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Viewpoint

Underlying Causes and Treatment Modalities for Neurological Deficits in COVID-19 and Long-COVID

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ABSTRACT: With reports of diverse neurological deficits in the acute phase of COVID-19, there is a surge in neurological findings in Long-COVID—a protracted phase of SARS-CoV-2 infection. Very little is known regarding the pathogenic mechanisms of Neuro-COVID in the above two settings in the current pandemic. Herein, we hint toward the possible molecular mechanism that can contribute to the signs and symptoms of patients with neurological deficits and possible treatment and prevention modalities in the acute and chronic phases of COVID-19.

KEYWORDS: *COVID-19, Long-COVID, Treatment Long-COVID, Post-COVID-19 sequelae, Neurological Deficits, Neuro-COVID*

A. INTRODUCTION

Back during the early days of the pandemic, patients admitted to hospitals with COVID-19 exhibited a syndromic picture of neurological deficits caused by SARS-CoV-2. Later, a large group of patients with acute COVID-19 started emerging who continued to experience the effects of neurological damage caused by SARS-CoV-2 to the brain and spinal cord for periods ranging from months to over a year after the acute phase.[1,2] Astonishingly, newer symptoms have been reported to appear, which with or without the symptoms suffered in the acute phase of COVID-19 have become the basis of the diagnosis of Long-COVID.[2] Very little is known about the molecular mechanism(s) that could explain the neurological signs and symptoms of Long-COVID. For the acute phase of COVID-19, the contributing mechanisms have been coined, which include a combination of direct neuronal injury coupled with the damaging effects of the neuroinflammatory cytokines.[1] The exploration into the pathological basis of the neurological signs and symptoms of Long-COVID remains a pivotal area of current research, as delays in knowing and targeting them could result in permanent disabilities in patients suffering from Long-COVID.[1] Because the brain and spinal cord are rarely biopsied, and such an attempt can itself damage the neurological tissues, delays are expected to unravel the exact molecular and biochemical basis of the ongoing cellular injury causing the neurological signs and symptoms exhibited in Long-COVID. It is important to remark here that, though microscopic findings of the autopsied brains in Long-COVID are expected to clue toward the end lesions that caused fatality, like zones of gliosis and microinfarcts, they can contribute very little toward the mechanisms that had led to these changes. Likewise, imaging of the central nervous system (CNS) is important but could reveal only gross morphological changes and not mechanisms at the molecular level that contribute to worsening neurological features seen in Long-COVID. The factors contributing to the chronic phase neurological features in Long-COVID appear to be most likely cascades that had their origins in the acute phase and had continued into chronicity due to inadequate removal of SARS-CoV-2 and/or its proteins that continue neuronal injury in Long-COVID (Figure 1A,B). Ongoing inflammation and slowly evolving neurodegenerative changes due to SARS-CoV-2-mediated (Figure 1B3) direct neuronal and glial damage appear to be the underlying cause[1] as it has been seen that neurological signs and symptoms (Figure 1A1) in Long-COVID continue to worsen with time (Figure 1A2) with findings of hypometabolism in neurons.[3] No treatment is available at present for neurological damage reported in Long-COVID. A delay in recognition of this neurological damage is considered by many to be because of the myth it was a psychosomatic disorder without any organic basis for the syndromic presentation.

B. HINTS FROM PATIENTS WITH ACUTE COVID-19

Changes like the deposition of amyloid and tau protein within the neurons and features consistent with demyelination are significant clues in patients who have died of COVID-19 (Figure 1B3). It has been postulated that the viral components, like the E protein, of SARS-CoV-2 in the brain can induce the activation of microglial TLR2, thereby increasing the susceptibility of Aβ and α-syn deposition in patients. Preliminary postmortem analysis in studies has revealed that the accumulation of phosphorylated α-syn, one of the

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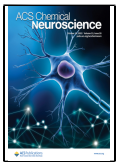

