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Persistent Post-COVID Syndrome (PPCS): Neurological Sequelae

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Background

Infection with SARS-CoV-2 commonly leads to respiratory symptoms typical of a viral pneumonia, including fever, cough, dyspnea, and sore throat but also, interestingly, smell disorders, and dysgeusia or other taste disorders, which suggests that the virus is neurotropic [1]. While clinical trials for safe and effective antiviral agents are ongoing, and while vaccine development programs are being accelerated, long-term sequelae of SARS-CoV-2 infection have become increasingly recognized and are of increasing concern [2].

The transmission and spread of SARS-CoV-2 did not follow the pattern of other respiratory viruses. According to the currently available evidence, SARS-CoV-2 can affect every organ in the body, leading to multi-organ damage and long-term sequelae [3]. Currently, no guidelines are available for postinfectious care or recovery and there is a notable dearth of information on strategies about how to assess and manage post-COVID patients. Persistent post-COVID syndrome, also referred to as long COVID, is a pathologic entity, which involves persistent physical, medical, and cognitive sequelae following COVID-19, including persistent immunosuppression as well as pulmonary, cardiac, and vascular fibrosis. Pathologic fibrosis of organs and vasculature leads to increased mortality and severely worsened quality of life [4].

The purpose of this article is to raise awareness for persistent post-COVID syndrome (PPCS), to provide an update on the mechanisms involved in the development of the long-term sequelae of SARS-CoV-2 infection in neuronal injury, and management of these potential long-term sequelae.

Epidemiology of Neurological Sequelae caused by COVID-19

Rodrigo et al. systematically reviewed patients in China (n = 214), Iran (n = 120), Israel (n = 42), the UK (n = 1,702). and the US (n = 262). Lechien and colleagues (n = 417) studied patients in four countries in Europe. The frequency of anosmia in COVID-19 patients ranged from 22 % to 68 %. The definition of taste impairment was more heterogenous, with dysgeusia present in 33 % of COVID-19 patients, ageusia in 20 %, and distorted taste was found in 21 % of patients with COVID-19 [5]. In a retrospective case series of 214 patients in Wuhan, China, a high incidence of neurologic symptoms was seen. Seventy-eight (36.4 %) patients had central nervous system (CNS) (24.8 %), peripheral nervous system (PNS) (8.9 %), or

skeletal muscle symptoms (10.7 %). The two most common CNS symptoms were dizziness (16.8 %) and headache (13.1 %). Acute cerebrovascular disease, ataxia, epilepsy, and impaired consciousness were also reported [6]. Montenegro, et al. (2022) estimated the prevalence of post COVID-19 condition in a community setting and see whether there are gender differences. Study results found an overall population prevalence of 14.34 % (95 % CI 11.58–17.46 %) of post-COVID-19, and prevalence was higher in women than men (15.63 % versus 13.06 %) and the most frequent persistent symptoms were fatigue (44.6 %), smell impairment (27.7 %) and dyspnea (24.09 %). Increasing reports have shown that SARS-CoV-2 infection involves the central nervous system (CNS) and the peripheral nervous system (PNS) and directly or indirectly damages neurons, leading to long-term neurological sequelae [7]. The central nervous system (CNS) and the peripheral nervous system (PNS) are both acutely damaged by SARS-CoV-2 and also show long-term damage. The neuronal damage caused by COVID-19 may be the driving force behind chronic degenerative diseases of the nervous system [8]. Regardless of its direct or indirect effects, damage to the CNS following COVID-19 may be permanent.

Underlying Mechanism of Neurological Sequelae

According to current evidence, the first mechanism is cytokine storm with rapid viral replication, direct cell damage, and activation of the immune system and inflammatory mediators, including cytokines, and this is the likely causes of the acute symptoms of COVID-19 and may explain the long-term sequelae of SARS-CoV-2 infection. The systemic increase in inflammatory mediators, now termed 'cytokine storm,' may explain the multi-organ damage found in some patients with COVID-19 and may also explain the effects of SARS-CoV-2 on the CNS [9]. These cytokines may also have a role in increasing microvascular permeability in the CNS, facilitating the entry of SARS-CoV-2 through the blood brain barrier (BBB) and into the brain [10, 11]. With disruption of the BBB due to cytokine storm, for example, or direct viral injury to nervous tissue, scar formation is induced [4].

Furthermore, the SARS-CoV-2 RNA genome and all sub-genomic RNAs integrate into the host mitochondrial matrix, resulting in a viral-mitochondrial interaction that leads to virus replication and increased vital load, and SARS-CoV-2 RNA transcripts in cell mitochondria 'hijack' mitochondrial function to suppress the immune response and promote virus replication. Eventually, the infected cells, including neurons, may undergo necrosis, apoptosis, or dysfunction due to oxidative stress and calcium ion influx, with impaired mitochondrial function [12, 13].

Additionally, SARS-CoV-2 infection results in organ damage at the cellular level in several ways. Autophagy and apoptosis occur in the fierce battle between the virus and the host. Infected host cells gather a large number of autophagosomes to activate autophagy-linked apoptosis, aiming to cut off the loop of virus replication [14, 15]. Therefore, it is speculated that the virus does its best to delay the formation and aggregation of autophagosomes in the infected host cells at the beginning of infection and to use the time available to replicate. To achieve maximal replication and spread, viruses have formed a very special survival law. Paradoxically, the virus does not actively induce autophagy and apoptosis with the purpose of using the remnants of cell destruction as vehicles for further propagation or as a strategy to avoid immune attacks [16].

Oronsky, B et al. in review found that inhibiting transforming growth factor beta (TGF-β), an immuno- and a fibrosis modulator, may attenuate these post-COVID sequelae [17]. Since multiple neurological disorders including AIDS dementia complex, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis, anxiety, depression, and schizophrenia are linked to the deregulation of the TGF-β signaling pathway, this cytokine is a potential therapeutic target for COVID-19-induced neuropsychiatric symptoms [18]. Previous studies have shown an association between coronavirus infection and the onset of multiple sclerosis (MS) [19]. If an association between SARS-CoV-2 infection and demyelinating neurological disease does exist, this will result in a therapeutic dilemma, as immunotherapy is used to treat these diseases, including MS [20].

Management of Post-COVID of Neurological Sequelae

Management strategies for the treatment of post-COVID neurological sequelae will vary greatly depending on the symptomatic profile and needs of each individual patient. Management strategies should account for prior pre-existing medical conditions and care teams should provide regular follow-up for each patient until symptoms subside and for some time thereafter. Researchers suggest that additional strategies include educating patient in the possible manifestations of

persistent post-COVID-19 also known as long COVID-19 sequelae, and continuing regular patient follow-up and encouraging patient to seek medical care at onset of worsening symptoms. Therefore, there is a need for more long-term clinical follow-up on patients who have had COVID-19, and for more attention to the management of neurological sequelae. Further in-depth researchers must include the economic impact of this disorder together with study of patient care.

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