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SARS-CoV-2 infection's link to Behavior: A Review of Coronaviruses and the Potential for SARS-CoV-2 to Damage the Brain's Structure and Function

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A Capstone in Neurobehavioral Sciences by Grace Anne Wilgucki

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ABSTRACT

Human Coronaviruses were discovered in the 1960s and were found to be a cause of the common cold, inducing mild symptoms on those infected (Santacroce et al., 2020). However, due to adaptation and co-evolution, more dangerous variations of Coronaviruses emerged in the early 2000s, causing severe infection of the respiratory tract (Ye et al., 2020). Notably, the outbreaks of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) were devastating, as these HCoVs could inflict respiratory disease that can be fatal (Wong et al., 2016). Most recently, the emergence of a new strain of Human Coronavirus has taken the world by storm. SARS-CoV-2 was discovered in December of 2019 in Wuhan, China, and is responsible for the current global outbreak of the Coronavirus Disease 2019 or COVID-19 (Santacroce et al., 2020). The World Health Organization has declared SARS-CoV-2 as a worldwide public health threat due to its high rate of transmissibility, pathogenicity, morbidity, and mortality (Ye et al.,2020). As of May 20th, 2021, there has been a total of 35,855,010 confirmed cases and 584,975 deaths in the United States alone (Centers for Disease Control and Prevention (CDC), 2021).

The most notable and commonly known symptoms experienced by COVID-19 patients all pertain to respiratory complications, including cough, shortness of breath or difficulty breathing, congestion, and fever (Mao and Jin, 2020). However, recently, there has been growing evidence that SARS-CoV-2 not only ambushes the respiratory system but also may invade the central nervous system (CNS) and give rise to neurological complications (Mao and Jin, 2020). Examples of neurological manifestations that have been documented thus far in COVID-19 patients include anosmia, ageusia, headache,

stroke, impairment of consciousness, seizure, and encephalopathy (Zubair et al., 2020). Currently, scientists are most concerned with investigating the neuropathology of SARS-CoV-2, along with both the acute phase and long-term neurological implications (Cheng et al., 2020). This capstone project is a literature review of Human Coronaviruses, specifically SARS-CoV-2, and the current exploration of its relationship with the nervous system. Additionally, this capstone will highlight the present hypotheses postulated by researchers regarding the neuroinvasive and neuroinflammatory events that may lead to short or long-term neurobehavioral consequences.

BACKGROUND

Introduction to Coronaviruses (CoVs)

Coronaviruses (CoVs) are members of the family *Coronaviridae*, consisting of a group of RNA viruses that are enveloped, single-stranded, and positive-sense (Ye et al., 2020). This particular family of viruses contains the largest known genome compared to other RNA viruses, with its size of approximately 26-32 kilobases (Su et al., 2016). CoVs received their designation due to their crown-like morphology, spike proteins that project from the virus membrane, which is visible under electron microscopy (Su et al., 2016). All Coronaviruses share a similarly organized genome that is non-segmented. One portion of the CoV genome includes two large overlapping reading frames, ORF1a and ORF1b, which encode the 16 nonstructural proteins, nsp1-nsp16, at the 5' end (Ye et al., 2020). The remaining section of the genome includes additional ORFs, which encode for the structural proteins spike (S), envelope (E), membrane (M), and nucleocapsid (N) at the 3' end. Along with this, the different derivations of CoVs encode for distinct accessory proteins, specific to their lineages (Su et al., 2016).

The Coronaviruses are classified into four genera predicated on their varying protein sequences: alpha-CoV, beta-CoV, gamma-CoV, and delta-CoV (Ye et al., 2020). The predominant gene source for alpha-CoVs and beta-CoVs are bats and rodents, while for gamma-CoVs and delta-CoVs, birds are the origin. The beta-CoV genera have been identified as containing most human Coronaviruses (HCoVs) and subdivided into four lineages, A, B, C, and D (Ye et al., 2020). Currently, there are seven known HCoVs. HCoV-229E and HCoV-NL63 are classified as alpha-CoVs, while the remaining five,

HCoV-OC43, HCoV-HKU1, severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2, are beta-CoVs (Ye et al., 2020). Most HCoVs typically result in minor symptoms, such as the common cold or diarrhea, since they primarily infect the upper respiratory tract and the gastrointestinal tract (Su et al., 2016). However, in contrast, it has been established that SARS-CoV, MERS-CoV, and SARS-CoV-2 are highly pathogenic and cause severe distress to the lower respiratory tract. Additionally, these CoVs are associated with a higher incidence of pneumonia, acute respiratory distress syndrome (ARDS), kidney failure, and death (Santacroce et al., 2020).