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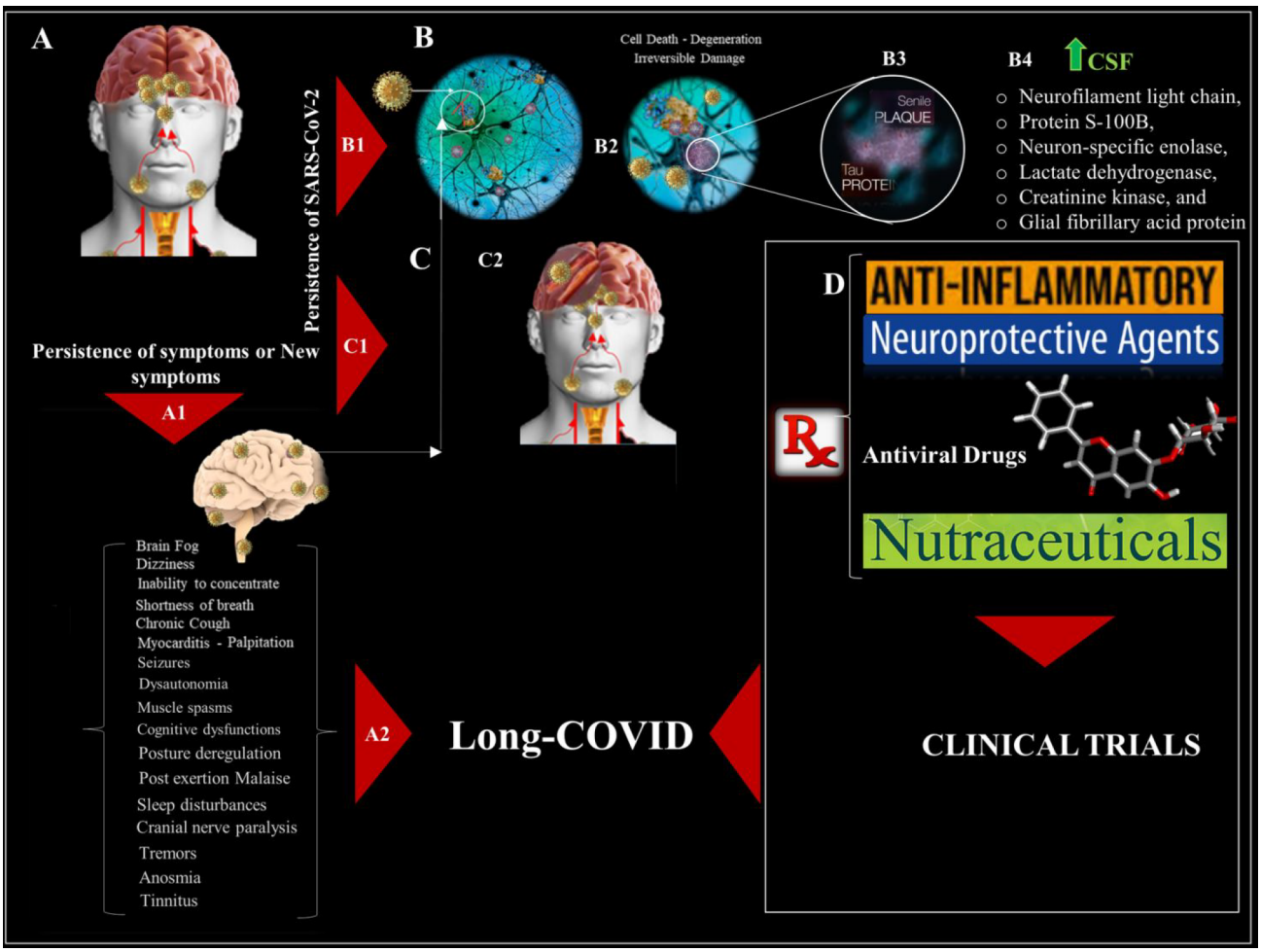

