ABSTRACT: Entry of SARS-CoV-2 into the central nervous system (CNS) activates microglia, triggering chronic neuroinflammation and possibly neurodegeneration. The complex transcriptome of SARS-CoV-2 shares molecular similarities with diverse human CNS protein epitopes, leading to a cytokine storm and various autoantibodies, potentially culminating in an autoimmune state. A COVID-19 initiated CNS autoimmune cascade may occur via multiple pathways including molecular mimicry, bystander activation, epitope spreading, production of autoantibodies, and immortalization of effector B-cells.

KEYWORDS: COVID-19, SARS-CoV-2, cytokine storm, autoimmunity, neuroinflammation, blood–brain barrier, neurodegenerative disease, Alzheimer’s disease, dementia

INTRODUCTION

Since its initial outbreak in December 2019, coronavirus disease 2019 (COVID-19) has posed a significant threat to humankind and an enormous burden upon healthcare systems. To date, nearly 180 million cases have been diagnosed globally, with 3.8 million deaths (https://coronavirus.jhu.edu/map.html). In addition to acute respiratory symptoms, COVID-19 also presents with neurological manifestations resulting from either direct or indirect brain damage. The SARS-CoV-2 virus enters the central nervous system (CNS) via multiple routes: hematological spread with associated blood–brain barrier (BBB) penetration; trans-synaptic viral spreading; entry through circumventricular structures and the blood–cerebrospinal fluid. Upon CNS entry, the virus binds to multiple cell types (e.g., neurons, astrocytes, oligodendrocytes, and microglia across diverse brain regions) by various interactions but principally via the angiotensin-converting enzyme-2 (ACE2) protein, a primary receptor for SARS-CoV-2. This CNS entry subsequently activates microglial and inflammatory mediators, which in turn activate T-lymphocytes. As a consequence, immunopathological mechanisms such as autoimmunity, direct immune cytotoxicity, and indirect bystander damage are responsible for the neurological manifestations of COVID-19. The severity of this COVID-19 neurological damage correlates with the innate and adaptive host immune response to the virus and upon the existence of previous or concomitant CNS disease.

HOW COVID-19 TRIGGERS AUTOIMMUNE BRAIN DISORDERS

Autoimmune diseases develop as a result of an aberrant immune response when recognizing self- versus non-self-antigens, thereby leading to a misguided attack on healthy host tissue. The biological mechanisms that lead to the hyper-stimulated immune response in autoimmunity are the same as the mechanisms occurring during the body’s overactive immune response following COVID-19 infection and occur via multidirectional mechanistic pathways as discussed herein (Figure 1).

a. Molecular Mimicry. Molecular mimicry involves structural similarity of a pathogen’s antigens to self-antigens, which in turn activates T- and B-lymphocytes and leads to a cross-reactive response involving conformationally similar human proteins, thereby causing autoimmune disease. Molecular mimetics between SARS-CoV-2 and several neuronal autoantigens in brain and CSF from individuals afflicted with COVID-19 have been identified (Table 1).1

b. Bystander Activation. As an acute first line of defense, the innate immune system mounts a forceful response to SARS-CoV-2 infection resulting in elevated levels of
proinflammatory cytokines (e.g., interleukin (IL)-1β, IL-6, IL-8, TNF-α, interferon (IFN)γ) and chemokines (e.g., granulocyte colony stimulating factor (G-CSF), interferon γ-induced protein 10 (IP-10), monocyte chemoattractant protein 1 (MCP-1), and macrophage inflammatory protein 1α (MIP-1α)). This nonspecific and over-reactive antiviral immune response produces a “cytokine storm” characterized by an exaggerated proinflammatory environment which further initiates self-tissue (blood–brain barrier, myelin sheath) damage along with production of self-antigens that mimic COVID-19 antigens. These self-antigens are ultimately taken up by antigen presenting cells (APCs), simulating surrounding autoreactive T-cells and further triggering the ongoing autoimmune response. Thus, the CNS tropism of SARS-COV-2 leads to maladaptive innate immunity and hyper-inflammation with stimulated microglia and astrocytes contributing to neurodegenerative processes, including demye-
lation, BBB disintegration, and aberrant activation of CNS innate immunity signaling pathways.

