# Post-COVID-19 Syndrome or Long COVID: From Patient Symptoms to Current Pathophysiological Hypotheses

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## Abstract

Mounting evidence supports the existence of significant sequelae of coronavirus disease 2019 (COVID-19), the so-called post-COVID-19 syndrome or "long COVID", whose real incidence is unknown. Paradigmatic examples of this syndrome, whose pathogenesis and mechanisms are currently being investigated, emerge from outpatient consultations of persons who recovered from COVID-19. These patients are deeply involved psychologically and struggle to find the cause of their symptoms. They often look for other "long COVID" patients on the web, sharing "diagnostic workup" and "therapeutic choices" that, however, are not defined at present. There is no specific clinical definition of "long-term COVID-19" agreed by the medical community. The clinical picture can be extremely variable, including non-specific symptoms, such as fatigue and low-grade fever, or symptoms that could be related to organ damage, such as cough, breathlessness, palpitations, joint pain and abdominal pain. Residual organ injury can be detected through routine investigations. Persistent symptoms following COVID-19 include symptoms related to chronic inflammation, symptoms related to organ damage and symptoms related to hospitalization and/or isolation. Having been affected by COVID-19 may have a profound impact on patients' mental health. Moreover, persistent direct viral effects have been advocated as a possible cause of long COVID-19, including neuronal injury, post-viral post-traumatic stress disorder and mast cell activation syndrome. Also, several drugs are possibly involved in post-COVID-19 syndrome onset. At present, no defined treatment for this syndrome can be recommended. Its impact in terms of morbidity and late mortality has yet to be determined. Since studies have been limited by a relatively short follow-up of post-acute patients, well-designed, prospective, long-term follow-up studies are clearly warranted.

**Keywords:** Post-COVID-19 syndrome; Long COVID; SARS-CoV-2

## Introduction

Mounting evidence supports the existence of significant, possibly common, sequelae of coronavirus disease 2019 (COVID-19), the so-called post-COVID-19 syndrome or "long COVID" or "post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC)". A paradigmatic example of this syndrome, whose pathogenesis and mechanisms are currently being investigated, is provided by a letter a young man sent to his doctor after an outpatient clinic consultation (Supplementary Material 1, www.ciijournal.org).

A 35-year-old man came to our attention complaining of symptoms manifested after recovering from COVID-19. According to his past clinical history, he had suffered from bronchial asthma during childhood, but there were no other known comorbidities.

He complained of weakness, breathlessness, hyperthermia, tachycardia, orthostatic hypotension, difficulty concentrating, insomnia, weight loss and a mild pain under the 10th left rib. During the clinic consultation, the patient seemed to be very emotionally affected by the symptoms he was experiencing, telling us that these were having too strong an impact on his life. This was mostly because the exacerbations were always preceded by a physical or emotional effort and, therefore, he was not able to live as he used to. He expressed the fear of never getting back to normal conditions and of being re-infected. Also, he seemed emotionally disturbed by the prolonged hospital stay he was subjected to during the "acute phase" of COVID-19.

Our first impression was that this man showed clear signs of post-traumatic stress disorder (PTSD) after COVID-19. The set of his clinical manifestations, started after recovering from COVID-19 and not associated to any other clinical condition, also allowed us to classify the patient as possibly suffering from post-COVID-19 syndrome or "long COVID".

Four months before presenting to us, the patient had been hospitalized elsewhere for about 40 days, during which he had received high doses of steroids and multiple types of antibiotics, despite of a mild form of COVID-19. Indeed, the patient had suffered with low-grade fever for a few days before admission and had subsequently had persistently normal levels of lactate dehydrogenase and C-reactive protein. His lymphocyte count had maintained above 1,000 cells/μL and only tiny foci of interstitial pneumonia were visible at both initial and

follow-up chest computed tomography (CT) scan. Consistently, he underwent oxygen therapy with nasal cannulas for only a few days. His molecular nasal swab became negative for SARS-CoV-2 RNA 38 days after admission, allowing his discharge from hospital.

