

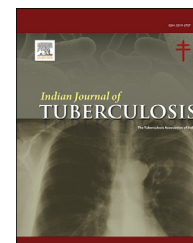


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## Review article

## Post COVID fatigue: Can we really ignore it?

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## ABSTRACT

Long-COVID, also referred to as post-acute COVID-19, chronic COVID-19, post-COVID syndrome, or post-acute sequelae of SARS-CoV-2 infection (PASC), generally refers to symptoms that develop during or after acute COVID-19 illness, continue for  $\geq 12$  weeks, and are not explained by an alternative diagnosis. It is not yet known whether “long-COVID” represents a new syndrome unique to COVID-19 or overlaps with recovery from similar illnesses. It's difficult for physicians to predict when symptoms will improve as it varies differently in different people. Patient's recovery depends on various factors including age, associated comorbidities, severity of COVID-19 infection. Some symptoms, like fatigue, might continue even while others improve or go away. This review addresses the pathogenesis, presentation of post covid fatigue, its severity and its management.

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## 1. Introduction

Although COVID-19 is a short term, self-limited illness in majority of people, still a large proportion of patient enters into an entity called long COVID haulers<sup>1,2</sup> and present to the physician with most common symptom i.e., fatigue. The British Medical Journal defines ‘long COVID’ as illness in people who have either recovered from COVID-19 but are still reporting lasting effects of the infection or have had the usual symptoms for far longer than would be expected”.<sup>3</sup> Even

syndrome under the section of “diseases of the nervous system”.<sup>4</sup> It is defined as a complex medical condition characterized by long-term fatigue and other symptoms which vary to such a degree that they limit a person's ability to carry out ordinary daily activities. Simply it is a long-term state of chronic fatigue characterized by post-exertional neuro-immune exhaustion.<sup>5</sup> Rio and Malani highlighted that fatigue is commonly seen in COVID-19 epidemic, and also, the patients still have high levels of fatigue and anhedonia after recovery from infection.<sup>6</sup>

World Health Organization has classified post-viral fatigue

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## 2. Prevalence

Data from UK's COVID-19 symptom app<sup>7</sup> found that around 300,000 UK people have reported symptoms lasting for more than a month. Over 60,000 were still experiencing symptoms after three months. A team of researchers from Italy reported that nearly nine in 10 patients (87%) discharged from hospital after recovering from covid-19 were still experiencing at least one symptom 60 days after onset. They found that 13% of the 143 people were completely free of any symptoms, while 32% had one or two symptoms, and 55% had three or more. Although none of the patients had fever or any signs or symptoms of acute illness, many still reported fatigue (53%), dyspnea (43%), joint pain (27%), and chest pain (22%). Worsening of quality of life was reported in around 2/5th of patients.<sup>8</sup> One study of 143 people with COVID-19 discharged from a hospital in Rome found that 53% had reported fatigue an average of 2 months after their symptoms started.<sup>9</sup> A study of patients in China showed that 16% were still fatigued.<sup>10</sup>

In a multistate telephone survey of symptomatic adults who had a positive outpatient test result for SARS-CoV-2 infection, 35% had not returned to their usual state of health when interviewed 2–3 weeks after testing. One in five had not returned to their usual state of health among persons aged 18–34 years with no chronic medical conditions.<sup>11</sup>

In a study, fatigue was assessed using the Chronic fatigue score (CFQ-11 questionnaire in 128 patients 52.3% (67/128) met the criteria for fatigue, with the mean ( $\pm$ SD) CFQ-11 score in this group being  $20 \pm 4.4$ .<sup>12</sup>

Post-COVID fatigue is a different entity and cannot be just defined as normal tiredness. Along with total exhaustion, people with post-COVID fatigue feel generally unwell which can also be seen in patients recovering from other viruses (flu or mumps). It is generally associated with unexplained muscle and joint pain, poor concentration, sore throat, headaches and rarely it can be extremely debilitating.

Unfortunately, any patient can be affected by this entity irrespective of the severity of initial infection.

