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PERSPECTIVES

Understanding Post-COVID-19: Mechanisms, Neurological Complications, Current Treatments, and Emerging Therapies

Kevin Zambrano[1–5], Karina Castillo[1,2], Sebastian Peñaherrera[1,2,4], Henry C Vasconez[1,2], Andrés Caicedo[1–4], Antonio WD Gavilanes[1,3]

[1]Department of Health Sciences, Universidad San Francisco de Quito USFQ, School of Medicine, Quito, Ecuador; [2]Institute of Biomedical Research (Ibiomed), Universidad San Francisco de Quito USFQ, Quito, Ecuador; [3]School for Mental Health and Neuroscience (Mhens), Maastricht University, Maastricht, the Netherlands; [4]Mito-Act Research Consortium, Quito, Ecuador; [5]Neuroscience Institute, Universidad San Francisco de Quito USFQ, Quito, Ecuador

Correspondence: Andrés Caicedo; Antonio WD Gavilanes, Email acaicedo@usfq.edu.ec; danilo.gavilanes@mumc.nl

Abstract: COVID-19, a highly infectious disease, caused a worldwide pandemic in early 2020. According to the World Health Organization (WHO), COVID-19 has resulted in approximately 774 million cases and around 7 million deaths. The effects of COVID-19 are well known; however, there is a lack of information on the pathophysiological mechanisms underlying the symptoms that comprise Post-Acute COVID-19 Syndrome (PACS) or Long COVID-19. Neurological sequelae are common, with cognitive dysfunction being one of the foremost symptoms. Research indicates that elevated inflammatory levels and increased oxidative stress may play a role in the etiology and severity of PACS. Treatment options are extremely limited, and there is no consensus among the medical and scientific communities on how to manage the disease. Nevertheless, many scientists advocate for using antioxidants for symptomatic therapy and cognitive behavior therapy for supportive care. Additionally, current research aims to ameliorate several aspects of the inflammatory cascade. This review highlights the intracellular and extracellular pathways crucial to the neurological manifestations of PACS, providing valuable information for healthcare professionals and scientists. Given the complex nature of PACS, understanding these pathways is essential for developing new treatment options. Assessing PACS is challenging, and reviewing current therapeutic options while proposing a triad of potential therapeutic elements will add value to clinical assays and guidelines. Current therapeutic strategies, such as antioxidants/vitamin supplements, neurogenic stem cell therapy, and mitochondrial therapy, could be combined to enhance their effectiveness. Future research should focus on validating these approaches and exploring new avenues for the effective treatment of PACS.

Keywords: post-acute COVID-19 syndrome, PACS, long COVID-19, cognitive dysfunction, mitochondrial therapy

Introduction

SARS-CoV-2 is a highly transmissible virus that causes the acute multisystem illness known as Coronavirus Disease 2019 (COVID-2019).[1,2] The widespread infection and high mortality rate led the World Health Organization (WHO) to declare COVID-19 a pandemic on March 11, 2020.[3] By the start of 2022, it had already spread to 237 countries and territories around the world.[3] It has been estimated as of early 2024, that COVID-19 is responsible for 774 million cases and around 7 million deaths.[4] To put this into perspective, the leading cause of death in 2019 was ischemic heart disease with around 8.9 million deaths.[5] This comparison is astonishing because mortality due to infectious disease has not been a lead cause of death for decades. Moreover, this highlights the importance of establishing early alarm signs of a pandemic danger, how to prevent fast dissemination, research consortiums to understand the pathophysiology of the disease, better understand sequelae, and develop interdisciplinary approaches.

During COVID-19 infection, patients can present a variety of symptoms with the most common being fever, cough, fatigue, dyspnea, increased sputum, joint pain, diarrhea, altered smell, and altered taste.[6,7] Most patients' symptoms will

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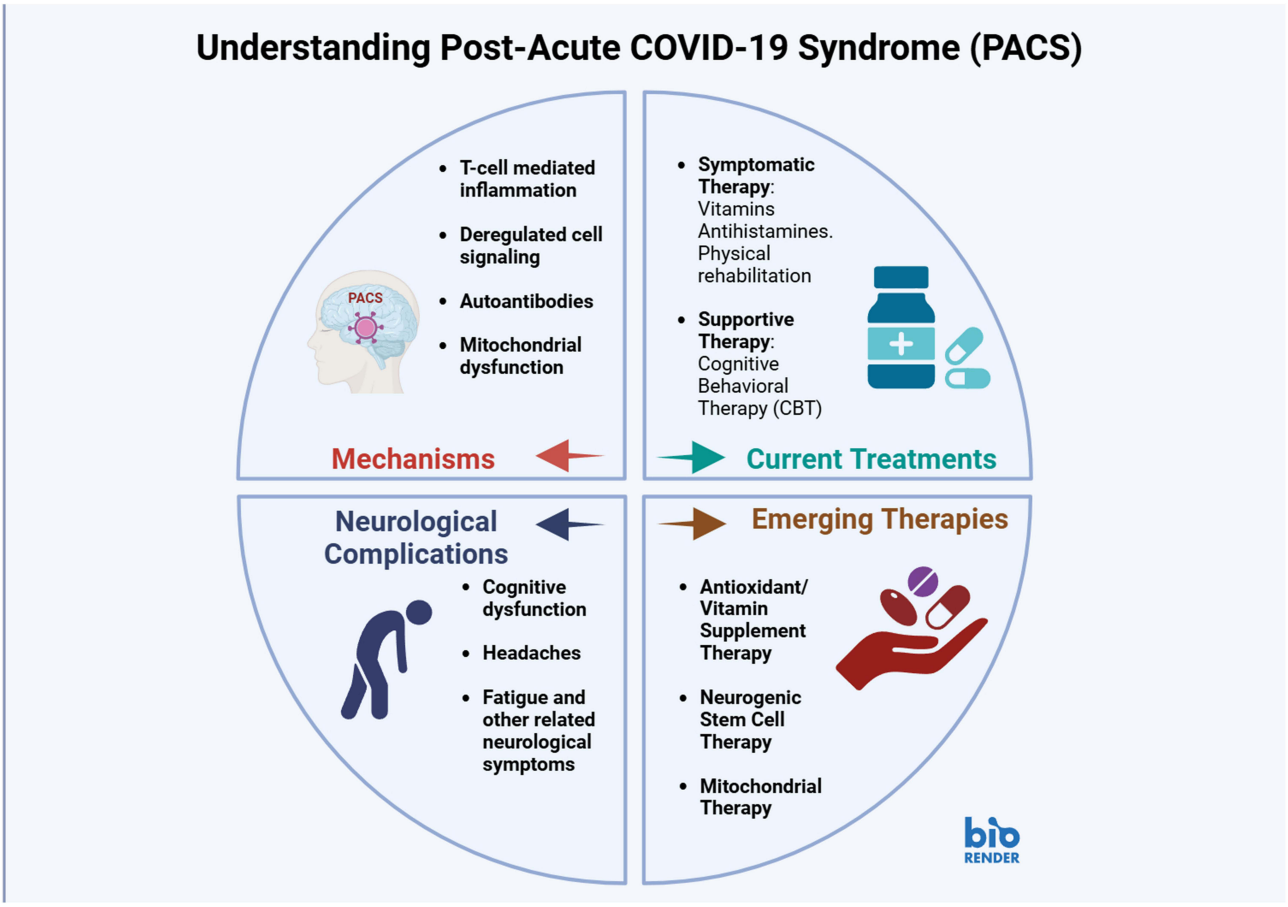
Graphical Abstract



resolve themselves in a couple of weeks. Nevertheless, some individuals may develop new symptoms such as fatigue, headache, and anosmia, among others, weeks after a presumed recovery. Approximately 10% of COVID-19 patients experience persistent or recurring symptoms that extend beyond 4–12 weeks post-infection.[1,8] The United Kingdom National Institute for Health and Care Excellence has established that ongoing symptomatic COVID-19 can occur from 4–12 weeks after infection while Post-Acute COVID-19 syndrome (PACS) or Long COVID-19 persists for more than 12 weeks.[1] This ongoing burden of persistent symptoms highlights the critical need for continued research and effective management strategies for PACS to improve patient outcomes and quality of life.

