Psychoneuroendocrinology 131 (2021) 105295

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Short Communication

Interleukin-6 as potential mediator of long-term neuropsychiatric symptoms of COVID-19

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ARTICLE INFO

Keywords:
COVID-19
Long COVID
Interleukin-6
Fatigue
Sleep
Depression

ABSTRACT

The majority of COVID-19 survivors experience long-term neuropsychiatric symptoms such as fatigue, sleeping difficulties, depression and anxiety. We propose that neuroimmune cross-talk via inflammatory cytokines such as interleukin-6 (IL-6) could underpin these long-term COVID-19 symptoms. This hypothesis is supported by several lines of research, including population-based cohort and genetic Mendelian Randomisation studies suggesting that inflammation is associated with fatigue and sleeping difficulties, and that IL-6 could represent a possible causal driver for these symptoms. Immune activation following COVID-19 can disrupt T helper 17 (T_H17) and regulatory T (T_{reg}) cell responses, affect central learning and emotional processes, and lead to a vicious cycle of inflammation and mitochondrial dysfunction that amplifies the inflammatory process and results in immuno-metabolic constraints on neuronal energy metabolism, with fatigue being the ultimate result. Increased cytokine activity drives this process and could be targeted to interrupt it. Therefore, whether persistent IL-6 dysregulation contributes to COVID-19-related long-term fatigue, sleeping difficulties, depression, and anxiety, and whether targeting IL-6 pathways could be helpful for treatment and prevention of long COVID are important questions that require investigation. This line of research could inform new approaches for treatment and prevention of long-term neuropsychiatric symptoms of COVID-19. Effective treatment and prevention of this condition could also help to stem the anticipated rise in depression and other mental illnesses ensuing this pandemic.

1. Viewpoint

A notable proportion of acute COVID-19 survivors experience long-term physical and neuropsychiatric symptoms (Huang et al., 2021; Lerner et al., 2021), which according to the UK National Institute for Health and Care Excellence (NICE) can be classed as "ongoing symptomatic COVID-19" (symptoms persisting for 4–12 weeks after illness onset) and as "post-COVID-19 syndrome" or "long COVID" (symptoms persisting >12 weeks) (Venkatesan, 2021). These ongoing symptoms broadly fall into two categories: respiratory (e.g., cough, shortness of breath, chest tightness) and neuropsychiatric (e.g., fatigue, cognitive dysfunction, sleeping difficulties, depression, and anxiety) (Carfì et al., 2020; Davis et al., 2020; Huang et al., 2021; Lopez-Leon et al., 2021; Mazza et al., 2020; Taquet et al., 2021, 2020). A recent cohort study based on data from 1733 hospital-discharged patients from Wuhan, China, reported that about 75% of patients still experience at least one physical or mental health symptom six months after hospitalisation, with fatigue or muscle weakness (63%), sleeping difficulties (26%), and depression or anxiety (23%) being the most common (Huang et al., 2021). Another cohort study reported that COVID-19 survivors had a higher incidence of several psychiatric disorders compared with matched patients with influenza or other respiratory tract infections, indicating specific pathophysiologic mechanism(s) may underpin neuropsychiatric sequela of COVID (Taquet et al., 2021). While compromised cardiopulmonary function, increased muscle catabolism and persistent breathing difficulties are common after pulmonary infections and hospitalisation, and can contribute to ongoing fatigue and sleeping difficulties, we propose that neuroimmune cross-talk via

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https://doi.org/10.1016/j.psyneuen.2021.105295
Received 2 March 2021; Received in revised form 15 April 2021; Accepted 20 May 2021
Available online 3 June 2021

inflammatory cytokines such as interleukin-6 (IL-6) could underpin some of the long-term neuropsychiatric features of COVID-19. The aim of this viewpoint is to provide a mechanistic framework on how IL-6 could underlie long-term neuropsychiatric COVID symptoms to inform future research and therapeutic approaches.