Structure and Properties of Coronaviruses

Coronaviruses are spherical shaped and approximately about 125 nm in diameter (Malik 2020). As mentioned previously, CoV's contain various structural proteins that contribute enormously to its function.

Essential to recognize in the Coronavirus' structure is the only protein located inside the core of the virus, the Nucleocapsid (N) protein. The N-protein contains an N-terminal domain and a C-terminal domain, both of which have the capability to bind directly and optimally to the RNA (Fehr & Perlman, 2015). The N-protein is also highly phosphorylated, instigating a structural modification to the protein that augments its affinity to the viral RNA (Fehr & Perlman, 2015). Functionally, the N-protein serves to protect the viral RNA genome. In addition to this protective role, the N-protein is also vital in CoVs replication and transmission. The other structural proteins characteristic of CoVs are all embedded in the viral envelope (Boopathi et al., 2020).

Coronaviruses' most notable structural feature is the Spike (S) proteins, located on the outer surface of the virus. The S-protein is a Class I fusion protein, trimeric, heavily glycosylated, and contains the Receptor Binding Domain (RBD) (Kirtipal et al., 2020). The RBD has been classified as the most variable structure in Coronaviruses. The S-protein functions to promote viral entry into the host cell through fusion by facilitating the attachment of the virus to the host cell receptors (Boopathi et al., 2020). In most CoVs, the S protein is cleaved by a host-cell protease, separating the protein into two distinct polypeptides, S1 and S2 (Fehr & Perlman, 2015). S1 is more prominent and comprises the RBD, while S2 becomes the stalk of the spike (Fehr & Perlman, 2015).

The Envelope or E-protein is a small transmembrane protein and is sparse in quantity in the virus. Despite the limited amount, the E-protein has critical tasks. The E-protein facilitates the assembly and release of the virus by affecting membrane permeability (Boopathi et al., 2020). In addition to this, the coronavirus E proteins contain an N-terminal ectodomain and a C-terminal endodomain that has an ion channel that contributes to the virus function depending on the particular type of coronavirus. For example, as Fehr & Perlman (2015) noted, SARS-CoV E protein is not needed for viral replication, but it is essential for pathogenesis. Furthermore, E protein is imperative in virus production and maturation, as it has been identified that recombinant CoVs without E protein are less virulent (Malik 2020).

The Membrane (M) protein is the most abundant structural protein and defines the shape of the viral envelope (Malik 2020). The M protein has three transmembrane domains, featuring a small N-terminal glycosylated ectodomain and a larger C-terminal endodomain that extends 6-8 nm into the virion (Fehr & Perlman, 2015). Current

research on M proteins suggests that it exists as a dimer in the viral particle and has the ability to change conformations. The capacity to alter conformations allows the M protein to promote membrane curvature and bind to the nucleocapsid (Malik 2020). The M protein also has critical interactions with other CoV structural proteins. The relationship between the M protein and the S protein is required for retention of the S protein in the ER-Golgi intermediate compartment and creating new virions (Malik 2020). Additionally, it is imperative for the M protein to bind to the N protein in order to stabilize the nucleocapsid and internal core of the virus. The interactivity between the M and N proteins facilitates the packaging of the genome and release into viral particles (Fehr & Perlman, 2015).

An additional structural protein has also been identified in a particular group of Coronaviruses, beta-CoVs. Hemagglutinin-esterase (HE) is a dimer located on the surface of the Virion (Boopathi et al., 2020). HE has a dual function of binding sialic acids on the surface of glycoproteins and acting as an acetyl-esterase. These activities have been considered to strengthen S protein-mediated cell entry and infection of the host cell (Fehr & Perlman, 2015). However, HE is not required for virus replication (Boopathi et al., 2020).