PACS has been found to be prevalent in 10–35% of the general population, however, this number increases up to 85% in hospitalized patients.[9,10] However, these numbers are still under debate as meta-analyses have reported that the global prevalence of PACS symptoms was 43% to 34% for outpatients, and 54% for hospitalized patients.[11,12] With females being the most predominant population group that develops the variety of symptoms of PACS.[11] A systematic review employing the PICO (Population or Patient, Intervention, Comparison, Outcome) and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) frameworks analyzed literature published between July 5, 2021, and March 13, 2022, to assess region-specific prevalence rates of PACS. The pooled estimated prevalence of PACS varied by region: Asia reported the highest prevalence at 51% (95% Confidence Interval [CI]: 37–65%), Europe had a prevalence of 44% (95% CI: 32–56%), and the United States showed the lowest prevalence at 31% (95% CI: 21–43%). Significant within-region variability was observed, particularly in Europe, where prevalence estimates ranged widely from 9% to 81%. Globally, the prevalence of PACS at various time points post-infection was estimated to be 37% (95% CI: 26–49%)

at 30 days, 25% (95% CI: 15–38%) at 60 days, 32% (95% CI: 14–57%) at 90 days, and 49% (95% CI: 40–59%) at 120 days after infection. Among the reported symptoms, fatigue was the most common, affecting approximately 23% of individuals (95% CI: 17–30%), followed by memory problems, which affected about 14% (95% CI: 10–19%).[12]

Interestingly, PACS does not present with a distinctive symptom but rather a complex array of physical and mental features that appear to affect a variety of tissues, making it a challenge for effective therapy.[13] Some of these symptoms include fatigue, muscle pain, fever, cough, shortness of breath, chest pain, headache, and cognitive impairment[13] (Figure 1). The pathophysiology of PACS is still being elucidated, nevertheless, some potential elements in PACS mechanisms of action include endothelial dysfunction, re-activation of other pathogens, host-microbiome alterations, autoimmunity due to molecular mimicry, persistent reservoirs of SARS-CoV-2, persistent inflammatory response, immune dysregulation, and cell dysmetabolism.[10,14]

PACS has been reported to affect an array of systems such as the neurological, cognitive, psychiatric, pulmonary, renal, cardiac, gastrointestinal, and musculoskeletal.[10] Lately, there has been growing research and focus on the neurological manifestations that PACS patients can present. Studies have reported that 36.4% of COVID-19 patients will have both central and peripheral neurological complications[14] (Figure 1). The symptoms can vary from mild such as dizziness, headache, fatigue, dysgeusia, and anosmia to more serious complications such as stroke, seizure, and ataxia, as well as increased risk of neurodegenerative diseases such as Alzheimer's and Parkinson's disease.[10,14] Some studies have

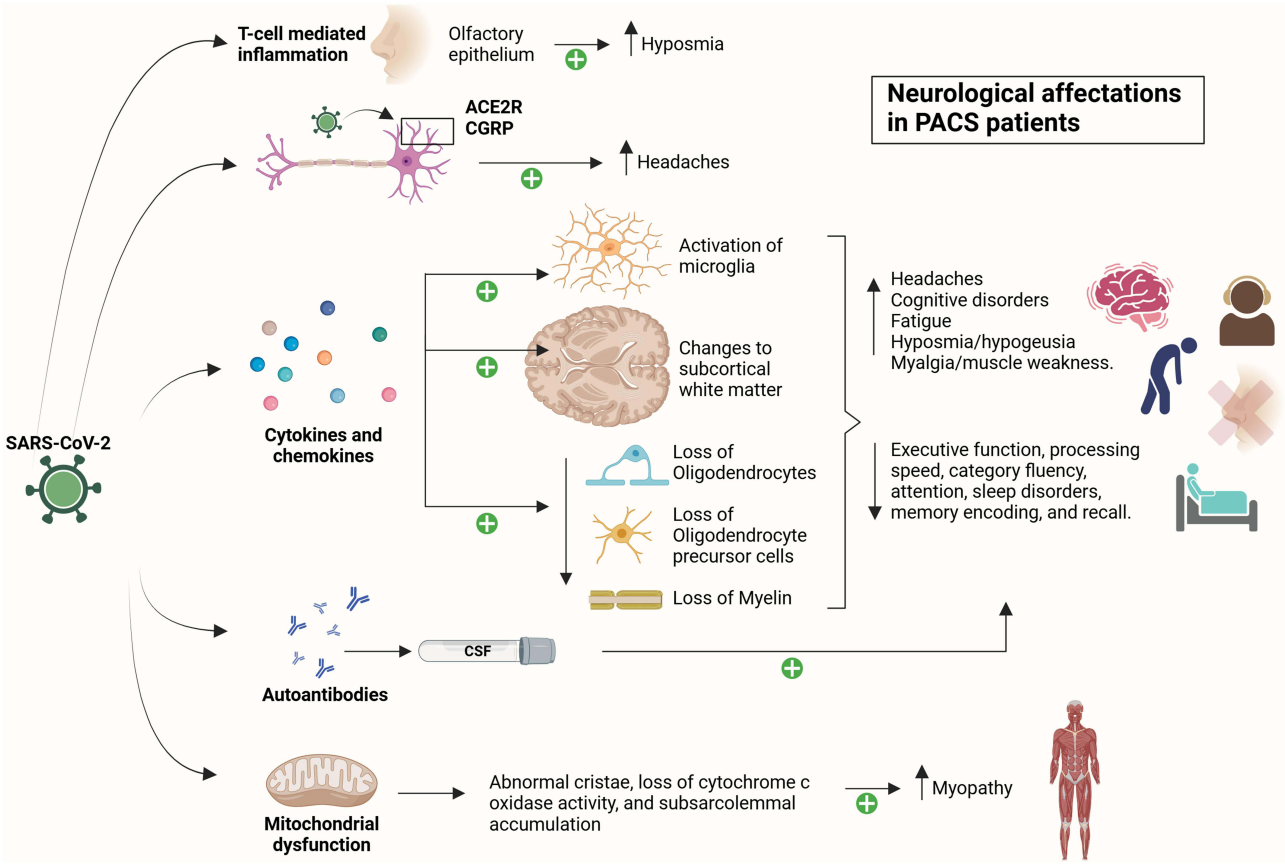


Figure 1 Neurological affectations in PACS patients. Patients suffering from PACS can develop symptoms such as cognitive disorders, fatigue, headaches, hyposmia/ hypogeusia, and myalgia/ muscle weakness. Cognitive dysfunction can be further divided in forms such as executive function, processing speed, category fluency, attention, sleep disorders, memory encoding, and recall. This is due to neuroinflammatory cytokines and chemokines that lead to activation of microglia and changes to subcortical white matter, loss of oligodendrocytes, loss of oligodendrocyte precursor cells and myelin. Autoantibodies also play a role and have been found to be involved in the etiology of PACS in the CSF of patients. Patients can also present with headaches as the virus is interconnected with receptors such as angiotensin-converting enzyme 2 (ACE2) receptors in neurons and gene-related peptide (CGRP). Moreover, SARS-CoV-2 also plays a role in T-cell mediated inflammation in olfactory epithelium which is potentially an etiology for hyposmia. Furthermore, metabolic issues have been implied in the pathophysiology of PACS patients in the form of mitochondrial dysfunction. Moreover, mitochondrial changes such as abnormal cristae, loss of cytochrome c oxidase activity, and subsarcolemmal accumulation could also be involved in myopathy in PACS patients. Created in BioRender. Rivadeneira, (M) (2024) https://BioRender.com/z91b271.

pointed out that there can be associated structural changes in the brain of PACS patients such as a reduction in global brain size, loss of gray matter thickness, and tissue contrast in the parahippocampal gyrus and orbitofrontal cortex, as well as tissue damage to the primary olfactory cortex[15] (Figure 1). The findings mentioned shed light to the critical research as well as the clinical awareness that needs to be raised to provide better quality care for these patients.

As previously mentioned, cellular dysmetabolism as a sequela of COVID-19 has been proposed as a potential causative factor of PACS. Cell dysmetabolism has also been the subject of recent reviews that explore its association with the pathogenesis of neurodegenerative diseases such as prion disease, Alzheimer's, and Parkinson's disease.[16–18]Recent observations suggest that mitochondria, beyond their role in cellular metabolism, actively transfer between cells to repair loss of function and may even play a crucial role in immune regulation.[19–23] Extracellular mitochondria can have regenerative effects when they act as activators of immune cells in order to dispose of damaged cells.[24] On the other hand damaged mitochondria have been found to have a tight link with the etiology of neurological proteinopathies.[16–18] The essential functions of mitochondria, both within and outside the cell, along with their diversity in our bodies, tissue-specific physiology, and ability to transfer between cells, could be pivotal in understanding the diverse symptoms of PACS, where mitochondria may exert a significant influence.[25–27] We believe that targeting cellular metabolism or metabolic homeostasis could also be a key element in producing new therapeutic agents.

Nevertheless, the specific pathways of how this occurs in PACS are still puzzling. To provide a robust foundation for this perspective review, we conducted a comprehensive analysis of the best available information to our knowledge. This methodological approach involved an in-depth examination of peer-reviewed literature, employing a broad and integrative search of studies and reviews related to the neurological manifestations of PACS, the role of extracellular vesicles (EVs), and treatment modalities. Our aim was not to replicate systematic reviews but to synthesize key insights and identify gaps in current understanding, providing a stepping stone for further studies.