1.1. The neuroimmune basis of neuropsychiatric symptoms

Animal and human studies employing different research designs have provided evidence that fatigue, sleeping difficulties and other mood symptoms have a neuroimmune basis (Dantzer et al., 2014). First, it is well-known that sick animals exhibit a characteristic pattern of behaviours such as lethargy, sleepiness, inactivity, and disinterest in surroundings, collectively known as sickness behaviour (Hart, 1988). These resemble so-called somatic/neurovegetative symptoms of depression. Second, symptoms of fatigue and sleeping difficulties are common in illnesses characterised by inflammation such as autoimmune diseases, cardiometabolic disease, or microbial infections (Dantzer et al., 2008). Third, treatment with pro-inflammatory interferon-α induces fatigue in cancer patients (Capuron et al., 2002) while treatment with the anti-tumour necrosis factor (TNF)-α drug etanercept reduces fatigue in patients with psoriasis (Tyring et al., 2006).

Recent large-scale population-based epidemiological and genetic studies also support a role of inflammatory cytokines in the aetiology of neuropsychiatric symptoms typically seen in patients with ongoing symptomatic COVID-19 and long COVID. Studies based on general population samples have demonstrated associations between elevated concentrations of circulating inflammatory markers, such as C-reactive protein (CRP), IL-6, and TNF-α with depressive symptoms generally (Khandaker et al., 2014; Wium-Andersen et al., 2013), and specifically with somatic symptoms of depression such as fatigue, sleeping difficulties, and appetite alterations among others (Fried et al., 2019; Jokela et al., 2016; Milaneschi et al., 2021; Moriarity et al., 2020; White et al., 2017). Similar findings have also been reported from studies comparing individuals meeting clinical diagnosis of depression versus healthy controls (Badini et al., 2020; Köhler et al., 2017; Lamers et al., 2020).

Using data from the UK Biobank and the Netherlands Study of Depression and Anxiety (NESDA) cohorts, we have recently shown that fatigue and sleeping difficulties exhibit the most consistent links with inflammatory markers among all depressive and anxiety symptoms, even after controlling for various sociodemographic, lifestyle, and metabolic confounders (Milaneschi et al., 2021). Furthermore, Mendelian randomisation analysis, which uses genetic variants as proxies to disentangle the problems of reverse causation and residual confounding (Lawlor et al., 2008), suggests that altered IL-6 activity could represent one causal immunological driver for fatigue and sleeping problems (Milaneschi et al., 2021). Mendelian randomisation studies using the same genetic variants as proxies for altered IL-6 activity have also reported potentially causal associations of IL-6 with cardiovascular disease, type 2 diabetes, rheumatoid arthritis, and notably with COVID-19 hospitalisation (Bovijn et al., 2020; Georgakis et al., 2021, 2020). Cardiovascular disease and rheumatoid arthritis have established immune basis/links, and are associated with severe COVID-19 (Hyrich and Machado, 2021; Nishiga et al., 2020). Taken together, this evidence supports a potential neuroimmune basis for long-term neuropsychiatric symptoms of COVID-19 potentially mediated by inflammatory cytokines such as IL-6. A better understanding of this neuroimmune basis may lead to new approaches for treatment and prevention of long-term symptoms of COVID-19 (Mondelli and Pariante, 2021).

1.2. The immune signature of COVID-19 and long COVID

SARS-CoV-2 enters the body primarily through the nasal cavity and pulmonary alveoli where cellular infection triggers inflammatory and type I interferon-mediated antiviral responses (Schultze and Aschenbrenner, 2021). In turn, adaptive immunity develops following antigen-presentation of SARS-CoV-2 Spike and other proteins leading to production of virus-specific neutralising antibodies and activation of $CD4^+$ and $CD8^+$ T cells (Sette and Crotty, 2021). Clinically, asymptomatic and mild COVID-19 are thought to result from fast production of virus-specific antibodies and T cell responses while severe disease is associated with delayed and unabated innate immune response, deficient production of SARS-CoV-2-specific T cells, and direct viral toxicity (Sette and Crotty, 2021). Studies have mainly characterised these processes in patients with severe COVID-19, who show substantial immunological diversity regarding T cell dysregulation, dendritic and B cell composition, and cytokine activity such as of IL-6, IL-10, and interferon-γ-induced protein (IP)-10 among others (Laing et al., 2020; Mathew et al., 2020; Schultze and Aschenbrenner, 2021). Importantly, excessive cytokine response and elevated IL-6 have been shown to contribute to severe course of acute COVID-19 and associated mortality (Cummings et al., 2020; Wiersinga et al., 2020; Zhang et al., 2020). IL-6 and TNF-α have also been found to predict survival even after adjusting for disease severity (Del Valle et al., 2020). Therefore, current approaches to treating severe COVID-19 include use of both broad anti-inflammatory drugs such as dexamethasone and specific anti-cytokine drugs such as the anti-IL-6 receptor (IL-6R) drugs tocilizumab and sarilumab that showed favourable effects in addition to dexamethasone on reducing rates of mechanical ventilation and death in critically ill COVID-19 patients (Gordon et al., 2021; Salama et al., 2021; The RECOVERY Collaborative Group, 2020; Veiga et al., 2021).