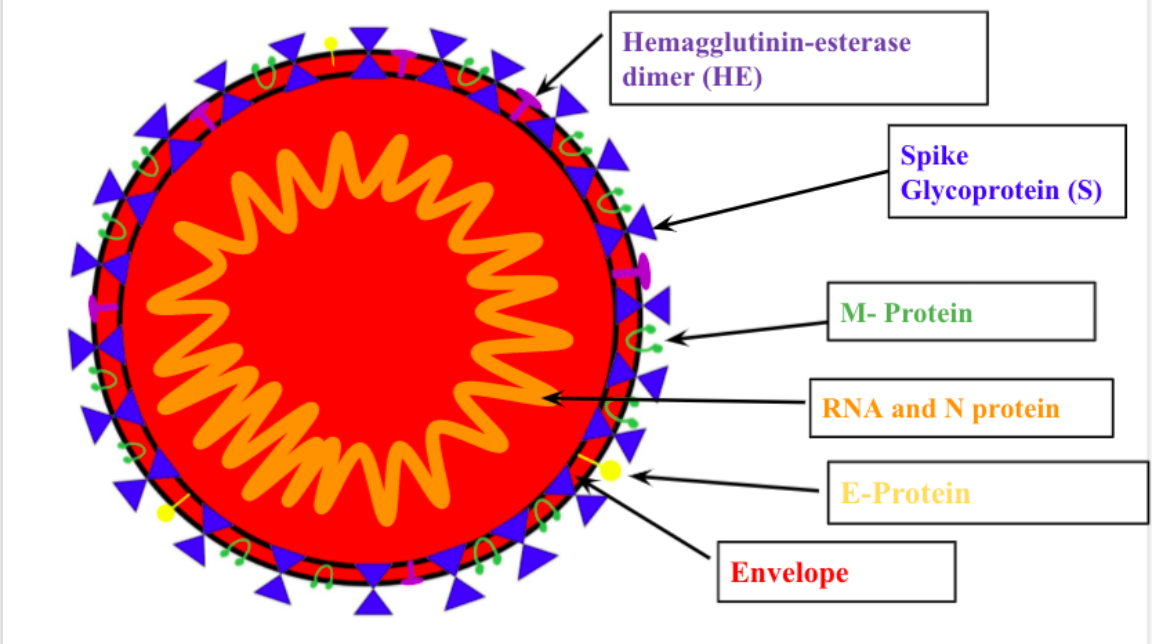

Figure 1. Structure of a Coronavirus

Origin and Transmission of SARS-CoV-2

SARS-CoV-2 is highly pathogenic and the third coronavirus in the past two decades to globally induce severe disease in humans (Wiersinga et al., 2020). Due to their ability to rapidly undergo genetic recombination and variation, Coronaviruses can adapt and infect a wide variety of hosts (Wiersinga et al., 2020). Examples of these hosts include birds and mammals, such as pigs, cows, chickens, dogs, and cats. However, bats are considered the major evolutionary and ecological reservoir for SARS-CoV-2 (Umakanthan et al., 2020). The food market in Wuhan, China that sold live animals, most notably bats, was identified as the zoonotic source for the Coronavirus outbreak. Despite bats being the most promising reservoir for SARS-CoV-2, researchers speculate that humans were infected with the virus via an intermediate host, particularly the pangolin or snakes (Kirtipal et al., 2020).

Human-to-human transmission of SARS-CoV-2 primarily occurs through respiratory droplets. These droplets can be excreted and inhaled by coughing, talking, or sneezing during face-to-face contact (Umakanthan et al., 2020). SARS-CoV-2 can also be transmitted through direct contact with a contaminated surface, aerosols (tiny droplets suspended in the air), and the fecal-oral route (Harison et al., 2020). Generally, contact with oral, nasal, and eye mucous membranes results in the spread of the COVID-19 virus (Umakanthan et al., 2020). High risk of transmission is characterized by prolonged exposure to an infected person or within 6 feet of the infected for at least 15 minutes (Wiersinga et al., 2020).

Symptoms of the COVID-19 Infection

The potential symptoms of COVID-19 due to SARS-CoV-2 infection are non-specific, and presentation varies. The clinical manifestations of SARS-CoV-2 are classified as either asymptomatic, mild, moderate, severe, or critical. The three most common symptoms are fever, cough, and shortness of breath. Other symptoms include myalgia (fatigue), weakness, nausea, diarrhea, vomiting, and changes in taste or smell (Wiersinga et al., 2020). Asymptomatic COVID-19 patients are characterized by not experiencing any clinical symptoms, chest imaging appearing normal, and still having a positive COVID nucleic acid test (Yuki et al., 2020). Mild cases of COVID-19 are denoted by symptoms of an upper respiratory tract infection, which includes fever, fatigue, cough, congestion, or digestive symptoms, which are nausea, vomiting, diarrhea, or general abdominal pain. Moderate COVID-19 disease is distinguished by experiencing pneumonia with frequent fever, cough, and no obvious hypoxemia. Chest CT in moderate COVID-19 cases presents lesions. Severe COVID-19 classification includes pneumonia

with hypoxemia, or when SpO2 saturation is less than 92%. Finally, critical classification of COVID-19 is characterized by acute respiratory distress syndrome (ARDS), shock, encephalopathy, myocardial injury, heart failure, acute kidney injury, and coagulation dysfunction (Yuki et al., 2020).

