

EDITORIAL

Sick and tired of COVID-19: long haulers and post viral (fatigue) syndromes

COVID-19 patients may face a long and winding road to recovery. Outcomes of critically ill patients have been well described, including in China, Italy and the USA, and particularly in the comorbid elderly.¹⁻³ However, short-, medium- and long-term health consequences are being realised not only in those that were hospitalised, but also in outpatients with milder or asymptomatic illness. At the end of July, the Centers for Disease Control and Prevention (CDC) in the USA reported that 35% of 292 COVID-19 patients, young and old, with mild disease, had not returned to their usual state of health, 2–3 weeks post testing positive for the virus.⁴ Common residual symptoms included cough (43%), fatigue (35%), or shortness of breath (29%). Noteworthy, was that prolonged convalescence occurred in 20% of young adults who had no chronic comorbidities, potentially leading to loss of function at work, studies, or other activities. In Germany, enduring cardiac involvement in 100 recently recovered COVID-19 patients (median age 49 years) has also been described.⁵ Cardiovascular MRI performed during the early convalescent stage at a median time interval since COVID-19 diagnosis of 71 days, revealed signs consistent with persistent myocardial inflammation in 60% of patients, which, importantly, was independent of the severity of the original presentation and pre-existing comorbidities. Prolonged coma in COVID-19 patients following ventilation is a new perplexing concern, while post-infectious neurological complications, including Guillain-Barré syndrome and other diseases of the central and peripheral nervous system, may also rarely manifest after COVID-19.⁶ The latter are likely the result of immune activation.⁷

It is also possible that following physical recovery of the acute illness, which may range from mild to severe,⁸ and despite no evidence of replication-competent virus, some may go on to suffer a distinct chronic post SARS-CoV-2 viral syndrome. Long-lasting symptoms such as unrelenting exhaustion, diffuse myalgia, depressive symptoms, and disordered sleep are reminiscent of the complex debilitating mysterious illness, myalgic encephalitis/chronic fatigue syndrome (ME/CFS), previously associated with not only Epstein-Barr virus, but also with SARS and MERS coronaviruses.⁹⁻¹² ME/CFS symptoms classically include at least six months of fluctuating post-exertional malaise (PEM) following minimal physical or mental activity, severe and disabling fatigue, cognitive impairment making it difficult to concentrate, muscle or joint pain, non-restorative sleep, as well as immune, autonomic, neurological, endocrine, and gastrointestinal symptoms. The overall prevalence of this chronic condition ranges from 0.89–1.14% depending on which diagnostic criteria are used.¹³ The severely affected may be house- or bedbound, unable to move, speak or tolerate noise or light.^{14,15} Limited treatment options

include good nutrition, sleep hygiene, graded exercise therapy and cognitive behavioural therapy.¹⁶

To date, there is very little published on COVID-19 potentially triggering this long-term complication. A pre-print, not-yet-reviewed study of 128 patients in Ireland reports persistent fatigue in 52.5% of patients, at a median 10 weeks after initial COVID-19 symptom onset.⁸ These preliminary results show that fatigue is not associated with inflammatory and cell turnover markers or with pro-inflammatory molecules. This is interesting because postulated pathogenesises of ME/CFS or other post viral syndromes include inflammation or hyper immune responses, including stress-induced auto-immunity.^{17,18} Other proposed pathogenesises include SARS-CoV-2 utilising choroid plexus and olfactory bulb entry factors such as ACE-2 receptors, and from there, traversing the blood brain or cerebrospinal fluid barriers to gain access to the central nervous system.¹⁹ Furthermore, it has been suggested that there is a disturbance in CNS lymph drainage via the cribriform plate to the nasal mucosa leading to a surfeit of post-infectious cytokines such as interferon gamma and interleukin 7, possibly causing autonomic dysfunction which may manifest in the longer term as sleep/wake cycle dysregulation, cognitive dysfunction and unremitting and profound lack of energy.⁹

Self-identified long-haulers are patients, who range from very young to extremely old, who have cleared SARS-CoV-2, yet remain ill, typically for more than 10 weeks. They have organised online recovery support groups, including LongCovidSOS, Survivor Corps, Long Haul Covid Fighters (80+ days), Body Politic Covid-19 Support Group and #LongCovid on Facebook, Slack or Twitter, allowing a great opportunity for patient-led research. An Indiana School of Medicine (USA) survey of COVID-19 long hauler symptoms revealed that 1 567 Survivor Corp online group members listed the respiratory and vascular systems, as well as the brain, whole body, eye, and skin symptoms as frequently-occurring health problems for people recovering from COVID-19.²⁰ The report lists 50 most common long hauler symptoms and these include fatigue (100%), muscle or body aches (66.8%), difficulty breathing (65.1%), difficulty concentrating (59%), inability to exercise/be active (58.5), headache (57.6%), difficulty sleeping (49.9%), anxiety (47.6%), memory problems (45.6%) and dizziness (41.9%). Approximately a quarter (26.5%) of symptoms described by these long haulers are painful; body aches, nerve pain, and joint pain are reportedly difficult to control. The prevalence of this post COVID-19 syndrome and the robustness of the data are not known, but likely give a good indication of what is happening on the ground.

It has now been exactly six months since the first (05 March 2020) documented case of COVID-19 in South Africa. To date, many (633 015) have been infected with SARS-CoV-2, most (554 887) have recovered from the acute illness, and a significant minority (14 563) have sadly died. Yet, questions about long-term COVID-19 sequelae remain unanswered. Time will tell how many present with chronic post-COVID symptoms, if these are caused by lingering virus, latent virus reactivation, re-infection, or an overactive immune response, and whether or not SARS-CoV-2 causes irreparable organ damage. Long haul truck drivers remind one another that "There's two miles of ditches for every mile of road." Despite our COVID-19 fatigue, we may also be in for the long haul. Therefore, "Truck 'em easy," – which is CB radio slang for drive safely – for as long as it takes to get home.

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