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# Neurobiology of long-COVID: Hypotheses and unanswered questions

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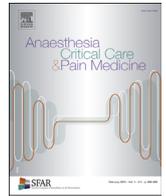
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## Editorial

## Neurobiology of long-COVID: Hypotheses and unanswered questions



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The SARS-CoV-2 pandemic and the successive waves linked to the different variants have greatly affected the health systems of many countries. The situation has however improved given the advent of vaccination as well as the progression of natural immunity, but also better patient care and the development of new therapies. Nonetheless, significant vigilance is still required. The acute disease has a wide spectrum of clinical phenotypes, ranging from asymptomatic infection to respiratory failure and multiple organ dysfunction. In addition, a long form of the disease may develop in a fraction of people infected with SARS-CoV-2. This is primarily named "long-COVID" or post-acute sequelae of SARS-CoV-2 infection (PASC). The pathogenesis of these complications is complex and dependent on many factors. Long-COVID has been defined as a myriad of physical and psychological symptoms, some characterized more than others, that persist for weeks or months after initial infection. The signs or symptoms described affect a wide range of organs, mainly involving neurological and cognitive impairment, but also other organs and systems, such as the lung, kidney, and cardiovascular and neuromuscular systems [1,2]. Given the great variability in symptoms, the definition of long-COVID is not always clear and can differ between countries. Overall, it is generally considered that patients falling into this category present with signs and symptoms that develop after confirmed or probable SARS-CoV-2 infection, usually months from the onset of COVID-19, continuing for at least 2 months, and that cannot be explained by an alternative diagnosis [3].

Common symptoms of long-COVID include shortness of breath, fatigue, depression, headache, dizziness, anxiety, brain fog, and other cognitive dysfunction [4]. Symptoms may be of recent onset after recovery from an acute episode of SARS-CoV-2 infection or may persist since the initial disease. Symptoms may also relapse or fluctuate over time depending on the patient. It is likely that long-COVID is expressed differently depending on the patient's immunological status, hormonal factors, genetic background, viral load at the time of infection, or even the variant responsible for the

infection. Neurological symptoms associated with long-COVID are observed after moderate-to-severe respiratory disease, but also among cases with mild forms of SARS-CoV-2 infection and even people initially not showing any symptoms. It is estimated that approximately 30–60% of all COVID patients still exhibit symptoms 6 months after disease onset [5–7]. Nevertheless, estimates of symptom prevalence should be interpreted with caution; studies without uninfected comparison groups may overestimate symptoms attributable to prior SARS-CoV-2 infection. It is noted that some symptoms associated with long-COVID are not significantly more frequent after COVID-19 infection compared to other respiratory viruses while others symptoms are very specific to COVID [8]. The prevalence of post-COVID-19 disease symptoms does decrease over time, but more than 20% of those infected with SARS-CoV-2 still have symptoms 18 months after infection [9]. The impact of this high prevalence of long-COVID, especially with neurological symptoms, has not been determined precisely. However, long-COVID is an emerging public health problem and a major issue for health authorities with significant socio-economic burdens due to the vast number of patients who have been infected worldwide by this coronavirus.

The pathogenesis of the neurologic sequelae during long-COVID is poorly understood, but given the range of these complications, it is likely that there is more than one underlying mechanism. COVID-19 may affect the central nervous system (CNS) in different ways, with some mechanisms being recently further deciphered. Indeed, several main mechanisms are currently being intensively investigated, highlighting different hypotheses that are not mutually exclusive or opposing each other.

These hypotheses include:

#### 1 Maintenance of neuroinflammation.

The immune response to SARS-CoV-2 in the respiratory system may cause neuroinflammation, increasing cytokine secretion, as well as immune cell trafficking in the brain [10–13]. Sustained inflammatory responses, via elevated expression of type I and type III interferons (IFN), can persist several months following initial SARS-CoV-2 infection [11]. This chronic inflammatory state can occur in different tissues, with consequences that are to date still poorly understood but do vary according to the organs affected. In the brain, neuroinflammation associated with resident microglial activation and other immune cells could explain the neurocognitive disorders seen in many patients.

#### 2 Formation of microbleeds and microclots.

Patients with COVID-19 are at increased risk of thrombotic complications [14] and develop endotheliopathy with extent depending on the severity of their COVID-19 symptoms [15]. The lungs are not the only organ affected. Inflammatory microthrombosis or microhemorrhage can also occur in other organs, including the brain [16]. Moreover, COVID-19 increases the risk of ischemic stroke [17]. These events could lead to poor tissue oxygenation and cause lasting neurological sequelae and impaired cognitive function in the vascular territories, thus explaining the sudden episodes of malaise, pain (muscular, cardiac), or brain fog that long-COVID patients complain about.