Adverse reactions or outcomes to COVID-19 are primarily associated with increasing age or other underlying comorbidities. Other comorbidities include hypertension, diabetes, cardiovascular disease, and lung disease (Yuki et al., 2020).

Mechanism of SARS-CoV-2 into Host Cells

Once SARS-CoV-2 enters the host through the respiratory tract, the potential severity of the disease that can ensue depends on the susceptibility and permissiveness of the host cells or immune system (Harrison et al., 2020). The life cycle of SARS-CoV-2 in the host cell consists of 5 steps: attachment, penetration, biosynthesis, maturation, and release (Santacroce et al., 2020). Attachment begins when the virus binds to the host cells' receptors. Penetration occurs when the virus enters the cell either through endocytosis or membrane fusion. Replication transpires when the viral contents are delivered to the inside of the host cell, and the viral mRNA can enter into the nucleus. The viral mRNA is also used for biosynthesis or the production of viral proteins. Once the new viral proteins are constructed during maturation, they are released in the final step of the life cycle (Yuki et al., 2020).

Attachment and penetration are primarily mediated through the actions of the S protein. The interaction between the S protein and the host cell receptor is the principal factor in determining if the virus will infect the host species and the element controlling

viral tissue tropism (Malik 2020). The S protein is a trimeric class I fusion protein that is densely glycosylated. As mentioned previously, the S protein contains two functional subunits. The first, S1, is the receptor-binding domain, and the second, S2, is responsible for the fusion of the viral and host cell membranes (Yuki et al., 2020). The binding of the S1 subunit to the host cell receptor is the instigating event for the fusion process of the viral membrane to the host cell membrane (Kirtipal et al., 2020).

The central receptor identified as SARS-CoV-2's primary entry point into host cells and aid in viral propagation is angiotensin conversion enzyme 2, or ACE2. ACE2 is a monocarboxypeptidase that interacts with many substrates in the human body, ranging from molecules in the renin-angiotensin system to molecules that aid in regulating blood sugar and insulin sensitivity (Santacroce et al., 2020). There are two different configurations of ACE2, the full-length form, and soluble form. The full-length form of ACE2 includes a transmembrane domain that has the ability to attach its extracellular domain to the plasma membrane (Santacroce et al., 2020). This functional variation of ACE2 is significant for the entry of SARS-CoV-2 into host cells, as the extracellular domain on ACE2 serves as a receptor for SARS-CoV-2. The soluble form of ACE2 is available in small quantities and circulates in the blood. Notable of the soluble form of ACE2 is that it lacks the membrane anchorage compared to its other structural counterpart (Santacroce et al., 2020).

It is proposed that the strong affinity SARS-CoV-2 has to ACE2 is due to the virus's S protein. The S protein binds to the ACE2 receptor, which results in a 2-step sequential protease cleavage cascade that eventually promotes viral uptake. Type 2 transmembrane serine protease (TMPRSS2), an enzyme that exists in the host cell, is the

enzyme that has been identified as being the primary protease responsible for cleaving the S protein and thus activating it (Morris et al., 2020). Additionally, scientists have also determined a possible alternative spike cleavage protease in cells that may express the ACE2 receptor but lack TMPRSS2, as cathepsin (Morris et al., 2020). The fusion of the S protein to the ACE2 receptor triggers TMPRSS2 to cleave and activate the S protein, which mediates coronavirus entry into host cells (Wiersinga et al., 2020). Although the protease cleavage mechanism for SARS-CoV-2 is not precisely understood, researchers have been following a model instituted by other highly pathogenic Coronaviruses that share similar characteristics, SARS-CoV and MERS-CoV. This model consists of protease cleavage at the S1/S2 site on the S protein for priming and cleavage at the S2 site, located within the S2 subunit, adjacent to a fusion peptide (Yuki et al., 2020). Following the cleavage at the S1/S2 site, the S1 and S2 subunits stay non-covalently bound. The S1 subunit stabilizes the S2 subunit that is membrane-anchored at the prefusion state (Yuki et al., 2020). The second cleavage step at the S2 site is seemingly the event that activates the S protein for membrane fusion through irreversible conformational changes (Yuki et al., 2020). In addition to this, a characteristic unique only to SARS-CoV-2 is that its spike protein also contains a unique furin cleavage site at the S1/S2 junction. This specific cleavage site contributes to the virus pathogenicity by allowing other cellular polyprotein convertases, such as furin and capthesin, to cleave and activate the S protein, which enhances Coronavirus entry utilizing endocytosis (Morris et al., 2020).