First, we introduce current research on the neurological manifestations of PACS, including the signs and symptoms observed in patients, as well as diagnostic tools that can aid healthcare professionals in recognizing these conditions. Next, we explore the involvement of EVs in the pathophysiology of COVID-19 and PACS, highlighting their potential role as biomarkers or therapeutic targets. We then evaluate the limited treatment options currently available for general PACS and its neurological manifestations, emphasizing the unmet clinical needs in this area. Finally, we discuss emerging therapies under investigation, particularly those focused on neurogenesis and brain matter recovery, which hold promise for restoring metabolic homeostasis and combating the long-term effects of PACS.

Neurological Affectations of Post-Acute COVID-19-Syndrome (PACS)

As mentioned previously, many patients who recovered from COVID-19 will have some form of persistent neurological complaints (Figure 1). These symptoms can be categorized into different groups such as cognitive disorders, fatigue, headaches, hyposmia/hypogeusia, and myalgia/ muscle weakness. Cognitive dysfunction can be found during both acute stages and in the subsequent course of COVID-19.[11] This dysfunction can manifest as impairments in executive function, processing speed, semantic fluency, attention, sleep disorders, memory encoding, and recall, with 28% of PACS patients presenting memory impairment.[11,28–30] (Figure 1). Interestingly, several intracellular and extracellular pathways have been described with a strong influence on PACS; Azcue et al propose that fatigue could be due to autonomic nervous system involvement.[29] One study by Fernández-Castañeda et al evaluated the effects of SARS-CoV-2 infection in murine models and found that there were changes in neuroinflammatory cytokines and chemokines.[31,32] The authors found changes in protein C-C motif chemokine 11 (CCL11) in cerebrospinal fluid (CSF) as well as serum 7 weeks after infection.[31,32] Moreover, Li et al argue that the initial cytokine storm and neuroinflammation caused by the virus can disrupt neural circuits and their connections leading to vast neurotransmitter changes.[30] Additionally, researchers have reported activation of microglia and changes to subcortical white matter, loss of oligodendrocytes, loss of oligodendrocyte precursor cells and myelin[31,32] (Figure 1). This could explain more of the pathways of cognitive dysfunctions. Some authors have identified that delivering CCL11 intraperitoneally to healthy mice induces the activation of microglia and macrophage which, in effect leads to the suppression of neurogenesis.[31,32]

This finding highlights the role of CCL11 as a potential biomarker in the diagnosis of PACS with neurological affectation. Franke et al mentions that there is a significant association between cognitive dysfunction and anti-nuclear

antibodies which could indicate autoimmunity as another physiological element in PACSe.[11,33] The author has suggested that it is common to find autoantibodies that target brain epitopes in patients with PACS who have pathological cognitive screening tests, especially when found in the CSF.[33] Other authors have also suggested that neurological manifestations in PACS mainly cognitive dysfunction, and fatigue could be due to autoantibodies against β2 adrenoceptors, α1-adrenoceptors, AT1R, MAS receptors, muscarinic type 2 receptors, and nociceptin-like opioid receptors.[14] Additionally, Hosp et al suggested that there is an association between altered cerebral metabolism in cognitive impairment as 10 out of 15 patients presented frontoparietal hypometabolism using fluorodeoxyglucose (FDG) positron emission tomography (PET) scan.[34] This could be due to the energy metabolism in neuronal cells that is compromised by the viral genome which consequently results in mitochondrial dysfunction.[35] Moreover, Stefano et al suggested that cognitive dysfunction through mitochondrial dysfunction holds an evolutionary advantage for virus propagation and interaction.[35] Other authors have reported that through light scattering they found that PACS patients have reduced mitochondrial density and volume as well as a decrease in density of brain matter.[36] Nevertheless, this area of COVID-19 research is still young, and much remains to be enlightened in the pathways of cognitive dysfunction.

Headaches are one of the most common complaints of PACS. With 8–15% of COVID-19 patients presenting with persistent headaches during the first 6 months after infection.[37] They can be described as moderate to severe and persistent.[38] It is important to note that headaches can be the result of either systemic infection or even the neuroinvasive mechanisms of the disease.[38] Chhabra et al argue that respiratory viral infectors can be associated with headaches regardless of direct central nervous system (CNS) infection.[38] Furthermore, the authors state that they can be the result of fever as well as the activation of inflammatory cytokines and cytokine storms.[38] Other hypotheses for the mechanisms behind headaches in PACS include the ability of the virus to bind to angiotensin-converting enzyme 2 (ACE2) receptors in neurons and glia of CNS structures such as olfactory groove, olfactory bulb, and trigeminal ganglia.[38,39] Additionally, the presence of ACE2 in cerebral blood vessels as well as the immunoreactivity of the cells in the endothelium and leptomeninges to SARS-CoV-2 proteins further supports this hypothesis.[39] Moreover, calcitonin gene-related peptide (CGRP) has also been associated with headache in PACS as the peptide is released during viral infection and has a role in the regulation of immunoinflammatory response.[39] Moreover, this peptide has been found to be elevated in patients with migraine, and therefore has been proposed as a possible reason for persistent headaches in PACS patients.[39,40] Garate et al argues that the elevation in CGRP supports a role for trigeminal activation in the pathophysiology of this symptom in PACS.[40] Nevertheless, one study that analyzed CGRP levels in patients with headaches in PACS patients found no significant association.[41] Despite the different hypotheses behind the etiology of headaches in COVID-19, authors such as Bobker & Robbins et al propose that headaches in the early stages of COVID-19 are most likely due to systemic infection while headaches in later stages can be explained by neuroinvasion and cytokine release storm.[38,42]

Hyposmia/anosmia and hypogeusia/ageusia have also been reported in recovered COVID-19 patients as they can last longer than 6 months after initial infection.[11,43] Finlay et al reported that despite the lack of SARS-CoV-2 RNA or protein, gene expression in the barrier-supporting cells of the olfactory epithelium, showed there was still substantial inflammation.[44] The authors suggested that T-cell-mediated inflammation is a possible mechanism for smell loss.[44] Additionally, other authors have stated how olfactory receptor neurons can become infected and that the virus can travel along the axons and infect post-synaptic neurons using the same neurotransmitter neurons.[45] It is important to note that there could be a type of viral tropism for this type of neuron and that there could be cell-cell mechanisms through the secretion and absorption of EVs that could aid in the propagation of the virus.[45] Similarly, muscle pain and muscle weakness can persist after infection with some patients reporting symptoms up to 6 months after infection.[11] Hejbøl et al reported that mitochondrial changes such as abnormal cristae, loss of cytochrome c oxidase activity, and subsarcolemmal accumulation could be factors in the pathophysiology of myopathy in PACS patients.[46] Meanwhile, critical illness neuropathy was been reported in 10% of intubated patients with COVID-19, with prolonged insults such as intense inflammation and nerve compressions as potential etiological agents.[47] Oaklander et al stated that inflammation markers might still subside but can leave residual axonopathy and that regeneration can take up to two years or might remain incomplete.[47] Interestingly, long-lasting neurodegeneration and neuropathy in patients who survive acute infection are also present in other coronavirus diseases.[48]

It is also important to highlight that PACS can present itself with more serious, albeit uncommon manifestations such as epilepsy, stroke, Guillain-Barre syndrome, and encephalopathy.[49–51] Moreover, dementia and loss of brain matter have also been reported among PACS patients.[52] It has been suggested that there can even be signs of cellular metabolic stress that precede dementia and that this can and should be observed in these patients.[15,52] Moreover, it has been suggested that there is a correlation between cortical atrophy, white matter hyperintensities, and hypometabolism with neurological complaints of patients.[53] The damage to structures such as the hippocampus could be due to silent brain hypoxia as well as an immune response against the virus, which can also affect the blood-brain barrier (BBB).[53] It is important to note that the virus can cause both an increase in oxidative stress (and therefore inflammation), as well as mitochondrial dysfunction which can lead to a loss of proteostasis and increase in endoplasmic reticulum stress.[54] Additionally, it has also been proposed that cytokine storm syndrome is one of the main mechanisms behind SARS-CoV-2-induced brain damage[54] which could have long-term consequences such as the neurological manifestations of PACS. The virus infects neurons and microglia which promotes the release of tissue tumor necrosis factor-alpha, cytokines (interleukin-6 (IL-6), IL-2, IL-5), and reactive oxygen species (ROS)[54] causing further stress and damage to the nervous system. We believe this is a potential area where more research remains to be done, not only on pathways but on potential treatments. More studies should be conducted to fortify the blood-brain barrier and decrease cytokine-induced inflammation by targeting the oxidative cascade and preventing oxidative stress by enhancing mitochondrial function.