Before coming to our attention, and after COVID-19 recovery, the patient performed numerous blood tests and imaging investigations, including cardiac magnetic resonance imaging (MRI), brain MRI and chest CT scan; all of these exams did not show any pathological finding, except for a ferritin level, which was slightly higher than normal. Also, cardiac MRI showed a left ventricle ejection fraction of 47% and a reduced cardiac index. A recent arterial blood gas analysis revealed an overcompensated metabolic alkalosis and a mild hypokalemia. Levels of C-reactive protein, interleukin-6 (IL-6) and the erythrocyte sedimentation rate were normal.

On physical examination, he presented no pathological findings: the two hemithorax were symmetrical and expandible, the vesicular sound could be appreciated over the entire lung area and no added sounds were audible. The abdomen was non-tender upon superficial and deep palpation, and neither the spleen nor the liver was enlarged, with valid bowel movements. Cardiac sounds were rhythmic, heart rate was 75 bpm lying flat, raised to 80 bpm after 1 min standing, and no cardiac murmurs could be heard. Blood pressure was 110/70 mm Hg flat and there was no change upon standing. The tongue appeared to be whitish, suggesting oral candidiasis. There was no leg edema.

We advised the patient to perform peripheral nerve electroneuromyography in order to detect any involvement of skeletal muscles or the peripheral nervous system and to repeat echocardiography to check left ventricle function. We also ordered: 1) dosage of the N-terminal pro-B-type natriuretic peptide, to further rule out any cardiac dysfunction; 2) assessment of serum iron levels, ferritin, transferrin, transferrin saturation and transferrin iron binding capacity, to check for possible hemochromatosis; 3) dosage of adrenocorticotropic hormone (ACTH) and aldosterone in orthostatic position, to verify adrenal failure due to high-dose corticosteroids received during hospital stay; and 4) evaluation of 24-h urinary sodium, potassium and calcium excretion to better study electrolyte balance and assess 24-h urinary catecholamines to exclude a pheochromocytoma.

We also prescribed bisoprolol 1.25 mg daily to control heart rate excursions, and advised the patient to resume physical activity in a progressive manner.

We then kept in touch with the patient, asking him to inform us about the results of exams, the outcome of therapy with bisoprolol and the possible appearance of new clinical manifestations. A few days later, the patient communicated that he had started taking bisoprolol 1.25 mg but he was very scared because even if the heart rate went down there was still instability (55 bpm in sitting position and 85 bpm standing), despite he noticed a reduction of fatigue, while all the other clinical manifestations had not changed. In addition, new dermatological signs appeared: red burning and itchy rash on the central part of the chest and diffuse pimples on the back and the forehead.

The results of the laboratory exams that we received were all normal: the B-type natriuretic peptide was < 35 pg/mL, and there was no alteration of iron metabolic pattern, urinalysis, urine electrolytes and ACTH. Urinary catecholamines and echocardiography were also normal.

At present, the patient remains deeply involved psychologically and is struggling a lot to find the cause of his symptoms. For this reason, he often speaks to other "long COVID" patients, sharing the diagnostic workup and therapeutic choices. He returned to us asking whether he should start new drugs such as ivabradine or ivermectin, used by other patients. He also asked to undergo bronchoscopy, an invasive investigation, for broncho-alveolar lavage to assess for lymphocytic inflammation in the lungs, just because another "long COVID" patient did it.

## Current Evidence on Post-COVID-19 Syndrome or Long COVID

There is no specific clinical definition of "long-term COVID-19" agreed by the medical community, nor clear recommendations for a therapeutic path. However, according to National Institute for Health and Care Excellence (NICE), post-COVID-19 syndrome is defined as the set of signs and symptoms that develop during or after COVID-19 that last more than 12 weeks and are not explained by an alternative diagnosis [1]. More recently, in addition to the term "long COVID", this syndrome has been defined as post-acute sequelae of SARS-CoV-2 infection or "PASC". Long COVID is estimated to affect up to 10% of those who survive SARS-CoV-2 infection [2, 3].

The clinical picture can be extremely variable, including non-specific symptoms, such as fatigue and low-grade fever, or symptoms that could be related to organ damage, such as cough, breathlessness, palpitations, joint pain and abdominal pain.