Figure 1. Acute COVID-19 caused by SARS-CoV-2 (A) has been reported to continue symptoms (A1) into Long-COVID (A2). Neurons (B−B1) in COVID-19 (B-circle) have been reported to accumulate beta-amyloid and tau proteins (B2−B3) like Alzheimer's disease. Elevated biomarkers (B4) should be investigated in CSF and serum of patients with Long-COVID to establish ongoing slow neuronal damage and neurodegeneration. Circulatory causes (C) like chronic brain hypoxia after COVID resulting from thrombosis in microcirculation can also cause neuronal atrophy (C1−C2). With neuroinflammation and direct neuronal injury accelerating neurodegeneration, diverse treatment modalities (D) should be tested in clinical trials to prevent neurological disabilities in Long-COVID.

pathogenic forms of α-syn, was increased in the brains of SARS-CoV-2-infected patients.[4] In addition, the levels of total tau, phosphorylated tau, and glial fibrillary acidic protein, all biomarkers for AD, were elevated in SARS-CoV-2-infected patients with severe symptoms, suggesting a potential correlation between AD and SARS-CoV-2 infection severity. Dysregulation of other proteins like cereblon, autophagy regulating proteins and their role in the deposition of Aβ, and deposition of Aβ and α-syn in Long-COVID need to be investigated to target them to slow down the neurodegeneration in these patients.

C. CIRCULATORY BASIS OF NEUROLOGICAL DAMAGE IN COVID-19 AND LONG-COVID

Factors that can cause generalized hypoxia and ones that can cause hypoxia at the cellular level leading to progressive neuronal injury (Figure 1C−C1) in the brain and spinal cord appear to be at play in COVID-19 and Long-COVID patients.[1] Progressive pulmonary fibrosis coupled with thrombotic microangiopathy is a known feature in Long-COVID patients. The former causes generalized hypoxia resulting from an inadequate gaseous exchange and later on nonocclusive microthrombi causing ischemic hypoxic injury. This can best explain the decline in cognitive functions and focal progressive neurological deficits as has been reported in Long-COVID patients. An excessive prothrombotic tendency and defective thrombolysis are now been being reported in Long-COVID.

D. CSF AND SERUM BIOMARKERS AS CLUES TOWARD NEURONAL DAMAGE IN COVID-19 AND LONG-COVID

The evidence of ongoing neuronal injury hinted by the chemical and structural nature of the leaking biomarkers in CSF and serum can provide valuable clues toward the nature of the neuronal and glial injury and target the underlying pathways. Neurofilament light chain, protein S-100B, neuron-specific enolase, lactate dehydrogenase, creatinine kinase, and glial fibrillary acid protein, which is of astrocytic origin, are a few examples that can hint toward an ongoing cellular injury in the neuronal milieu. Research on the discovery of newer biomarkers is needed that can provide more specific information on the nature of the injury to the neurons and glia in the CNS. Inadequate drainage of the CSF in Long-COVID with disturbances in sleeping hours can also lead to

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the accumulation of excessive metabolites in the CSF that can serve as biomarkers in Long-COVID.

E. ELECTROPHYSIOLOGICAL STUDIES IN COVID-19 AND LONG-COVID

Electroencephalography (EEG), electrocorticography (ECoG), electromyography, and electro-olfactography if possible can provide information on their discharge patterns in Neuro-COVID affected patients. As reversible cell injury causes neuronal and muscle cell membrane permeability changes to ions, abnormal discharge patterns compared to controls (healthy subjects) can hint at an ongoing damaging influence in effect in COVID-19 and Long-COVID patients. Neuropsychological test findings on ^{18}F-FDG PET scans should be performed in a larger sample size, and longitudinal studies in the near future are expected to provide clues toward the ongoing neuronal and glial damage in Long-COVID, as it has been shown that Long-COVID patients exhibited brain hypometabolism in the right parahippocampal gyrus and thalamus[3]

F. ROLE OF THE BREACHED BLOOD−BRAIN BARRIER IN COVID-19 AND LONG-COVID

Damage caused by inflammatory cytokines or resulting from SARS-CoV-2,[1] the Spike protein in particular in inducing endothelial injury, can breach the integrity of the blood−brain barrier (BBB) in the acute phase of COVID-19. A continued infection and reinfection cycle or persistence of the virus causing episodes of viremia can be a source of entry of serum factors across the BBB to the CNS, which are normally not allowed to incite glial and neuronal damage. Also, the leak of growth factors that maintain the healthy state of the nervous system into the circulation across a breached BBB can evoke neuronal damage by impairing the ability of the glia, neurons, and their sheath to repair, leading to neuronal damage in acute and chronic phases of Long-COVID.

