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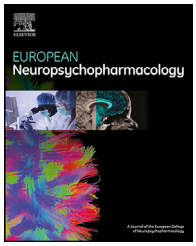

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INSIGHTS

Mind long COVID: Psychiatric sequelae of SARS-CoV-2 infection

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Frank Herbert, the renowned American science-fiction writer and author of the novel Dune, among others, once stated "There is no real ending. It's just the place where you stop the story". Recently, we as scientific community have come to learn that the meaning of this sentence can be of a special relevance among patients affected by COVID-19. Indeed, the discharge from a hospital setting, far from the end of the story, often represents just the beginning of the process.

A constellation of both physical and mental symptoms can either continue or emerge in the afterwards, shaping a multisystemic and disabling syndrome (Nalbandian et al., 2021) that varies from patient to patient and that fluctuates over time, which has been diversely labelled under the "Long COVID-19", "Post-acute Sequelae of COVID-19", "Chronic COVID-19", "Long-hauler COVID-19" or the most recent "Post-Acute COVID-19 syndrome" terms. Although there is no universal consensus on the definition of its start period, last NICE guideline on the issue(National Institute for Health and Care Excellence, 2020) proposes a 4-week and 12-week time span of maintained symptomatology for the ongoing symptomatic COVID-19 and the post-COVID-19-syndrome, respectively. Recent reviews (Nalbandian et al., 2021) summarize the most frequently observed clinical picture: fatigue/muscular weakness and ache, dyspnea, chest and joint pain, low-grade fever, cognitive disturbances, and an overall decline in quality of life. Besides, potential organ dysfunctions lead to many other symptoms.

The presence of numerous psychiatric symptoms are also highlighted in many reviews (Nalbandian et al., 2021; Taquet et al., 2021). The most frequently disclosed are low mood, mood swings, hopelessness, heightened anxiety, sleep/wake cycle dysregulation and neurocognitive disturbances including brain fog, difficulties with memory, concentration and executive function. Post-traumatic stress disorder symptoms have also been reported. Notably, the range of patients experimenting one or more psychiatric symptoms could be around 25–56% (Nalbandian et al., 2021), and this is consistent with past SARS pandemics. This is in turn associated with an approximately two-fold higher probability (estimated around 5.8%) of being newly diagnosed with a psychiatric illness within 14–90 days of the acute infection, in comparison with controls diagnosed with other health events (Taquet et al., 2021). Interestingly, this might suggest a COVID-19-specific burden of disease. What is more, initial inpatient admission is linked with a higher risk of psychiatric sequelae, thus indicating a potential dose-response relationship. Anxiety (4.7%) and mood (2%) disorders were the most frequent diagnostic categories, followed by insomnia (1.9%) and, concerningly, dementia (1.6% in patients over 65 years). Hence, up to two-thirds of hospitalized patients with Covid-19 may show clinically relevant cognitive impairments that impact their quality of life and daily functioning 4 months after hospital discharge (Miskowiak et al., 2021). Cognitive disfunctions may be

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associated with d-dimer levels during acute illness and residual pulmonary dysfunction.

Adding the previously described exhaustion, which seems to be a nuclear symptom, they all appear to conform a post-viral chronic fatigue-like syndrome (CFS), also referred as Myalgic Encephalomyelitis (ME) in past pandemics. Far from being a novelty, many historical reports describe a range of psychiatric symptoms arising from past pandemics such as influenza and other coronavirus infections. Considering ME's own history (Nature Editorial, 2020), it would be important not to make the same mistakes from the past and recognize the syndrome in all its dimensions. This way, and although it's not yet a well-determined disease, we might be at the gates of defining a new and particular entity which we have called "Mind Long COVID".

By all means, the nature of these long-term psychiatric symptoms is multifactorial, and it's relevant to consider in first place the psychosocial consequences of the pandemic. Individual psychological traits can also modulate the expression of psychopathology. However, a growing body of literature focuses on the potential biological mechanisms (Troyer et al., 2020). First, coronaviruses (CoV) are known for their neurotropism, and neuronal and glial dysfunctions and death can be triggered by either direct or indirect mechanisms. Shortly after the virus detection, a host immunological response takes place via a massive upregulation of pro-inflammatory interleukins. This results into a neuroinflammatory status that compromises the blood-brain barrier permeability, favors the immune cell transmigration and the expression of radicals and other pro-oxidative molecules, and disrupts the mechanisms of neurotransmission.

Some studies show that CoV can be persistently detected in leukocytes beyond the acute infection stage (Desforges et al., 2019). Other immunologically privileged sites could play a role in extending the presence of the virus within the organism. Ultimately, the persistence of the virus could lead to a low-grade neuroinflammation that provides a theoretical basis for the psychiatric long-lasting manifestations. Other possible approaches would involve the role of post-infectious autoimmunity through molecular mimicry between CoV epitopes and host molecules such as human myelin, the impairment of the "Glymphatic System", the endocrine system or the mitochondrial function, and the presence of ion channelopathies or an altered cerebral perfusion. Second-messenger systems and expression of gene products such as Brain-Derived Neurotrophic Factor (BDNF) could also be involved in the disease pathophysiology. All these factors could be involved in the continuation of the symptoms even if a complete eradication of the virus is achieved. Finally, a gut-brain axis alteration has also been speculated (Troyer et al., 2020), once the ACE2 Receptor is largely expressed by gut epithelial cells supporting the idea of a local infection that might precipitate a gut microbial translocation. Be that as it may, the confluent dysfunction of specific brain areas such as the right temporal lobe, connected limbic and paralimbic regions including the amygdala and the hippocampus, the brainstem, the cerebellum and the hypothalamus might be especially relevant for developing the above described psychiatric and dysautonomic manifestations (Guedj et al., 2021).

Many questions remain to be answered in relation to Mind Long Covid: Which are its risk and protective factors? How long can it last? Which are its biological underpinnings? Can we elaborate useful diagnostic and rating tools? Can we use digital monitoring to track the course of the condition (Jagesar et al., 2021)? Is there a role for psychostimulant drugs in treating it? Perhaps antidepressants, or lithium? Erythropoietin (Ehrenreich et al., 2020)? What is the role of cognitive and functional remediation? A more precise knowledge via basic and translational research, and an interdisciplinary approach targeting both physical and psychiatric symptoms, perhaps through specialized units, could be of an utmost importance to offer an optimal and more specific evidence-based response and a glimpse, at last, of a "real ending" for our patients and society.

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Declaration of Competing Interest

CDL declares no conflicts of interest.

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