Residual organ injury can be detected through common routine investigations, such as 6-min walking test, spirometry, electrocardiogram (ECG), cardiopulmonary exercise test (CPET), echocardiography, chest X-ray or CT scan and MRI; also, full blood count, kidney and liver function tests as well as C-reactive protein measurement are useful in the assessment of patients with suspected long COVID. As a matter of fact, a study on mid-term effects of the disease, that enrolled 58 COVID-19 patients after hospital discharge, demonstrated that after 2 or 3 months from disease-onset, 64% of patients experienced breathlessness and 55% reported fatigue. MRI screening revealed that organs most involved were lungs (60%), heart (26%), liver (10%) and kidneys (29%) [4].

Multi-organ dysfunction was unrelated to a specific age or ethnic group, and no specific risk factors were identified. In some young individuals, who did not have risk factors for severe forms of COVID-19 and were not hospitalized during COVID-19, symptoms related to the heart, lungs, liver and pancreas damage emerged; these lasted for up to 4 months and the findings, obtained through investigations such as MRI, showed significant organ involvement. Young athletes, who were enrolled in a study to evaluate residual damage after COVID-19, showed heart injury (including myocarditis) over

3 months following infection, despite having a healthy life-style and exercising every day [5].

Persistent symptoms following COVID-19 should be distinguished into: 1) symptoms related to chronic inflammation, which are typically found in the convalescent phase of an acute infection; 2) symptoms related to organ damage, such as pulmonary fibrosis, acute kidney injury (AKI) and chronic kidney disease (CKD); and 3) symptoms related to hospitalization and/or isolation, such as nutritional anemia and muscle wasting [6].

Young patients who had a mild form of COVID-19 stated that their most common persisting symptoms were fatigue (98%), muscle aches (88%), shortness of breath (87%) and headache (83%) [5].

Fatigue, which many studies have shown to be the most frequent symptom of long COVID-19, could be related to anemia, vitamin D deficiency, hypothyroidism, cortisol insufficiency and CKD, but currently there are no data to substantiate these hypotheses [6].

Our young patient presented symptoms most probably due to damage of the autonomic nervous system, complaining of orthostatic hypotension and postural orthostatic tachycardia syndrome. This may be linked to an abnormal response of the autonomic nervous system (ANS) that is handled by baroreceptors located in the heart and in the aorta regulating the adrenergic tone. Neurological damage could be related to the virus itself, as in the case of other post-viral neurological syndromes, or it could be related to the immune inflammatory response [7].

## Mental Health Disorders as COVID-19 Sequelae

Having been affected by COVID-19 may have a profound impact on patients' mental health. Because of absence of contacts with their families and loved ones during quarantine and hospital stays, physical discomfort, fear of virus transmission to other people and drug-related adverse effects, COVID-19 patients can develop psychological instability [8], experiencing depression, anxiety, post-traumatic stress symptoms and even psychosis, which can then have a negative impact on individuals' functioning and quality of life [9].

A systematic review and meta-analysis [10] assessed the point prevalence of different psychiatric sequelae after severe coronavirus infections (i.e., severe acute respiratory syndrome and Middle East respiratory syndrome). In this study, point prevalence of PTSD was 32.2% (95% confidence interval (CI): 23.7 - 42), that of depression was 14.9% (12.1 - 18.2) and that of anxiety was 14.8% (11.1 - 19.4).

The organism responds to COVID-19 through a hyper-inflammatory state, during which there is an increased release of inflammatory markers such as C-reactive protein, ferritin and IL-6. It has been studied that the higher the levels of C-reactive protein, the more remarkable are the depressive symptoms of these patients, suggesting a direct correlation between inflammatory marker elevation and depression in COVID-19 patients [11].

Patients affected by COVID-19 may develop traumatic

memories related to it and present PTSD in the recovery phase [12]. In a study in Wuhan, China, 1 month after the beginning of the pandemic, the prevalence of PTSD was 7% in the most involved areas [13].

Some studies assessed the association of COVID-19 with psychosis: antibodies against some coronavirus strains have been found in patients with psychotic disorders, especially in those who had a recent psychotic episode with respect to non-psychiatric controls [14]. There has been demonstration that 0.9-4% of COVID-19 patients develop psychotic symptoms [15].