G. TREATMENT PROPOSALS FOR NEUROLOGICAL DAMAGE IN COVID-19 AND LONG-COVID

Based on the possible underlying causes that incite neurological damage in COVID-19 and conceivably Long-COVID, treatment plans can be crafted and tested in human clinical trials to make them available as early as possible. The use of existing anti-neuroinflammatory drugs and chemical compounds that have been used in clinical practice can be repurposed for their use in COVID-19 in patients suspected of having neuronal injury caused by ongoing inflammatory processes within the CNS. The viral persistence due to inadequate clearance by the immune system, the ability of SARS-CoV-2 to conceal itself in body spaces to evade the immune response, and reinfections with SARS-CoV-2 are emerging as the possible central mechanisms behind Long-COVID. The latter can be best managed by antiviral agents that can either exert virucidal effects or paralyze the ability of SARS-CoV-2 to infect the host cells. It is worth mentioning that some natural compounds, herbs, and nutraceuticals are known for their anti-inflammatory and virucidal effects and therefore can be candidate drugs for slowing down the progression of neuronal damage in COVID-19 and Long-COVID. Of the many examples of these drugs, agents like hesperidin, cinnamon, baicalin, curcumin, rutin, glycyrrhizin, selenium, epigallocatechin gallate, and quercetin have been reported in published studies to be tested in COVID-19 and have been recently considered for treatment in Long-COVID. These agents exert the aforementioned anti-inflammatory, antioxidant, cytoprotective, and antiviral effects with some of them having the added benefits of antithrombotic actions that can limit the thromboembolic complications in both acute and Long-COVID. To avoid the adverse effects of these drugs when given individually, the rationale of drug synergism can be implemented, where a single preparation of a mixed formulation of these compounds in reduced doses can be tested in human clinical trials in Long-COVID patients to determine its efficacy. Preclinical studies on immunomodulatory imide drugs (IMiDs), particularly the ones that are adamantly derivatives shown to inhibit TNF-α in animal models of diseases such as ALS, Parkinson's disease (PD), and Alzheimer's disease (AD), have shown promise, which indicates their potential for the advancement from the bench to the bedside of patients of neurological diseases in need of treatment, after clinical trials.[5] In Long-COVID, selective IMiDs that cross the BBB and achieve an effective concentration in CNS, with fewer or tolerable side effects, can be tested for their neuroprotection, antioxidative action, and inhibition of cognitive decline.

Drug synergism with agents that exert direct virucidal effects like nirmatrelvir, which inhibits a SARS-CoV-2 protein to stop the virus from replicating, and ritonavir, which slows down nirmatrelvir's breakdown to help it remain in the body for a longer period at higher concentrations, is now proposed for treatment in Long-COVID to address the removal of viral persistence mentioned above. Drugs with avid binding to the receptor-binding motif (RBM) of the Spike protein in SARS-CoV-2 are also promising agents, as by preventing the entry of the virus into host cells,[6] these drugs can minimize the syndromic manifestations of Long-COVID in general and, if they reach the CNS, the neurological damage in particular.[1] Treatment or cures by stem cell replacement therapy are limited, as transplantation of embryonic stem cells into the core areas of the CNS would prove challenging. Clinical trials would show the advantage of stem cell therapy if done in the future on patients suffering from Neuro-COVID with focal neuronal loss.