Extracellular Vesicles (EVs) Role in COVID-19 Infection and PACS

The human body is constantly adapting to changing conditions, deploying robust mechanisms to maintain homeostasis and combat diseases like COVID-19.[55] EVs, including exosomes, microvesicles (MVs) and apoptotic bodies (ABs), are essential components of adapting systems involved in maintaining our health. These EVs facilitate intercellular communication via the bloodstream, coordinating metabolic responses across tissues to orchestrate the organism's immune response.[56] EVs achieve this by transferring proteins, nucleic acids, lipids and other cargo to recipient cells, thereby inducing specific metabolic changes essential for immune function.[56]

Different tissues, such as the CNS and the immune system, exhibit distinct requirements for the production and uptake of EVs, reflecting their specific size, function, origin, and cargo load.[57] The analysis of EVs, particularly exosomes, provides valuable insights into the physiological and pathological states of their cells of origin.[57] This understanding enables the use of exosomes from blood samples as a minimally invasive method to assess the CNS's condition and metabolic processes during pathological states, such as COVID-19 and PACS.[58] The link between COVID-19 and EVs is significant, as EVs have been suggested to support virus propagation and reflect the physiological state of the parent cell, making them potential biomarkers for predicting disease severity and the development of PACS (Park et al, 2022; Su. et al 2023). Additionally, EVs have shown an important role in the development of complications such as thrombosis, cytokine storm and most importantly PACS. In essence, EVs have been shown to facilitate intercellular communication, coordinate metabolic responses, and play a pivotal role in recovery processes by directly transmitting nucleic acids and molecules to target tissues, thereby inducing necessary metabolic responses to fight disease.[59] Therefore, in this section, we will present key studies that show how EVs could be of value for predicting disease progression and informing therapeutic strategies against COVID-19 infections and the development of PACS.

As the role of EVs is diverse, so are their types and cargo. EVs have been found to contain over 500,000 proteins, approximately 50,000 RNAs, and more than 3000 lipids and metabolites (Vesiclepedia & Exocarta database, 2024). Hence, to study EVs, they have been classified into three main categories based on their size. The smallest category is exosomes, which range in size from 30 to 100 nm. Exosomes originate from endosomes and subsequently from multivesicular bodies, and they are released into the bloodstream after merging with the plasma membrane.[60] This highlights their importance in COVID-19 infections as they serve as biomarkers of what cells are exchanging.[61] EVs in COVID-19 have been associated with antigen presenting functions, cell activation and more.[58,62] These vesicles require high specificity for targeting and merging with recipient cells, which is why they consistently contain high concentrations of tetraspanin proteins—such as CD9, CD63, CD81, and CD82—that confer these essential characteristics.[63]

The next larger type of EVs are MVs, which vary significantly in size, ranging from 30 to 1000 nm.[64] They are formed through a direct evagination process from the cytoplasmic membrane, characterized by the presence of distinct

molecules such as mitofilin, actin-4, and GP96 (Díaz-Godínez et al 2022). Interestingly, EVs have been implicated in COVID-19 as contributors to procoagulant, thrombin, and inflammatory activities. Elevated levels of procoagulant MVs and tissue factor (TF)-bearing MVs in COVID-19 patients have been suggested as early potential markers for predicting disease severity. These findings suggest that MVs could serve as novel circulatory biomarkers for assessing procoagulant activity and determining the overall severity of COVID-19.[65] A significant challenge in distinguishing and purifying exosomes from MVs or ABs lies in their overlapping size ranges.[60] A critical factor for differentiation during purification is the presence of distinct molecules, as previously described and highlighted by Hernández-Díazcouder et al.[64]

The third and largest type of EVs are ABs, ranging from 500 to 5000 nm, which form during the late stages of apoptosis. These vesicles are characterized by the external display of phosphatidylserine. In the context of SARS-CoV-2 infection, ABs have been linked to dysfunctional efferocytosis—the process by which apoptotic cells are cleared. This dysfunction is associated with the suppression of macrophage anti-inflammatory responses and impaired immune function, illustrating how EVs can modulate tissue repair processes. Consequently, this can lead to the excessive production of pro-inflammatory cytokines and the accumulation of tissue damage.[66]

It is crucial to understand the implications of EVs and their cargo in patients with acute COVID-19 infections, PACS, and those whose post-acute COVID-19 infections resolved without developing PACS. To address this need, several studies have isolated EVs from whole blood using tetraspanin markers.[67] SARS-CoV-2 infection induces deregulation in cellular metabolism and mitophagy, leading to abnormal levels of mitochondrial proteins within EVs. Goetzl et al investigated whether EVs and mitochondrial proteins (MP) could also be useful in predicting the course of the infection. It has been observed that SARS-CoV-2 proteins are present inside EVs, particularly the nucleocapsid (N) protein, which encases the virus's RNA genome, and the S1 protein, which aids the virus in entering host cells by attaching to the Angiotensin-Converting Enzyme 2 (ACE2) receptor. Goetzl et al's findings revealed that patients with PACS had significantly higher concentrations of the N protein in their EVs compared to those with acute COVID-19 and individuals who did not develop PACS. Interestingly, their study also showed that total EVs levels of the S1 protein were significantly elevated in patients with acute infections compared to uninfected controls, those who had recovered from COVID-19 without developing PACS, and even those with PACS. Interestingly, in patients who went on to develop PACS, there were notable reductions in the total EVs levels of the MPs Mitochondrial Open Reading Frame of the 12S rRNA-c (MOTS-c), Voltage-Dependent Anion Channel 1 (VDAC-1), and humanin, along with increased levels of Sterile Alpha and TIR Motif-Containing Protein 1 (SARM-1). Among PACS patients experiencing neuropsychiatric symptoms, a similar pattern was observed, with significant decreases in MOTS-c and humanin, but not VDAC-1, alongside elevated SARM-1 levels. The discovery of elevated N protein in the EVs of PACS patients is a key finding, as it suggests that the N protein could be a key factor in sustaining inflammation and immune dysregulation as it may indicate ongoing viral activity or a persistent immune response. However, they found that while these markers provided valuable insights into the acute phase of infection, they did not consistently predict the long-term evolution of the disease, highlighting their limitations as reliable indicators for the progression of PACS. Nevertheless, EV levels containing mitochondrial proteins during acute infections may predict a higher risk of developing PACS, and in patients with stabilized PACS, they could provide valuable insights into neuropsychiatric symptoms. A deeper understanding and classification of the origins of EVs could offer valuable insights into the dynamics of these vesicles and their cargo, shedding light on their significance in PACS and enhancing their predictive value.

In another study, researchers analyzed the levels of S1 and N proteins in different types of EVs, specifically neuron-derived extracellular vesicles (NDEVs) and astrocyte-derived EVs (ADEVs) found in plasma. They examined three groups of patients: those with PACS and neuropsychiatric symptoms (NPs), those with PACS but without neuropsychiatric manifestations, and those who had recovered from COVID-19 without any PACS symptoms.[68] It was observed that the levels of S1 and N proteins in both NDEVs and ADEVs were higher in all PACS sub-groups compared to healthy controls. However, the N protein levels were elevated in patients with PACS who had NPs compared to those without these symptoms. In addition, specific mitochondrial proteins in NDEVs, such as subunit 6 of respiratory chain complex I, subunit 10 of complex III, and the neuroprotective proteins Humanin and MOTS-c, were significantly reduced in PACS patients with neuropsychiatric symptoms, but not in those without these symptoms, relative to controls. Levels of other mitochondrial proteins, like VDAC1 and N-Methyl-D-Aspartate Receptor Subunit 1 (NMDAR1), were decreased in both

PACS groups (with and without NPs). In contrast, the levels of calcium channel-related proteins Mitochondrial Calcium Uniporter (MCU), Sodium Calcium Lithium Exchanger (NCLX), and Leucine Zipper and EF-Hand Containing Transmembrane Protein 1 (LETM1) were reduced only in PACS patients with neuropsychiatric symptoms. In ADEVs, the levels of MCU and NCLX were increased in both PACS groups, regardless of the presence of NP. Interestingly, the levels of N and S1 proteins in NDEVs and ADEVs, along with MP, were found to correlate with NP, suggesting they could serve as effective biomarkers for PACS.