Even if these psychiatric disorders have been identified as COVID-19 sequelae, it remains still unclear whether these are related to the viral infection or the host immune response. This is the reason why there is an urgent need for a strict follow-up of psychiatric manifestations related to SARS-CoV-2 infection and implementation of the health-care system in this field.

## Pathophysiology of Long COVID-19

The interaction between SARS-CoV-2 spike protein domain and angiotensin-converting enzyme 2 (ACE2) is the virologic event/mechanism that can explain many of the different pathological manifestations of "long COVID". According to the currently available evidence, SARS-CoV-2 can affect almost every organ in the body, leading to acute organ damage but also long-term sequelae, with the latter effects only recently starting to be recognized and studied [16].

### Neuronal injury

SARS-CoV-2 can infect and cause pathology to the human central nervous system (CNS), an emerging target organ in COVID-19 (Fig. 1). The ACE2 and nicotinic receptors are targets of viral-induced involvement of the CNS. SARS-CoV-2 reaches the CNS through the olfactory pathways and a more permeable blood-brain barrier due to the effects of cytokines released in the context of the viral inflammatory response. In the neuronal area, SARS-CoV-2, by inducing apoptosis, phagocytosis, autophagy and necrosis of neuronal cells, spreads into the brain and the periphery, leading to damage (formation of microthrombi and encephalitis) that could explain chronic neurologic sequelae [16].

One manifestation of the chronic neuronal damage induced by COVID-19 is the autonomic intolerance syndrome, characterized by tachycardia associated with arterial hypotension, fainting and sometimes syncope. Autonomic intolerance syndrome seems to be related to direct virus interaction with the autonomic nervous system (ANS) and to virus-triggered autoimmune responses.

In physiological conditions, the transition from lying to standing position reduces venous return to the heart. This causes the activation of baroreceptors and the release of catecholamines, adrenaline and norepinephrine, responsible for peripheral vasoconstriction and tachycardia, compensatory
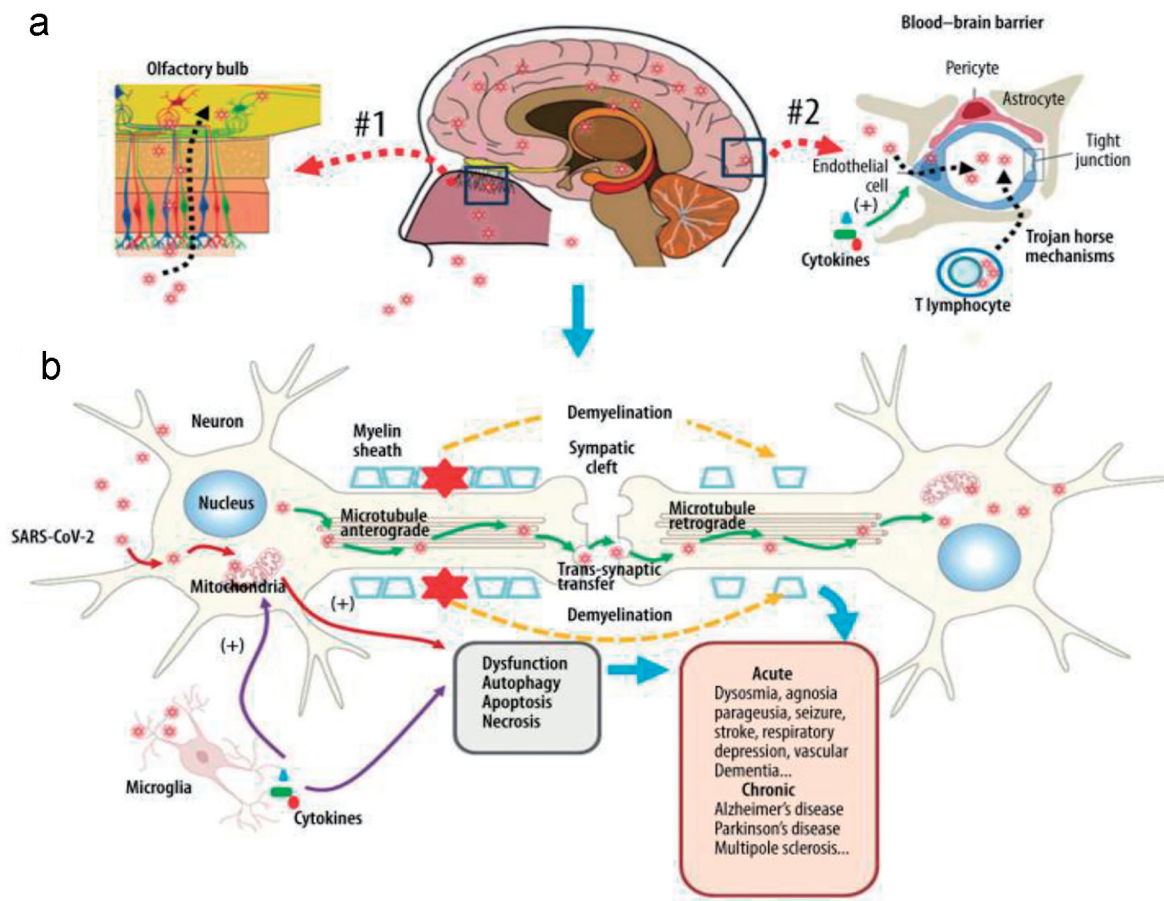
**Figure 1.** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) neurotropism. Image reused under permission (CC BY-NC-ND 4.0) from Ref [16]. Neuronal injury associated with SARS-CoV-2 infection. (a) SARS-CoV-2 enters the central nervous system (CNS) via two major routes: the olfactory pathway (#1), and the blood-brain barrier (BBB) pathway (#2). The virus can migrate into the CNS directly by endocytosis with the assistance of inflammatory cytokine-induced increased vascular permeability and indirect transfer via a "Trojan horse" mechanism. (b) After binding to its membrane receptor, angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 gets engulfed into neuronal cytosol and move to connect with cytosol-located ACE2. The viral RNA enters the mitochondria or forms into autophagolysosomes to initiate autophagy and/or apoptosis. Microglia and immune cells produce pro-inflammatory cytokines, which result in further abnormalities in mitochondrial function. When the virus enters the neurons, it combines with the axonal microtubules with anterograde and retrograde spread to the synapse and enters the next level of neurons by trans-synaptic transfer and endocytosis. Both the virus and the "cytokine storm" can destroy the myelin sheath of neurons, resulting in acute and chronic neuropathology [14].