c. Epitope Spreading. Upon continuous CNS self-tissue damage emerging from SARS-CoV-2 inflicted autoimmunity and neuroinflammation, additional self-antigens are produced that further activate autoreactive T-cells. Consequently, the viral infection spreads to stimulate T-cells with additional self-epitopes. SARS-CoV-2 initiated autoimmunity therefore may result in chronic and progressive CNS degenerative disease pathology.

d. Self-Attacking Autoantibodies and Immortalization of Effector B Cells. Along with immune-targeting autoantibodies and antiphospholipid antibodies, people with COVID-19 also sometimes exhibit high prevalence of other CNS-tissue associated autoantibodies (e.g., neuronal injury marker NINF1, metabotropic glutamate receptor GRM5, orexin receptor HCRT2R enriched in the hypothalamus). Moreover, immunological memory enabled by effector B-cells against self-antigens fosters ongoing antibody production against diverse CNS tissue targets in the BBB and myelin sheath. These diverse and varied self-targeting CNS tissue autoantibodies result in targeted, longer-term damage and may result in neurodegenerative disease severity in post-COVID-19 patients in coming decades. The SARS-CoV-2 virus therefore has the capacity to damage the human brain via complex indirect mechanisms, resulting in autoantibodies, predominantly against brain-based antigens as has been clinically demonstrated in cerebrospinal fluid samples from patients with COVID-19 neurological complications.

■ AUTOIMMUNE NEURODEGENERATIVE DISORDERS AND COVID-19

The clinical manifestations of autoimmune neurological disorders such as multiple sclerosis (MS) or Guillain–Barre syndrome (GBS) have been reported in COVID-19 case studies. For example, following 2–3 weeks of SARS-CoV-2 infection a 29-year-old female developed multiple sclerosis with right optic neuritis; MS-like demyelination may occur in COVID-19 patients due to autoimmune mechanisms resulting from T-lymphocyte activation secondary to M1 microglia phenotype activation with associated inflammatory mediator release. As presented in another case report, myelin oligodendrocyte glycprotein antibody-positive neuromyelitis optica was observed in a 26-year-old male who presented with bilateral optic neuritis and extensive longitudinal transverse myelitis, occurring several days after COVID-19 symptom onset. Upon the basis of these MS-based observations coupled with evolving insights pertaining to the pathogenesis of proteopathic dementia, we further speculate that SARS-CoV-2 infection may also play a role as a long-term risk factor for long-term protein-misfolding neurodegenerative diseases such as Alzheimer’s disease (AD) and Parkinson’s disease; ACE2-mediated accelerated production of neurotoxic proinflammatory cytokines with subsequent pathological innate and adaptive immune activation leads to CNS cellular organelle (mitochondria, lysosomes) impairment (as has been observed in so-called COVID-19 long-haulers) and may be the start of a neurodegenerative cascade.

■ CONCLUSIONS AND FUTURE DIRECTIONS

COVID-19 is a devastating multiorgan disease with global prevalence; we are still in the early days of this disease, but regretfully its legacy may be long-lasting, specifically as a risk factor for AD. The possibility that COVID-19 might emulate (after a latent phase) in AD is suggested by diverse accumulating data, including the neurotropic properties of SARS-CoV-2 and the neurological clinical features of COVID-19. Innate-immune activation, such as that instigated by SARS-CoV-2, is an early event in AD pathogenesis, occurring possibly 20–30 years prior to the first symptoms. This activation is triggered by pathogen-associated molecular patterns (PAMPs) which induce cytotoxic proinflammatory cytokine release. Long-past infections have thus been proposed as triggers of AD and include human herpes viruses and most recently Porphyromonas gingivalis. We are proposing that SARS-CoV-2 is a trigger similar to Porphyromonas gingivalis. In response to such PAMPs the subsequent sustained released of proinflammatory cytokines and activated microglia heralds a chronic autoimmune neurotoxic state creating the substrate for AD’s persistent preclinical progressive neuronal death over subsequent decades. Long-term cognition assessment and overall neurological competence are recommended in acute COVID-19 patients, specifically for patients having any history of autoimmune disorders.

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Notes

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