Given that neurological disorders, including PACS, exhibit a range of puzzling biochemical changes and diverse symptoms, there is significant interest in uncovering the key drivers behind these conditions and their parallels.[69] As previously observed, Peluso et al found consistent abnormalities in MP within NDEVs.[68] Similar abnormalities have been documented across various neurodegenerative diseases and mental illnesses that exhibit symptoms similar to those of PACS. Delgado-Peraza et al further reinforce this connection by demonstrating a strong predictive relationship between MP loads in EVs derived from both neurons and astrocytes, and brain pathology in mouse models of Alzheimer's disease.[70] This was established by comparing MP loads in EVs derived from both neurons and astrocytes from healthy individuals and with those in the Alzheimer's model. Analysis of the protein content in these vesicles reveals patterns of protein fluctuations that mirror those seen in major depressive disorder (MDD), early schizophrenia (first-episode psychosis, FP), and Alzheimer's disease.[71–73]

Insights into the immune responses causing severe and mild COVID-19 infections have been provided by EVs analysis.[62] Pesce et al studied EVs cargo variation in mild and severe infections and proposed that in mild infections EVs can act as antigen-presenting cells, modulate the immune response and in severe infections drive inflammation.[62] Pesce et al specifically isolated exosomes using tetraspanins (CD63, CD9, and CD81) markers from blood plasma samples, ensuring that the study focuses on a well-defined subset of exosomes. Intriguingly, confirmed through ELISA assay and flow cytometry, mild patients had a higher amount of circulating fragments for S protein in exosomes specially on CD41a + and CD9+ subpopulations; compared to patients with severe symptoms.[62] Interestingly, CD41a+ exosomes of mild COVID-19 patients were larger (50–160 nm) than those of severe COVID-19 patients (50–100 nm) suggesting differential cargo depending on the state of the infection.[62] Further analysis revealed that mild infection exosomes displayed fragments of S proteins, being indicative for potential immunological benefits. EVs markers allow them to elucidate their origin, therefore it was demonstrated that these EVs originated from B cells, dendritic cells, macrophages and antigen-presenting cell, as evidenced by the presence of specific markers: B-cell marker CD19, dendritic cell marker costimulatory molecule CD86, macrophage marker integrin CD11b, and the antigen-presenting cell marker Major Histocompatibility Complex Class II (MHC-class II), Human Leukocyte Antigen-DR (HLA-DR).[62] Therefore, it could be suggested that exosomes also function as antigen-presenting cells, enhancing cross-presentation and cell activation, including CD4+ T-cell activation. Pesce et al suggested that such interaction enhances the immune response, fostering a more coordinated and effective defense against the infection and typically resulting in milder symptoms and mitigating the effects of the virus more effectively.[62] Pesce et al also presented answers into the reason behind the contrasting profile in a mild and a severe infection. For instance during severe infections, exosomes are primarily produced by inflamed tissues and carry high levels of C1R (a protein that initiates complement activation), coagulation system components, inflammation modulators, and regulators including IL-6 pro-inflammatory signaling.[62] This suggests that exosomes from severe infections enhance cell chemotaxis and inflammation, leading to more widespread inflammation and greater tissue damage, which in turn worsens the severity of the infection. Therefore, this provides evidence that exosomes in mild infections from COVID-19 carry beneficial immunological properties while those in severe cases carry detrimental components suggesting new therapeutic avenues, as potential biomarkers for predicting disease severity.

EVs serve as a powerful form of extracellular communication between organs that can enhance immune responses and reflect the physiological state of cells, making them valuable biomarkers for COVID-19 infections. The consistent pattern of abnormal MP concentrations, including MOTS-c and Humanin, observed in both total and neuronal derived vesicles highlights EVs utility in diagnosing, predicting, and differentiating neuropsychiatric complications. EVs analysis has revealed a link between cellular metabolic dysfunctions and the neuropsychiatric sequelae observed in patients with PACS. This relationship provides putative mechanisms underlying neurological impairments and identifies specific therapeutic targets that address both the root pathophysiology and its wider systemic effects, providing a pathway to

precise treatment for neurological affectations and to appropriately treat the underlying causation. These studies require more extensive analysis of larger populations. More research teams are required to produce similar results to see breakthroughs to the clinical implementation approach.

Current Treatment for PACS

As PACS encompasses a diverse array of systemic affectations varying among patients its treatment has to be equally diverse and tailored to individual needs (Figure 1). Nevertheless, there is still a lack of consensus, even with the nomenclature for this disease, in establishing a specific treatment protocol for PACS and its chronic comorbidities.[74] It has been reported that patients with PACS often do not seek professional medical care and resort to polypharmacy.[74] This underscores the importance of research and publications that aim to expand our understanding of the various characteristics of PACS. Authors have suggested that PACS treatment can be categorized into three main approaches: symptomatic treatment, supportive care, and rehabilitative therapy with self-monitoring[74] (Figure 2).

For symptomatic treatment of patients with PACS healthcare professionals must establish the foremost symptom and focus attempts on reducing its severity or frequency. For example, Patients with extreme fatigue could benefit from high-dose Vitamin C.[75] Combining L-Arginine and Vitamin C has been reported to target endothelial dysfunction in PACS

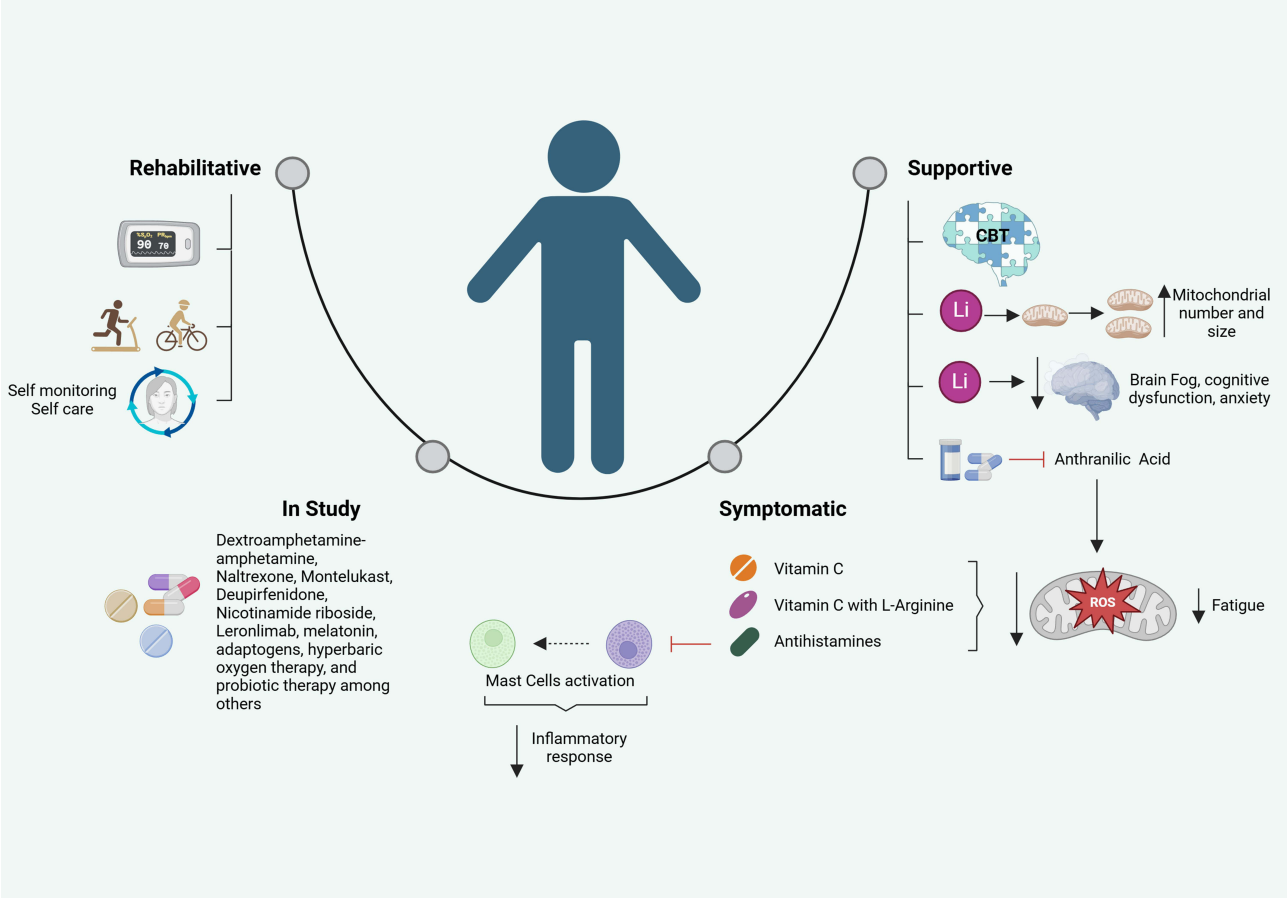


Figure 2 Current treatment options for PACS patients. Treatment for PACS patients can be categorized into symptomatic, supportive, and rehabilitative approaches. Symptomatic treatments include the use of Vitamin C alone or combined with L-Arginine to reduce fatigue by lowering ROS levels, as well as antihistamines to decrease mast cell activation. Apheresis has shown promise in some studies, while physical rehabilitation, particularly light aerobic exercise, has been effective in alleviating fatigue and dyspnea. Supportive treatment primarily targets the neurological and psychiatric symptoms of PACS, with Cognitive Behavioral Therapy (CBT) being the leading approach. Other pharmacological interventions, such as blocking anthranilic acid to reduce cognitive dysfunction and ROS levels, are under investigation. Lithium is also being used to mitigate brain fog, anxiety, and cognitive dysfunction by increasing mitochondrial number, size, and cytochrome c content. Additionally, other substances under study include Dextroamphetamine-amphetamine, Naltrexone, Montelukast, Deupirfenidone, Nicotinamide riboside, Leronlimab, melatonin, adaptogens, hyperbaric oxygen therapy, and probiotic therapy. Rehabilitative treatment includes self-monitoring strategies, such as serial pulse oximetry readings, along with self-care practices. Created in BioRender. Zambrano, (K) (2024) https://BioRender.com/m70j058.