events that are necessary to maintain adequate brain perfusion. In "long COVID", the physiological release of catecholamines occurs with consequent tachycardia but these catecholamines would cause an abnormal peripheral vasodilation and a paradoxical activation of the vagal nerve, leading to hypotension and possibly fainting and syncope. The pathogenesis is explained by hypovolemia and the inflammatory state caused by the infection and by prolonged hospitalization, which would reduce cardiac output and the strength of cardiac contraction.

Another pathogenetic mechanism could be related to an autoimmune response mediated by antibodies against muscarinic and adrenergic receptors, possibly produced by cross-reaction phenomena in the course of SARS-CoV-2 infection, which would explain some symptoms of the "long COVID"

patient [7, 17].

## Influence of PTSD on the immune response after COVID-19

Chronic stress is related to a switch in lymphocyte function from Th1 to Th2 and to a downregulation of cortisol receptor sites. Th1 cells mediate specific immunity, boost the immune response through the release of pro-inflammatory cytokines (IL-12, IL-1 and interferon (IFN)-gamma) and stimulate mostly cellular immune responses. In chronic inflammatory disorders, there is a downregulation of the immune system, which can cause a major susceptibility to infections, and a reduction of the bioavailability of steroid receptors. The downregulation

of cortisol receptors may reduce the capacity of lymphocytes to respond to anti-inflammatory signals and allow other cytokine-mediated processes to dominate in patients with PTSD [18, 19]. Thus, a vicious circle may occur involving PTSD-related immune dysfunction and subsequent additional viral and immune-mediated illnesses in long COVID patients.

