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COVID-19 as a Trigger of Brain Autoimmunity

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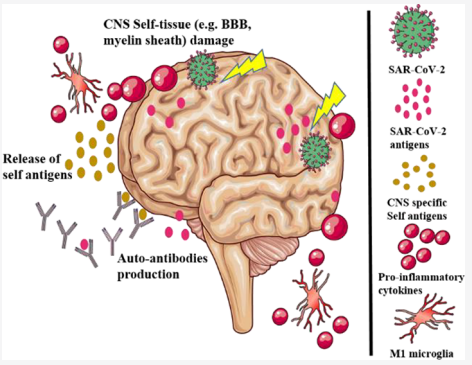
ABSTRACT: Entry of SARS-CoV-2 into the central nervous system (CNS) activates microglia, triggering chronic neuroinflammation and possibly neurodegeneration. The complex transcriptome of SARS-CoV-2 shares molecular similarities with diverse human CNS protein epitopes, leading to a cytokine storm and 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 mimicries 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

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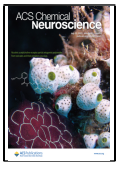

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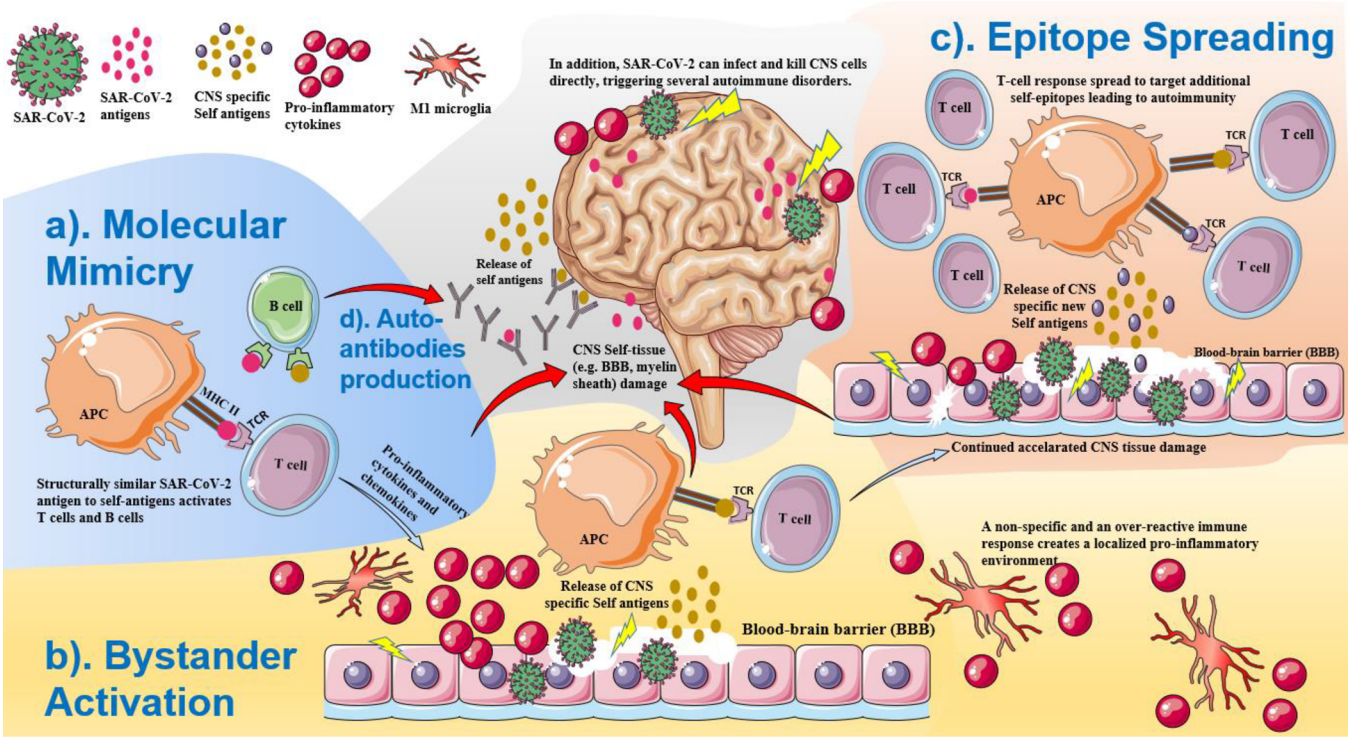