patients as this combination could also significantly reduce fatigue[76] (Figure 2). Additionally, the authors also propose that L-Arginine and Vitamin C also play a role in reducing ROS levels as they have been able to reduce ROS when combined to glucagon-like peptide 1 agonists in diabetic patients.[76] Other authors have hypothesized that the use of antihistamines could also prove to be beneficial, as mast cell activation in patients with PACS has been observed[77,78] (Figure 2). Apheresis has also gained increasing clinical importance as it has been used in patients with arteriosclerosis, coronary heart disease, rheumatological diseases, and neurological diseases.[77] Its use in patients with PACS is promising according to Tselmin et al.[79] Physical rehabilitation in the form of light aerobic exercise has been shown to improve symptoms of fatigue and dyspnea in PACS patients as well[79] (Figure 2). Surely, there are still various treatment options that are being studied that will hold beneficial critical value. Nonetheless, these supportive treatment options tend to not be offered and are limited to the availability of the region and health care institution.

Supportive treatment is a crucial treatment modality that is being used in the fight against PACS especially with the neurological and psychiatric affectations mentioned in this article[74] (Figure 2). Therapeutic treatment for PACS neurological sequelae is challenging and as of this date is still limited to non-drug measures.[80] Therefore, Banerjee et al argue that the mainstay method of treatment for these neurological affectations is supportive therapy in the form of cognitive behavioral therapy (CBT) as well as counseling.[74] CBT has been found to be effective in reducing fatigue in several different diseases such as breast cancer, chronic fatigue syndrome, and diabetes.[80] CBT in COVID-19 can be categorized into nine modules which are the following (1) goal setting; (2) sleep–wake pattern; (3) helpful thinking; (4) social support; (5) graded activity; (6) processing the acute phase of COVID-19; (7) fear and worries regarding COVID-19; (8) coping with pain; and (9) realizing goals. Kuut et al performed a randomized controlled trial evaluating hospitalized and nonhospitalized patients that received CBT and found that in nonhospitalized patients CBT was effective in reducing fatigue.[81] Norman et al has suggested that the blocking effect of anthranilic acid and other neurotoxic metabolites of the kynurenine pathway could prove to be useful in overcoming brain fog as well as cognitive dysfunction in PACS patients.[82] Norman et al argue that anthranilic acid is able to generate free radicals and increase oxidative stress and that it could play a potential role in the cognitive symptoms of PACS patients.[82] Moreover, Krishnan et al also states that sleep hygiene should also be managed in order to reduce insomnia in PACS patients as this is also a neurological/psychiatric condition often reported in PACS patients.[83]

It is important to note that some authors have also suggested that certain substances like antiviral drugs (Paxlovid) can be used to reduce neurological symptoms of PACS.[84] Moreover, the authors mention that oral lithium in 10 mg daily was being assessed for its ability to reduce fatigue, brain fog, anxiety, and cognitive outcomes in a randomized clinical trial.[84,85] Additionally, Fessel et al reported that patients with PACS could benefit from a combination of lithium and fluoxetine when psychotherapy falls short.[86] The authors suggested that lithium benefited mitochondria as it increased the number and size of neural mitochondria as well as cytochrome c content.[86] Consequently, this reduced neural oxidative stress and increased levels of antioxidant catalase and superoxide dismutase.[86] Dextroamphetamine-amphetamine was hypothesized to be a viable treatment option for brain fog as it has been used in attention-deficit disorders.[86] However, the study was terminated due to the evolving nature of COVID-19 related brain fog.[85] Naltrexone was also reported to show certain promise in regard to brain fog and fatigue, nevertheless, current clinical trials are still in the recruiting phase at the time of writing this article.[84,85] Similarly, other substances that are being studied are Montelukast, Deupirfenidone, Nicotinamide riboside, leronlimab, melatonin, adaptogens, hyperbaric oxygen therapy, and probiotic therapy among others.[84] Even though many of these studies show promise, more studies are required to fully explore what treatment options offer the most benefit and the least amount of risk for PACS patients.

In regards to rehabilitative treatment, patients and physicians need to have a delicate relationship in order to carry out adequate self monitoring and self care.[84] Patients and physicians have to set up regimens for daily serial pulse oximetry readings that could help visualize a rate of recovery.[84] Furthermore, this helps the patient visualize their healing process. It is interesting to suggest that this could be beneficial for the patients' psychiatric conditions. Pulmonary rehabilitation for chronic coughs can aid in the reconditioning of the diaphragm.[84] However, there is very limited information in what rehabilitative treatments should be used for PACS patients with neurological sequelae. Thus, we must emphasize the importance to attract more research into this area of the field as there is still a number of patients with PACS that have neurological sequelae.

New Potential Treatments for Neurological Sequelae

As mentioned previously, SARS-CoV-2 can have unfortunate and severe repercussions on the CNS. The virus can infect the host and cause an inflammatory cascade with the activation of microglia and expression of IL-1β, IL-2, IL-5, and IL-6[54,87,88] (Figure 3). The virus is able to induce inflammation as well as hypoxia in crucial areas of the brain that are in charge of motor function, learning, memory, and emotional response.[87] BBB disruption has been found to be present in acute COVID-19 infection and has been associated with cognitive impairment in PACS patients.[89] Fibrinogen leakage and thinning of endothelial cell basal laminae in the olfactory bulb have been found in deceased patients with COVID-19.[89] Alternatively, other authors have reported that there can be increases of fibrinogen in the hippocampus which could lead to regional alterations of human BBB integrity.[87] These changes in BBB can allow for a higher entrance of cytokines and the activation of glial cells.[87] It is important to note that some of these cytokines can affect critical neural processes as it has been reported that cytokines such as IL-1β and IL-17, can inhibit neurogenesis in certain parts of the brain.[90,91] Moreover, in both human and hamster models, this inflammation, cytokine expression, and BBB disruption can lead to