### The role of mast cells (MCs) in "long COVID"

In the acute and chronic pathogenesis of COVID-19, a role for MCs is emerging. There is an estimated prevalence of mast cell activation syndrome (MCAS) of 17% in the worldwide population and a similar prevalence occurs in severe COVID-19. MCAS is a multisystem multimorbidity driven by general MC-mediators of allergic-type inflammation.

MCs can recognize SARS-CoV-2 through Toll-like receptor 3, ACE2 and SP1 receptors, and MCs also express many serine proteases (including tryptase), which are necessary for SARS-CoV-2 infection. MCs are critical cells in the genesis of thrombotic events, endothelial damage and lung edema: the release of multi-action mediators, including histamine, proteases (chymase and tryptase), prostaglandins, leukotrienes and growth factors would favor the phenomenon of hyper-inflammation, typical of severe COVID-19. At the same time, there is a correlation between neuropsychiatric manifestations in COVID-19 patients and MCAS patients, due to inflammation-induced coagulation. The anti-inflammatory drugs used for COVID-19 treatment that act by inhibiting MCs activation and the positive outcomes of MCAS drugs in COVID-19 treatment could explain the critical role of MCs in this disease and the severity of the clinical manifestations associated with their pathogenic involvement.

In patients who received a diagnosis of MCAS and were on a pharmacological treatment for that, the clinical presentation of COVID-19 is milder compared to patients with a clinical history of atopic illness but not on any pharmacological treatment. The latter are more susceptible to severe COVID-19 associated with major lung and CNS involvement [20].

### Drugs possibly involved in post-COVID-19 syndrome onset

Another important cause of symptoms referred by "long COVID" could be represented by drugs received. The sudden, rapid, unknown SARS-CoV-2 pandemic caused major problems, especially in the early stages, regarding how to treat patients. Numerous clinical trials have been carried out on the different possible treatments and the different timing of administration of potential therapeutic drugs.

Our own patient, as many other patients in Italy, was treated for several weeks with large doses of corticosteroids and multiple types of antibiotics, despite numerous studies supporting the need to administer these drugs, especially at high doses, only in severe cases, where clinical impairment is no longer related to the damaging action of the virus, rather to an abnormal host immune response.

The prolonged use of corticosteroids is associated with clinical manifestations of hypercortisolism: hyperglycemia, hypertension, hypokalemic metabolic alkalosis, changes in mood and concentration.

## Overview of Possible Therapeutic Approaches to "Long COVID"

A study evaluating autonomic dysfunction in long COVID [7] suggests treating patients as follows: 1) performing regular, structured exercise programs with both aerobic and resistance phases; 2) ensuring fluid repletion (2 - 3 L of water per day and avoiding caffeine and alcohol); 3) avoiding exacerbating factors such as prolonged standing, warm environments and dehydration; and 4) wearing compression garments extending up to the waist, or abdominal binders, if tolerated.

If symptoms persist, despite full compliance with conservative measures, pharmacological therapy may be considered. Two drugs that have been used are: 1) fludrocortisone, a fluid expander, which can be used if hypovolemia is considered to be a dominant symptom. It is associated with side effects and it is not particularly well tolerated. Monitoring should take place for fluid retention and hypokalemia; and 2) midodrine, a sympathomimetic $\alpha$-1-agonist, that causes vasoconstriction and improves venous return to the heart.

## Conclusions

Long-term sequelae of COVID-19, currently referred to as "long COVID-19" or "post-COVID-19 syndrome" are emerging as a common, clinically significant and epidemiologically relevant condition, whose impact in terms of morbidity and, possibly, late mortality has yet to be determined. Many studies on this emerging topic have been limited by a relatively short follow-up of patients in the post-acute phase. A more comprehensive picture of the post-COVID-19 syndrome will likely come from well-designed, prospective, long-term follow-up studies aiming at evaluating the evolution of long COVID-19 symptoms over the course of many months or years.

## Supplementary Material

**Suppl 1.** A letter from a young man after outpatient clinic consultation.

## Conflict of Interest

None to declare.

## Author Contributions

All authors (AMP, OI, EA and EDM) gave a substantial contribution to the conception of this work, the acquisition and interpretation of data. All authors participated in drafting the work and in revising it critically for its intellectual content. Final approval of the version to be published was given by all authors. All authors agree to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author.

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