Alveolar epithelial cells, vascular endothelial cells, and alveolar macrophages are among the first cells to be targeted by the viral entry of SARS-CoV-2 (Harrison et al.,

2020). This targeting is attributable to the fact that these cells express a significant amount of ACE2. Generally, the nasopharyngeal and oropharyngeal tissues contain a substantial amount of ACE2. Specifically, in the respiratory tract, the ACE2 receptor is broadly expressed on epithelial cells of the trachea, bronchi, serous bronchial glands, alveoli, alveolar monocytes, and alveolar macrophages (Kirtipal et al., 2020). Due to this and the high-affinity SARS-CoV-2 has for ACE2, the virus is able to efficiently infect the upper respiratory system (URT), accounting for some of the most devastating symptoms of COVID-19. Most notably, ACE2 and TMPRSS2 are highly expressed by alveolar epithelial type II cells (pneumocytes), making lung tissue the primary viral tropism for SARS-CoV-2 (Harrison et al., 2020). ACE2 expression has also been identified in other tissues, including the esophagus, ileum, colon, kidney (proximal convoluted tubules), myocardium, and bladder tissue (Umakannthan et al., 2020). Additionally, it has been determined that ACE2 is diffusely expressed on immune cells and cerebral neurons (Kirtipal et al., 2020).

Host Response to SARS-CoV-2

Upon binding to host epithelial cells in the respiratory tract, SARS-CoV-2 begins the initial stages of infection by replicating and migrating down the airway, entering the alveolar epithelial cells in the lungs (Hu et al., 2020). As a result, the immune system begins to respond due to the rapid viral replication. The three components for innate immunity, specifically in the airway, are epithelial cells, alveolar macrophages, and dendritic cells (Yuki et al., 2020). The dendritic cells and macrophages begin to combat the virus as part of the innate immune response until adaptive immunity is activated.

The role of T cell-mediated response to SARS-CoV-2 is still being investigated. However, scientists have used the identified adaptive immune response in SARS-CoV, the Coronavirus most similar to SARS-CoV-2, to make inferences on the possible mechanism. Antigen-presenting cells (APCs), such as dendritic cells and macrophages, initiate a T cell response either when they phagocytize apoptotic cells infected by the virus or are primarily infected by the virus (Yuki et al., 2020). It has been determined that SARS-CoV can bind to dendritic-cell specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN), which is highly expressed on dendritic cells and macrophages. There is speculation that SARS-CoV-2 also shares this ability, which allows the virus to directly infect dendritic cells and alveolar macrophages (Yuki et al., 2020). As part of the immune response, these APCs migrate to the lymph nodes to present the viral antigen to the T cells. $CD4^+$ T cells and $CD8^+$ play an integral role in eradicating the virus by promoting the activation of B cells to generate virus-specific antibodies and directly killing infected cells, respectively (Yuki et al., 2020). However, research has observed that SARS-CoV-2 can escape the control of the immune system and, as a result, disrupt its normal function.

Studies have indicated that patients infected with SARS-CoV-2 presented with lymphopenia, or the decrease in the number of lymphocytes, to prevent the elimination of the virus (Santacroce et al., 2020). According to Morris et al. (2020), drastically reduced $CD4^+$ T cells, $CD8^+$ T cells, B cells, and natural killer cells are a characteristic feature of the COVID-19 disease. Additionally, there is accumulating evidence that patients infected by the virus experience excessive systemic immune activation and inflammation, also referred to as “cytokine storms” (Santacroce et al., 2020). Notably, patients enduring