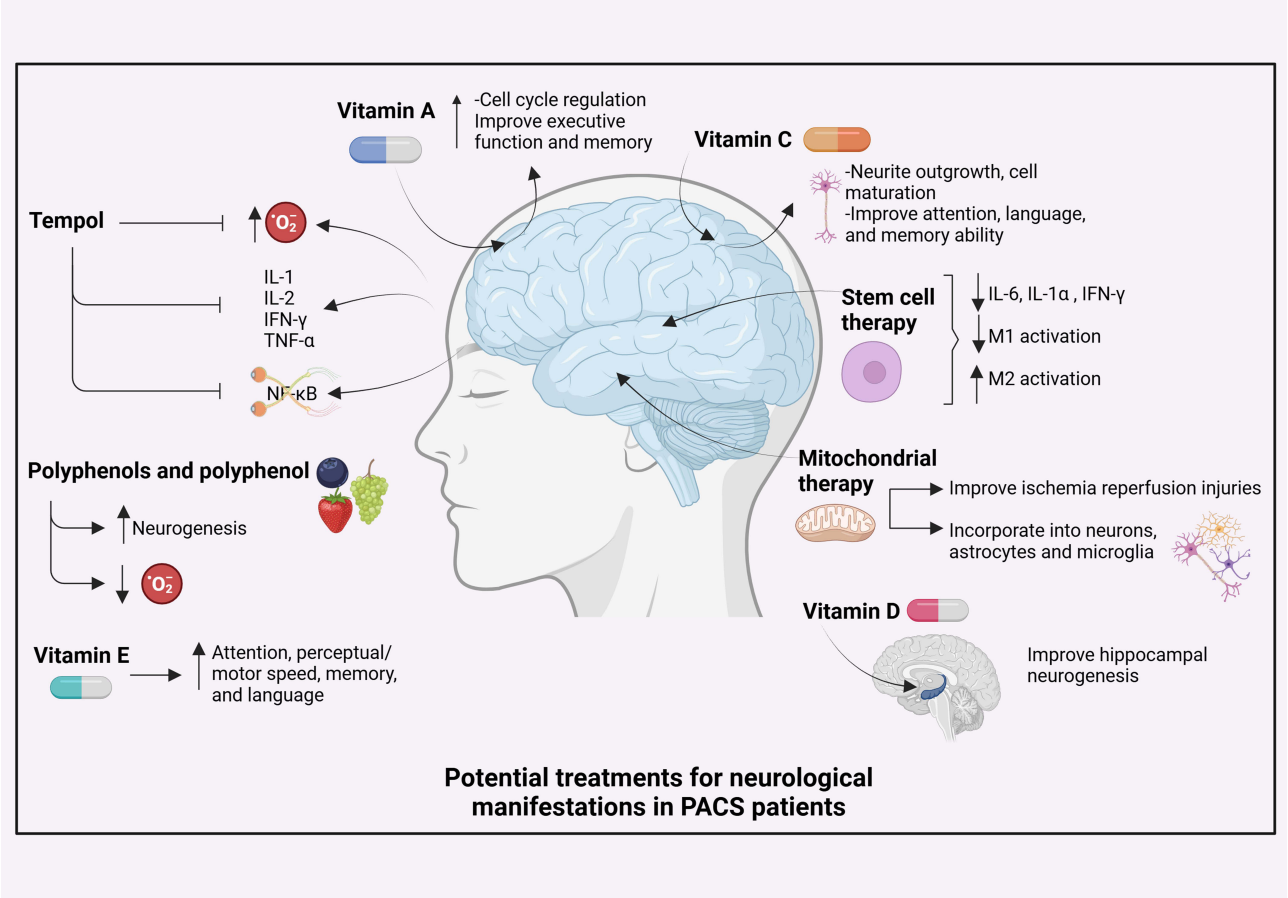


Figure 3 New potential treatments for neurological manifestations in PACS patients. We suggest a triad of antioxidant/vitamin supplements, neurogenic stem cell therapy and mitochondrial therapy. Due to high levels of ROS and inflammation seen in brain damage we suggest that supplementation such as Tempol (a synthetic antioxidant compound that mimics the activity of superoxide dismutase, an enzyme that naturally protects cells from oxidative stress by neutralizing superoxide radicals). can have promising results in neuroinflammation by reducing hydroxyl radicals, as well as decrease inflammatory cytokines such as IL-1, IL-2, IFN-γ, and TNF-α, along with a decrease in the activation of NF-κB in the optic nerve. Vitamin A can also help in cell cycle regulation and improve cognitive impairments in executive function and memory. Vitamin C can aid in neurite outgrowth, cell maturation and has been reported to improve attention, language, and memory ability. Vitamin D has been linked to improve hippocampal neurogenesis, while vitamin E has aided in preservation of attention, perceptual/motor speed, memory, and language. Additionally polyphenols and polyphenol rich food such as blueberries, strawberries and grape seeds increase and promote neurogenesis while simultaneously reducing ROS. Meanwhile, stem cell therapy has been suggested to be potential treatment in inflammatory states, this treatment has been known to reduce IL-6 and inhibit dendritic cells and B cells, T cells, and NK cells, decreasing M1 and enhancing M2 activation. Moreover, stem cell therapies has been known to decrease proinflammatory cytokine expression levels as is the case with IL-6, IL-1α, and IFN-γ. Mitochondrial therapy has also been used in several pathologies where they have shown the ability to improve ischemia-reperfusion injuries, mitochondria are able to incorporate into neurons, astrocytes and microglia. Mitochondrial therapy has had favorable results in Alzheimer mice models, diabetes associated cognitive impairment, and Parkinson mice animal models. Created in BioRender. Zambrano, (K) (2024) https://BioRender.com/h44d942.

the disruption of neurogenesis and contribute to neuronal dysfunction and loss which ultimately leads to neuronal PACS symptoms.[87]

Therefore, we suggest a triad of elements for further research that could prove useful in the fight against neurological PACS; antioxidant/vitamin supplements, neurogenic stem cell therapy, and mitochondrial therapy.

Antioxidant/Vitamin Supplemental Therapy

Excessive reactive nitrogen species and ROS can be formed when there is brain injury.[92] Subsequently, this can lead to secondary brain damage along with lipid peroxidation, and inflammatory mediators.[92] Endogenous enzymes (Superoxide Dismutase (SOD), Catalase (CAT), Glutathione Peroxidase (GPx)) and non-enzymatic molecules such as Reduced Glutathione (GSH), melatonin, and coenzyme Q10 (ubiquinone), aid in keeping free radicals in a homeostatic state.[93,94] Nevertheless, using supplementation through diet or medication is crucial in both the prevention and treatment of pathologies.[92] One study by Yang et al studied the effects of multifunctional antioxidant treatment, such as Tempol at 200 mg/kg/d to mice via subcutaneously implanted osmotic mini-pumps and found promising results in regards to neuroinflammation.[95] Tempol is a superoxide dismutase (SOD) mimetic, as well as a free-radical scavenger derived from peroxynitrite that is able to reduce hydroxyl radicals.[95] The authors found that there was a 2 fold decrease in titers in IL-1, IL-2, Interferon-Gamma (IFN-γ), and Tumor Necrosis Factor (TNF-α), as well as a decrease in the activation of Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells (NF-κB) in the optic nerve.[95] Similarly, it has been reported that antioxidant vitamins have a positive role in neurogenesis.[96] Vitamin A, which is involved in cell cycle regulation and cell proliferation has been associated with cognitive impairments in executive function and memory when a deficiency exists.[96] While vitamin C has a role in neurite outgrowth and cell maturation, therefore, it is not surprising that its supplementation has been reported to improve attention, language, and memory abilities.[96] Vitamin D has also been found to improve hippocampal neurogenesis and cognition in male wild-type and transgenic AD-like mice.[97] Through Y-maze tests, the authors were able to report improved working memory in comparison to control.[97] Similarly, vitamin E is involved in cell proliferation, and its supplementation aids in the preservation of attention, perceptual/motor speed, memory, and language.[96] Polyphenols and polyphenol-rich whole foods can have antioxidant and anti-inflammatory properties.[98] Foods such as blueberries, strawberries, and grape seed extract have been known to increase and promote neurogenesis.[98] Resveratrol, found in peanuts, tree nuts, grapes, cocoa, and wine have also been found to activate sirtuin 1 which can induce neurogenesis.[98] Furthermore, it has been proposed that antioxidants can even help reduce the severity of neurodegenerative diseases such as Huntington's disease, via the promotion of functional neurogenesis and neuroprotection.[99] Therefore, it is interesting to suggest that antioxidants and vitamin supplements can have a beneficial effect in PACS patients and it indirectly attacks the secondary effects that SARS-CoV-2 can have in the CNS as well as stimulate neurogenesis (Figure 3).

Neurogenic Stem Cell Therapy

One of the most captivating elements of the brain is its ability to have plasticity. The hippocampus has been known to be rich in plasticity as it is in charge of converting experiences into memory traces which will modulate behavior and ergo the ability to learn.[100] Moreover, this area goes hand in hand with neurogenesis, which can react to processes such as neuronal hyperexcitation or neuroinflammation.[100] This process involves neural stem cells (NSCs) which can be found in the adult brain in between the hilus and the granule cell layer of the dentate gyrus.[100] Nonetheless, processes such as aging, neurodegeneration, and (in the case of SARS-CoV-2) infection can be associated with a decrease in levels of neurogenesis.[100] It is interesting to suggest that if neuronal hyperexcitation is sustained, it could lead to an increase in neurogenesis; however, this would also imply a depletion of the NSC pool. This phenomenon is observed in epilepsy patients, who experience neural hyperexcitation and an accelerated depletion of NSCs.[100] Some authors have proposed that mesenchymal stem cells (MSCs) therapy could be a potential treatment for inflammatory or immunomodulatory conditions, as it may also activate endogenous regeneration.[101] One systematic review that analyzed stem cell therapy in COVID-19 patients found to be safe and that they decreased mortality and morbidity.[102] Moreover, they were found to suppress inflammation, ameliorate symptoms and improve organ function.[102] However, it is worth noting that some patients did present with fever after infusion with stem cells.[102] The authors reported that MSCs are able to reduce

systemic inflammation by reducing IL-6 in serum, inhibiting the activation of dendritic cells and B cells, T cells, and NK cells, decreasing Macrophage Type 1 (M1) and enhancing Macrophage Type 2 (M2) activation.[102] They are also able to inhibit mast cell degranulation and promote T regulatory and Th2 cells.[102] Bonsack et al reported that MSCs alleviate the neuroinflammation associated with brain injury.[103] The authors further stated that bone marrow-derived MSCs have had promising and regenerative properties in traumatic brain injury clinical trials.[103] The cells are able to decrease proinflammatory cytokine expression levels as is the case with IL-6, IL-1α, and IFN-γ.[103] Another study also reported a reduction in inflammatory cytokines, mortality, clinical symptom improvement time, and hospital time, with no significant adverse effects in MSC therapy.[104] Translating MSCs or other stem cell-derived products from bench to bedside could offer a therapeutic avenue for PACS patients with neurological manifestations. Stem cell infusions may reduce neuroinflammation, cytokine levels, and immune system dysregulation, which are key contributors to cognitive dysfunction, headaches, hyposmia/anosmia, hypogeusia/ageusia, and other severe complications of PACS. However, there are growing concerns about offering these therapies without sufficient evidence of their safety and efficacy. It is crucial that preclinical and clinical research, as well as the possibility of offering stem cell-based treatments, be closely scrutinized by regulatory bodies[105] (Figure 3).