Post-COVID-19 syndrome and long COVID is relatively less well understood. For COVID-19 patients who received intensive care, long COVID symptoms could result from post-intensive care syndrome, which is characterised by cognitive and psychiatric symptoms as well as immobility, microvascular and metabolic dysregulations (Nalbandian et al., 2021). However, not all individuals suffering from long COVID suffer from severe COVID-19, and incident psychiatric and neurological disorders are more common in hospitalised COVID-19 patients than in matched groups of hospitalised patients with influenza or other respiratory tract infections (Dennis et al., 2021; Taquet et al., 2021). This suggests other mechanisms could also be relevant. Since viral coronavirus particles have been observed in brain tissue, virus-specific pathophysiological changes could be possible contributors to neuropsychiatric symptoms of long COVID. However, SARS-CoV-2 does not seem to infect neurons directly, which leaves immunological alterations and inflammation following COVID-19 as a more promising explanation for these symptoms (Nalbandian et al., 2021). This idea is supported by findings that baseline CRP and immune cell counts characteristic for systemic inflammation are associated with depressive symptoms following COVID-19 (Mazza et al., 2021, 2020). This association also seems to be mitigated in patients who received the anti-IL-1β drug anakinra and the anti-IL-6 drug tocilizumab, which directly implicates the IL-6/IL-6R system (Mazza et al., 2021).

1.3. IL-6 as a mechanistic driver of long COVID

Multiple mechanisms could link IL-6 with long COVID. Immunologically, it is known that IL-6 signalling activates T helper (T_H) cells of the T_H17 lineage and represses regulatory T (T_{reg}) cells, respectively (Bettelli et al., 2006). This mechanism is proposed to contribute to risk for viral diseases such as hepatitis C (Zhang et al., 2015), and it could also be relevant for COVID-19 and long COVID. IL-6 activity leads to a shift in activated T_H cells towards the T_H17 lineage in patients with COVID-19-associated pneumonia (De Biasi et al., 2020; Ghazavi et al., 2021), which could promote T_H17 to T_{reg} imbalance (Sadeghi et al., 2021) or deficient T_H17 and T_{reg} responses (Meckiff et al., 2020). Such deficient T_H17 and T_{reg} responses have also been observed in patients suffering from depression (Grosse et al., 2016).

Centrally, IL-6 and other cytokines can signal the brain via volume diffusion in circumventricular zones, afferent nerves, and by active blood-brain-barrier transport (Dantzer et al., 2008). Once the immune

signal reaches the brain, IL-6 can influence memory processes such as long-term potentiation and depression (McAfoose and Baune, 2009), increase activity in regions implicated in depression such as the anterior cingulate cortex and reduce its connectivity to amygdala and medial prefrontal cortex (Harrison et al., 2009), and promote and regulate sleep-related processes (Rohleder et al., 2012). Activation of innate immune response due to severe infections like COVID-19 can also lead to a vicious cycle of inflammation and mitochondrial dysfunction that amplifies the inflammatory process and results in immuno-metabolic constraints on neuronal energy metabolism (Lacourt et al., 2018; West, 2017).

Together, these findings on T_H17/T_{reg} dysregulation; on learning, affective, and sleep-related brain processes; and on neuronal energy metabolism constraints provide plausible mechanistic links that could explain how systemic inflammation could manifest as long COVID symptoms of fatigue and sleeping difficulties. Therefore, increased cytokine activity that drives the inflammatory process, disrupts T cell responses, and imposes constraints on neuronal energy metabolism could be a suitable therapeutic target for treatment and prevention of long COVID.

