentage predicted value was above the 80% threshold of expected results [24]. If this reduction is genuine, the reasons for airflow obstruction are not clear. Monocyte-driven damage to the alveolar–capillary membrane would be likely to affect gas transfer rather than airflow, which was not seen in their study. However, the authors acknowledge the study was not powered to look for changes in lung function, which can be subtle in the early stages of disease, and the study leaves questions open as to the physiology underpinning dyspnoea in these patients. It is essential that future work continues to integrate clinical and immunological data, but large and carefully designed studies will be required to detect subtle changes in physiological parameters and provide clarity on how to interpret PFTs in the context of long COVID.

This work provides an important contribution to the growing body of evidence that long COVID is a multifarious disease with diverse causes. Given the growing evidence that different patterns of symptoms might be driven by distinct pathophysiological pathways (figure 1), it is essential that rigorous and evidence-based classifications of disease are used to design trials of specific interventions based on this knowledge. Many clinical trials are underway to identify potential treatments [8], but there is a risk that these trials will show no benefits if patients with different pathogenic pathways are not differentiated. By examining the underlying causes of different long COVID subtypes, studies such as that by Scott *et al*. [9] may ultimately lead to treatments aligned to specific patient phenotypes based on a deeper understanding of disease pathways.

The message of studies such as this is also one of hope for those who have suffered for many years from mysterious and hard to manage conditions termed variously post-viral fatigue, fibromyalgia, autonomic instability and other conditions that may be disabling but for which no underlying cause or treatment is evident. If the COVID-19 pandemic ultimately leads to a better understanding of what causes such ailments and how they might be treated, many will have cause to celebrate.

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