Mitochondrial Therapy

Recently, there has been a growing interest in mitochondrial therapy, especially in the form of artificial mitochondrial transfer/transplant (AMT/T) or the use of mitochondria as a "Living Drug".[106] This concept has already passed from bench side to bedside as there have been studies where mitochondrial transplantation has been used in pediatric patients who needed extracorporeal membrane oxygenation (ECMO) related to ischemia-reperfusion injury.[107] The authors harvested mitochondria from non-ischemic skeletal muscle tissue and later performed transplantation into the cardiac tissue and found promising results.[107] In the nervous system, transplanted exogenous mitochondria can pass through the endolysosomal system and later fuse with damaged mitochondrial networks and can therefore reduce inflammation and excessive oxidative stress and also increase ATP content.[108] In the CNS they can become incorporated into neurons, astrocytes, and microglial cells.[109,110] It is important to note that cells may not have the desired effect due to excessive mitochondrial concentration as this can also induce unwarranted stress.[111] Therefore it is important that future researchers and healthcare professionals establish adequate mitochondrial doses and concentration levels so that effective therapy can be used. Nevertheless, several studies have been done regarding neurological pathologies. Nitzan et al transferred mitochondria into Alzheimer's disease mice models and found an increase in cognitive performance when compared to the control.[112] Ma et al was able to improve oxidative stress, neuronal apoptosis, and cognitive performance in mice with diabetes-associated cognitive impairment after mitochondrial transplantation.[113] Chang et al transplanted mitochondria and found suppression of inflammatory cytokines in Parkinson's disease rats.[114] We, therefore, suggest that along with the aforementioned elements, mitochondrial therapy could serve as a potential therapeutic agent that could ameliorate the neurological manifestations of PACS patients. However, much exploration is still warranted in order to elaborate a fully comprehensive treatment plan for PACS patients (Figure 3).

Discussion and Conclusion

SARS-COV-2 is not just a virus that causes acute symptoms but also leads to long-lasting-sequelae known as PACS.[1] There can be a variety of symptoms such as fatigue, muscle pain, fever, cough, shortness of breath, chest pain, headache, and cognitive impairment.[13] Recently, there has been a growing interest specifically in neurological manifestations of PACS. Neurological complaints that patients can have include cognitive disorders/fatigue, headaches, hyposmia/hypogeusia, and myalgia/ muscle weakness.[11,37] However, more serious complications can include stroke, seizure, ataxia, loss of gray matter, and neurodegenerative diseases.[10,14,15] Regardless, of many patients suffering from these manifestations there is still much research to do on this topic, especially in formulating a specific, personalized, and tailored treatment for these patients.

The neurological manifestations that can be present in PACS patients can have similar etiologies. Cognitive dysfunction, which includes difficulty in executive function, processing speedy, category fluency, memory encoding, and recall.[11,29] One proposed hypothesis for these changes includes a higher level of neuroinflammatory cytokines and

chemokines.[31,32] This can lead to the activation of microglia and induce changes in white matter, subsequently causing loss of oligodendrocytes, oligodendrocyte precursor cells, and myelin.[31,32] Other causes for cognitive dysfunction and fatigue include antibodies against β2 adrenoceptors, α1-adrenoceptors, Angiotensin II Type 1 Receptor (AT1R), Mas receptor (MasR), muscarinic type 2 receptors, and nociceptin-like opioid receptors.[14] Furthermore, it has also been suggested that there can be alterations to cerebral metabolism as the virus can also cause mitochondrial dysfunction.[34,35] Inflammatory cytokine and cytokine storms have also been associated with headaches, which can be due to systemic or invasive infections.[38] The virus can adhere itself to ACE2 receptors in neurons and glia of multiple cerebral structures. Moreover, calcitonin gene-related peptide has also been associated with headaches and an inflammatory response in PACS patients. Meanwhile, the loss of smell or taste can be associated with inflammation.[44] Similarly, muscle weakness and neuropathy have been suggested to be due to prolonged intense inflammation, as markers can be present without the virus.[47] Therefore, a pattern can be observed as inflammation has been suggested as the etiological agent behind all the symptoms of this syndrome. This is further supported as the virus stimulates the secretion and release of TNF-α, cytokines, and ROS.[54] Thus, it is no surprise that new potential therapies of research will focus on this area of study and mitigate the inflammatory signals and immune system deregulation.

Despite the aforementioned treatment modalities, there are still limited therapies to manage these patients. PACS treatment has to be as equally diverse as of the systemic affectations, as well as being personalized. These treatments can be separated into symptomatic, supportive and rehabilitative treatment. Symptomatic treatment usually centers on reducing the severity or frequency of the most prevailing symptom. Patients that suffer from fatigue due to PACS could benefit from an array of treatment options such as vitamin C combined with L-Arginine, and apheresis.[75–78] However, non pharmaceutical options such as physical rehabilitation have also been shown to improve symptoms of PACS patients.[79] This is similar to supportive treatment in regards to neurological affectations of PACS, where the mainstay method of treating patients is through Cognitive Behavioral Therapy (CBT).[80] However, other authors mention that by reducing free radicals and oxidative stress, generated by compounds such as anthranilic acid, cognitive function could improve in PACS patients.[82] It is also important to note that new research has been carried out on pharmaceuticals such lithium and fluoxetine due to their metabolic role in the mitochondria and their antioxidant effect[84,85].[86] Similarly, other researchers tried to explore the role of drugs like Dextroamphetamine-amphetamine, Naltrexone, Montelukast, Deupirfenidone, Nicotinamide riboside, leronlimab, melatonin, adaptogens, hyperbaric oxygen therapy, and probiotic therapy.[84,85] However, much still remains to be elucidated and more research needs to be carried out.

Due to these key elements for treatment, we propose a triad of antioxidant and vitamin supplements, stem cell therapy, and mitochondrial therapy. Antioxidants can help combat excessive free radicals and pro-inflammatory states. The use of superoxide dismutase mimetics and free-radical scavengers has been shown to reduce levels of IL-1, IL-2, IFN-γ, and TNF-α, as well as decrease the activation of NF-κB in the optic nerve.[95] Supplementation of vitamin A, B, D, and E have also been associated with maintaining cognitive function.[96,97] Similarly, polyphenols and polyphenol-rich whole foods can stimulate and promote neurogenesis.[98] Stem cell therapy has been used in COVID-19 patients and found to decrease morbidity and mortality, while suppressing and improving inflammation.[102] This is done by reducing IL-6, inhibiting B cell, T cell, and Natural Killer (NK) cell activation, as well as decreasing M1 and enhancing M2 activation.[102] Other authors have reported a decrease in neuroinflammation associated with brain injury.[102] Similarly, there has also been a growing interest in mitochondrial therapy as new evidence shows that there is a mitochondrial disruption in PACS patients.[115] Mitochondrial therapy has been known to reduce inflammation and excessive oxygen stress while improving ATP concentration.[108] Additionally, there have been several studies that use mitochondrial therapy to improve cognitive impairment and reduce inflammation in animal models of neurodegeneration.[112–114]

Much time has passed since the WHO declared COVID-19 an international pandemic, leading to lockdown measures across numerous countries and continents. With vaccines now approved and widely distributed, the rate of new infections has decreased. However, new variants continue to emerge, and many individuals are still being infected. We urge researchers and clinicians to remain vigilant in the fight against COVID-19. The information provided in this article not only aids in the screening and treatment of symptoms but also highlights new potential therapies, such as antioxidant and vitamin supplements, stem cell therapy, and mitochondrial therapy, which have shown promise in addressing PACS. Our goal is to help bridge the gap from bench to bedside in addressing this disease and its challenging sequelae by

emphasizing where future research is headed. Additionally, we aim to underscore the integral role of mitochondrial dysfunction in PACS and how targeting mitochondria in therapy could be a highly promising area of research.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGPT to check grammar and clarity of the text when needed. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Andrés Caicedo is the scientific founder and advisor of Dragon Biomed, an entrepreneurial initiative at the Universidad San Francisco de Quito (USFQ). He also serves as a scientific advisor in the Research and Development department of Luvigix. In these roles, he provides scientific guidance and expertise but does not participate in the decision-making processes or operational activities of either company.

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