1.4. Clinical implications

It is widely anticipated that the COVID-19 pandemic will contribute to increased mental health difficulties in coming years (Holmes et al., 2020). We believe long COVID symptoms like fatigue and sleeping difficulties, which are already part of the symptom profile of depression, could exacerbate this issue. Therefore, whether persistent IL-6 dysregulation and/or activity of other inflammatory markers contributes to COVID-19-related long-term fatigue, sleeping difficulties, and depression or anxiety is an important hypothesis that requires investigation.

In particular, clinical epidemiological studies are needed to determine if IL-6 and/or other inflammatory cytokine levels predict subsequent development and persistence of long COVID. These studies can also help to disentangle to what extent long COVID symptoms are related to persistent IL-6 and/or initial COVID-19 illness severity.

Fatigue is a multifaceted trait comprising both physical and mental as well as sleep-dependent and sleep-independent processes, which are not differentiated in current long COVID questionnaires (e.g., Huang et al., 2021). While fatigue can be a consequence of inflammation-induced pain and sleeping difficulties (Hewlett et al., 2011; Nikolaisen et al., 2008; Rohleder et al., 2012), there is robust evidence that fatigue could arise from the effects of inflammatory cytokines on the brain (Dantzer et al., 2014). Therefore, future studies should include more detailed and repeated assessments of long COVID symptoms to enable systematic examination of relative contributions of, and interrelationships between, immunological and other processes in fatigue and other long COVID symptoms.

For greater insights into IL-6-related mechanisms of long COVID, future immunophenotyping studies would benefit from assays of soluble IL-6R (sIL-6R) and soluble glycoprotein 130 (sgp130). This would provide a more complete picture of IL-6 signalling, which occurs via two distinct pathways (Hunter and Jones, 2015; Scheller et al., 2014). IL-6 classic signalling occurs when IL-6 binds to membrane-bound IL-6Rs together with the ubiquitously expressed gp130. However, membrane-bound IL-6Rs are only present on hepatocytes and certain immune cells and this process is thought to be mainly responsible for central homoeostatic rather than inflammatory processes. In contrast, the pro-inflammatory effects of IL-6 are mainly mediated via IL-6 trans-signalling, whereby IL-6 binds sIL-6Rs and induces signalling on cells that naturally lack IL-6Rs.

IL-6 trans-signalling has been specifically associated with autoimmune conditions and with sleep-related processes (Dimitrov et al., 2006; Hunter and Jones, 2015), which provides a plausible link for the involvement of this form of signalling in long COVID. Blocking IL-6/IL-6R pathway is an established treatment strategy for various autoimmune and inflammatory diseases (Tanaka et al., 2012), which provides an opportunity for randomised controlled trials testing whether this could also be useful for treatment and prevention of long COVID. Such trials could include currently licensed anti-IL-6R monoclonal antibodies such as tocilizumab that inhibit both classic and trans-signalling, or novel IL-6 trans-signalling-specific drugs such as the soluble gp130 fused chimera (sgp130Fc) currently in development. These interventional trials would also be valuable for determining whether trans-signalling-specific drugs have a favourable risk-benefit profile compared to drugs that block both classic and trans signalling (Du et al., 2021).

We now need immediate, interdisciplinary research efforts to investigate proposed immunologic mechanisms for common, debilitating neuropsychiatric features of long COVID.

Funding

This research was funded in whole, or in part, by the Wellcome Trust (grant code: 201486/Z/16/Z). For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission. NK is supported by the International Max Planck Research School for Translational Psychiatry (IMPRS-TP). RD's research is supported by the National Institutes of Health, United States [R01 CA193522, R01 NS073939, and an MD Anderson Cancer Center Support Grant (P30 CA016672)). GMK acknowledges funding support from the Wellcome Trust (grant code: 201486/Z/16/Z), the MQ: Transforming Mental Health (grant code: MQDS17/40), the Medical Research Council, UK (grant code: MC_PC_17213 and grant code: MR/S037675/1), and the BMA Foundation (J Moulton grant 2019). The funding sources had no role in writing of this letter or the decision to submit it for publication.

CRediT authorship contribution statement

All authors were responsible for conceptualization and writing (including writing of the original draft, review, and editing).

Conflict of Interest

None.

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