## 3. Pathogenesis

Some are of the view that it is the effect of quarantine in COVID-19 infection leading to development of psychological and cognitive manifestations of post-COVID-19 depressive symptoms, stress, anxiety, chronic fatigue, and anhedonic state.<sup>13</sup> Like chronic fatigue syndrome, pro-inflammatory components like cytokines such as IFN gamma, and IL-7 are supposed to compromise the neurological regulation of the “Glymphatic System”.<sup>14</sup> Many cases of COVID-19 lands up in “post-COVID-19 Syndrome” which is a persistent condition of chronic fatigue, disturbed sleep/wake cycle, neuro-cognitive implications, and progressive anhedonia.<sup>15</sup>

The exact mechanism behind post-viral fatigue is not clearly understood. One of the likely explanations can be neuro-inflammation in brain due to infection caused by COVID-19 or any systemic inflammation that which activate the innate immune system in the brain via both humoral and retrograde neural signals (largely involving the vagus nerve).<sup>16–18</sup> While our body is fighting

off a virus, the immune system releases chemicals called cytokines, which promote inflammation and cause many of the classic symptoms of post COVID fatigue (tiredness, aches and pains, malaise).<sup>19</sup>

## 4. Chronic fatigue syndrome/myalgic encephalomyelitis

The persistence of long-term symptoms in some COVID-19 patients has opened up a new line of research into the mechanisms underlying myalgic encephalomyelitis/Chronic fatigue Syndrome (ME/CFS).<sup>20–22</sup>

This is part of its frontline attack on the invading virus which normally stops once the virus itself has been dealt with, but in some cases cytokines levels fails to return to normal, causing on going symptoms. The buildup of cytokines in the Central Nervous System (CNS) may lead to post viral symptoms due to pro-inflammatory cytokines passing through the blood brain barrier in circumventricular organs such as the hypothalamus, leading to autonomic dysfunction manifesting acutely as a high fever and in the longer term to dysregulation of the sleep/wake cycle, cognitive dysfunction and profound unremitting anergia, all characteristic of CFS/ME.<sup>23</sup>

The symptoms are essentially the same as those of chronic fatigue syndrome, also called myalgic encephalomyelitis or ME, which is why the WHO places them under the same category of neurological disorders.<sup>24</sup> A key feature of the condition is the sudden worsening of symptoms following only minimal physical or mental activity. Sleep is non-restorative and the tiredness can intensify after very minor mental or physical exertion.

## 5. COVID-19 brain fog

It is a condition described as fatigue and forgetfulness/puzzled, in patients who recovered from COVID-19 irrespective of severity. Many people who have recovered from COVID-19 have reported feeling not like themselves: experiencing short-term memory loss, confusion, an inability to concentrate, and just feeling differently than they did before contracting the infection. This brain fog has different spectrum varying from mild reversible forgetfulness to drowsiness and totally withdrawn. Actual mechanism is not clearly understood yet but as per the clinicians dealing with these cases frequently, one of the proposed mechanisms can be<sup>25</sup> COVID-19 virus enters the body through an ACE-2 receptor. And these receptors are widely distributed all over the body. That is why the virus can gain access to every system.

It is known that it gains access to the nervous system also, and that is the reason for the loss of sense of taste and smell. Probably that is the reason for the brain fog. One reason could be actual damage by the virus to these organ systems, and the second could be also a byproduct of the stress a person undergoes during the whole COVID episode. However, the long-term neurological and cognitive consequence of SARS-CoV-2 infection will remain conjectural for some time and will likely require the creation of cohort studies that include uninfected individuals. Recent studies shows that the occlusion

of brain capillaries by large megakaryocyte cells, a new report suggests.<sup>26</sup>

## 6. Management

Sadly, there is no specific medication or speedy treatment for post-viral fatigue or chronic fatigue syndrome. The most effective current treatment is total rest. This means relaxing as much as possible, with no mental stimulation. People who have experienced the condition talk about lying in a darkened room for long periods to promote mental and physical rest. These are the steps which can be taken to manage post COVID Fatigue<sup>xxiv</sup>:

1. REST: One of the most important intervention implying no TV, phones or internet, instead use relaxation, breathing and meditation apps, reduce any sensory input that makes you feel tense or is demanding (noise and bright lights), use sensory input to help you rest and relax – (favorite relaxing music, blanket, fragrance, or a hot water bottle). If all this does not work, try something else until you find something that gives you relaxation physically and mentally. It will support your recovery.
2. ACTIVITY: Keep activity levels low – both physical and cognitive (thinking) activities as they both use energy.
3. NOURISH: Keep eating and drinking, with as normal a routine as possible and maintain a balanced diet, specially increase your fluid intake.
4. MOVE: Get up and move around slowly and gently a few times each day to keep your body moving and to aid circulation. If you are too unwell for this, then you can try and move around in bed a little (stretching out, moving all of your joints, and tensing and relaxing your muscles).
5. ALLOW TIME: COVID can affect people to varying degrees, so give yourself the time you need for recovery. Avoid pressure to get back to your usual activities as soon as possible.
6. HAVE FUN: Do some low energy enjoyable activities every day. Balance activity with regular rests.
7. STOP STUDIES/WORK: Unless you feel fully well, you should stop studies or work to allow your body to focus on fighting the infection and recovering.

## Conflicts of interest

The authors have none to declare.

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