### 3 Persistence of SARS-CoV-2.

It is now well accepted that some patients do not completely clear the SARS-CoV-2 coronavirus within the usual time frame. This persistence of the virus in the organism was initially noted in immunocompromised subjects. Numerous other recent works demonstrate that viral RNA or viral fragments, in the form of spike proteins, can also persist in many organs. This suggests the possibility of persistent reservoirs of SARS-CoV-2 infection or persistent circulating spike protein or a combination of both. A significant proportion of long-COVID patients have viral antigens in their serum, mainly the spike protein. This viral protein was found in these sera at several intervals over time periods of 2–12 months after infection, thus suggesting the persistence of the virus in the form of viral reservoirs [18]. Furthermore, the persistence of the virus was also shown when viral RNA was detected in stool samples of patients up to 210 days after infection [19], and the expression of SARS-CoV-2 RNA in the gut mucosa was detected 7 months after mild acute COVID-19 [20]. In addition, the virus and the spike protein have been found, sometimes several months after infection, in patient autopsies and various study models [21,22].

### 4 Direct brain infection.

Cases of SARS-CoV-2 neuroinvasion have been reported in autopsied patients with detection of SARS-CoV-2 in the brain and olfactory epithelium [23]. The blood-brain barrier (BBB), among other functions, protects the brain from pathogens, including viruses. There is currently no conclusive evidence that SARS-CoV-2 can cross or efficiently infect the BBB, but SARS-CoV-2 antigens have been detected in endothelial cells of the BBB in humans and in animal models [24]. The available data suggest that direct CNS infection is likely a rare event and does not account for the majority of acute or long-term neurologic sequelae of COVID-19.

### 5 Auto-immune mechanisms.

Another mechanism by which SARS-CoV-2 can damage the CNS is *via* autoimmunity. There is growing evidence that SARS-CoV-2 can lead to a dysregulation of the immune system with the development of autoimmunity. Several studies suggest that people with long-COVID are more likely to have autoantibodies that can persist for a year, maybe longer, even with no prior personal or family history of autoimmunity [25–27]. Autoantibodies target self-antigens, such as phospholipids, transcriptional and nuclear proteins, and interferons. However, whether or not this autoimmunity contributes to chronic neuroinflammation and lasting cognitive impairment remains to be determined.

### 6 Reactivation of latent herpes virus.

Herpes virus reactivation, such as herpes simplex virus (HSV) or Epstein-Barr virus (EBV), has been described as more frequent among those who develop long-COVID [28,29]. These reactivations could have a role in the neurological and neuropsychiatric complications of COVID-19 [30].

It should be noted that other mechanisms could also be involved in long-COVID, such as hypoxia, metabolic disorders, hypotension. . .

Systemic inflammatory response syndromes (septic or not) can also be associated with neurological symptoms, such as confusion, disorientation, and loss of consciousness. However, these symptoms are typically secondary to systemic inflammation and metabolic derangements. The pathogenesis of SARS-CoV-2-associated CNS disease and lasting cognitive symptoms is complex, and diverse, and cannot be explained by a single mechanism. Current data show that SARS-CoV-2 has limited neuroinvasive potential, has relatively limited neurotropism, and may be neurovirulent in at least some patient subgroups. The incidence of CNS complications associated with SARS-CoV-2 appears more minimal during the acute phase, but more substantial during the post-acute phase. Host factors, such as sex, age, immune status, metabolic status, and comorbidities complicate the clinical picture of the various CNS complications associated with SARS-CoV-2 infection. Different variables may influence the development of CNS disease, for example, the dose of infection, the site of primary viral replication, as well as the immune and vaccination statuses of the patient. In addition, many questions remain unanswered about lasting cognitive symptoms. Are there differences among SARS-CoV-2 variants in their neuroinvasiveness, neurotropism, and neurovirulence? Can SARS-CoV-2 infection exacerbates underlying neurodegenerative or neuropsychiatric diseases? What exactly are the risk factors associated with neurological forms of SARS-CoV-2? (sex, age, diabetes, obesity . . .). Besides, there is limited information in the literature on the possible risks of anesthesia (general or local) on neurocognitive abilities in long COVID patients. Some studies suggest that patients with long COVID may have an increased risk of cognitive impairment, including memory and attention deficits. However, the relationship between anesthesia and neurocognitive abilities in long COVID patients has not been extensively studied.

In summary, today there remain many unknowns regarding the current and future populations at risk of lasting cognitive symptoms, especially in the current context of increased vaccination and hybrid immunity. More large-scale population-based studies are needed to assess the long-term symptoms specifically attributable to SARS-CoV-2 infection and the mechanisms involved. Overall, the COVID-19 pandemic is not over and remains a major health concern. The regular appearance of new variants and the host immune waning encourage the maintenance of control and surveillance measures.

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