Figure 1. Mechanisms of SARS-CoV-2 induced autoimmunity. (a) Molecular mimicry. SARS-CoV-2 carries epitopes structurally similar to human CNS protein epitopes. Antigen presenting cells (APCs) present SARS-CoV-2 epitopes to activate T-cells, which in turn bind to self-antigens having similar epitopes and induce self-tissue damage. (b) Bystander activation. A nonspecific and an overactive immune response due to activation of M1 microglia and resulting cytokine storm create a localized proinflammatory environment. Antigens released from self-tissue (e.g., BBB, myelin sheath) are taken up and presented by APCs which leads to further tissue damage. (c) Epitope spreading. Continuous SARS-CoV-2 infection leads to persistent self-tissue damage and consequently to release of CNS specific self-antigens. New self-antigens are also presented by APCs to further activate T-cells. T-cell response then spreads to target additional self-epitopes leading to autoimmunity. (d) Autoantibodies production. Immunological memory of effector B cells against self-antigens continues to produce antibodies against CNS tissues (e.g., BBB, myelin sheath), which ultimately leads to manifestation of an autoimmune neurological disorder.

Table 1. Shared Peptide (≥6 Amino Acids) Sequences between SARS-CoV-2 Spike Glycoprotein and Human Proteins Present in Human CNS[a]

SARS-CoV-2 epitope	human protein name	human protein epitope	human protein intracellular localization
VYSTGSN	Neural cell adhesion molecule L1-like protein	R**VYSTGSN**VFQ - B lymphocytes	Plasma membrane, apical part of cell, dendrite, integral component of membrane and extracellular exosome.
TGRLQSL	Neuron navigator 3	LI**TGRLQSL** - T lymphocytes	Nucleus, nuclear outer membrane. Highly expressed in brain.
DEVRQIA	Histone-lysine *N*-methyltransferase 2C	VIRG**DEVRQIA**PG - T lymphocytes	In brain, highest expression is in hippocampus, caudate nucleus, and substantia nigra.
NSASFS	Neuron navigator 1	LY**NSASFS**TF - T lymphocytes	Cytoskeleton, microtubule, microtubule cytoskeleton, other locations, axon initial segment, cytoplasm; broadly expressed at low levels in forebrain.
LVLLPL	Corticotropin-releasing factor receptor 2	F**LVLLPL**VSSQCVNL - B lymphocytes	Plasma membrane, integral component of plasma membrane, axon terminus, dendrite; expressed in frontal cortex.
FLVLLP	Calcitonin gene-related peptide type 1 receptor	**FLVLLP**LVSSQCVNL - B lymphocytes	Endoplasmic reticulum, endosome, lysosome, plasma membrane, adrenomedullin receptor complex, calcitonin gene-related peptide (CGRP) receptor complex, integral component of plasma membrane, cytoplasm

[a]Data on proteins and their localization in CNS are from Uniprot (https://www.uniprot.org/).

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, axonal membrane) 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-

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lination, 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 NINJ1, 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.[2]

AUTOIMMUNE NEURODEGENERATIVE DISORDERS AND COVID-19

The clinical manifestations of autoimmune neurological disorders such as multiple sclerosis (MS) or Guillain–Barré syndrome (GBS) have been reported in COVID-19 case studies.[3] For example, following 2–3 weeks of SARS-CoV-2 infection a 29-year-old female developed multiple sclerosis with right optic neuritis;[4] 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 glycoprotein 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.[5] 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 regrettably its legacy may be long-lasting, specifically as a risk factor for AD. The possibility that COVID-19 might culminate (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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Author Contributions

The manuscript was conceptualized, drafted, revised, and edited by M.G. and D.F.W.

Notes

The authors declare no competing financial interest.

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