H. DISCUSSION

The neuron is among one of the few cells in the human body that is very sensitive to injurious stimuli and has a limited ability to regenerate by self-renewal. A consensus has developed on the fact that neurological deficits do occur in COVID-19 and that it could be due to the effect of either direct neurotrophic effects of the virus, a consequence of the accompanying inflammation, or both of them.[1] The evidence that a very substantial number of the population worldwide with lingering symptoms of the initial infection of COVID-19 do continue to suffer the symptoms for months[2] to years after the year 2020 is alarming. Long-COVID patients experience bothering symptoms mostly related to neurological issues. A list of over 20 complaints in Long-COVID can be linked to the nervous system due to possible ongoing injurious processes involving neurons and glia. Factors that could be contributing to this frightening syndromic picture are detailed above, but questions remain: (a) Can the neurological damage be reversed? (b) Can it be slowed down? (c) Would stem cell therapy be any good in neurological deficits for the possible recovery of the lost neurons and cognitive function? More

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troubling is the finding of neurodegenerative changes in COVID-19 and therefore expectedly in Long-COVID, which are now reported in an age group that should not have the type of neuronal degeneration that is seen in Alzheimer's[4] and other related neurodegenerative conditions. This, if not addressed and treated in time, is expected to result in a surge of large numbers of humans with permanent cognitive disabilities—the count of which is feared to cross into millions. Is it time to prescribe neuroprotective drugs at this point? Are drugs that target the neuroinflammation of any use in Long-COVID patients? Is the disease feared to progress to conditions like myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)? These are related questions that need quick and effective answers if we want to expeditiously avoid a surge of disabled individuals. The problem can be addressed by making specialized clinics operational where neurocognitive assessments of the Long-COVID patients are done with the recognition of the fact that this is a disease entity with an organic cause and not a psychological disorder. The more we delay in planning effective measures to combat Long-COVID the more chances there are that neurological damage could become irreversible. Research into the dilution or removal of the underlying causes is needed and needed urgently, as are treatment approaches (Figure 1D) that can slow down neuroinflammation and combat the residual virus in the body in Long-COVID.

I. CONCLUSION AND FUTURE DIRECTIONS

As the two known factors, (a) neuroinflammation and (b) direct neuronal damage by SARS-CoV-2, that initiate Neuro-COVID in the acute phase of the infection are known, there should be attempts to target them without any delay. Drugs that are known and have proven to be efficacious antineuroinflammatory agents and antiviral to SARS-CoV-2 mentioned above in our discussion should immediately undergo human clinical trials for their suitability for Neuro-COVID. Selective neuroprotective IMiDs, known herbs, and plant products with previously proven neuroprotective and antineuroinflammatory effects, like baicalin, quercetin, diosmin−hesperidin, curcumin, and piperine, should be given a chance in human clinical trials. If efficacious and safe as per their clinical trials, an emergency use authorization (EUA) for their use in Long-COVID and COVID-19 may provide increased chances to slow or stop progression into neurological deficits. ME/CFS, like Long-COVID, is a complex disease with a spectrum of symptoms including neurological ones like impaired memory, unexplained fatigue, postexertional malaise, and sleep disturbance. Understanding Long-COVID pathogenesis and treatment outcome can pave the way toward the understanding of and possibly treatment clues for ME/CFS as well.

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Author Contributions

A.M.B. drafted the manuscript with etiological factors in effect in Neuro-COVID. N.H.G. provided information on immunomodulatory imide drugs (IMiDs) related to anti-inflammatory effects in neurons and advised on references of the manuscript. J.G. and P.S. contributed to the knowledge, resources, and chemistry of the natural product and nutraceutical agents mentioned in the manuscript. V.V., T.A., and M.F. contributed through the wide range of literature published on the neurological deficits reported in Neuro-COVID across the globe and the current treatment modalities used to diagnose Neuro-COVID. M.F. reviewed the manuscript version that was submitted to the journal. All of the authors read the final draft before submission to the journal.

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The authors declare the following competing financial interest(s): N.H.G. and his group work on neuroprotective immunomodulatory IMiDs while J.G. and P.S. are associated with the research and development of nutraceuticals mentioned in this manuscript.

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