severe COVID-19 disease had increased plasma concentrations of pro-inflammatory cytokines, such as interleukin (IL)-6, IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1α, and tumor necrosis factor (TNF)-α (Rothan et al., 2020). It has been observed that this inflammatory effect can cause acute damage to the lung tissue and lead to acute respiratory distress syndrome (Santacroce et al., 2020). Numerous autopsy reports of patients with severe COVID-19 primarily included histological examination of lungs, which commonly revealed bilateral diffuse alveolar damage, hyaline membrane formation, desquamated type II pneumocytes, and fibrin deposits (Hu et al., 2020). Finally, reports of thrombosis and pulmonary embolism have been noted in severe COVID-19 cases. These findings are attributable to the fact that SARS-CoV-2 causes the hazardous activation of coagulation and consumption of clotting factors to occur (Wiersinga et al., 2020). SARS-CoV-2 inflicts severe endothelial injury, and the endothelium plays a vital role in thrombotic regulation (vasodilation, fibrinolysis, and anti-aggregation) (Yuki et al., 2020). Also, it is essential to note that endothelial cells express ACE2 (Yuki et al., 2020).

SARS-CoV-2 and the Connection to the Nervous System

Although the primary manifestations of SARS-CoV-2 mainly involve pulmonary complications, there has been steadily increasing evidence that the virus also infects the central nervous system (CNS), causing neurologic dysfunction (Mao et al., 2020). The various neurological symptoms of COVID-19 that have been reported include anosmia/ageusia, headaches, seizures, confusion, delirium, stroke, coma, and more

(Bougakov et al., 2021). Also, the development of different neurological diseases or conditions has been accounted for due to COVID-19, such as encephalitis and Guillain-Barré syndrome (Zhou et al., 2020). Neuropsychiatric symptoms are also an additional topic of interest for COVID-19. Not only have these symptoms come to rise in the population due to pandemic-associated psychological distress, but there may be psychological effects due to direct infection of the virus. There is concern for the acute phase and long-term neurological manifestations of SARS-CoV-2, as COVID-19 patients may be at increased risk for developing neurodegenerative diseases years later post-infection or experiencing permanent cognitive impairment (Bougakov et al., 2021).

Although the exact mechanism through which SARS-CoV-2 invades the nervous system is still unknown, researchers have been proposing various hypotheses from available information on the virus, previous coronaviruses, and evidence from patients infected. Scientists have been speculating that the brain can both be directly and indirectly targeted by COVID-19. So far, four main potential neuroinvasive pathways have been identified for SARS-CoV-2. One involves direct infection of the CNS by neuronal pathways via retrograde transport along peripheral nerves (Yavrpour-Bali & Ghasemi-Kasman, 2020). A neuronal pathway specifically highlighted in SARS-CoV-2 is axonal transport through the olfactory nerve, which is proposed to eventually infect the neuroanatomical structures that follow in that path (Bougakov et al., 2021). Another includes a hematogenous route, where SARS-CoV-2 enters the CNS by crossing the blood-brain barrier (BBB) (Cheng et al., 2020). Lastly, the two other identified courses of neuroinvasion are due to secondary hypoxia and immune injury (Wu et al., 2020). These two proposed mechanisms of neurotropic infection are classified as indirect.

DISCUSSION

Proposed Direct and Indirect Neurotropic Mechanisms of SARS-CoV-2

Neuronal Pathway

The main idea for this proposed mechanism is that SARS-CoV-2 can infect peripheral nerve terminals, move retrograde along the nerve synapses, and eventually gain access into the CNS (Zubair et al., 2020). Transcribrial and transsynaptic spread has been observed amongst several different Coronaviruses, both human and non-human. It is speculated that viruses migrate to the CNS and achieve retrograde neuronal transport by using motor proteins (Wu et al., 2020).

A prevalent symptom reported by COVID-19 patients is loss of taste (ageusia) and smell (anosmia). This clinical manifestation is strong evidence of SARS-CoV-2 affecting cells in the CNS due to the unique anatomical organization of the olfactory system and the brain (Dempsey, 2020). The olfactory nerve essentially serves as a channel between the olfactory epithelium and the forebrain, where the virus can spread transcribrially (Wu et al., 2020). The proposed transsynaptic mechanisms in which the virus spreads retrogradely towards the CNS include an endocytosis/exocytosis transfer and a fast axonal transfer (FAT), where vesicle transport is used to pass the virus along microtubules back to neuronal cell bodies (Zubair et al., 2020). This is extremely problematic because it has been observed that SARS-CoV-2 can infect the brain and cerebrospinal fluid through the olfactory nerve and inflict inflammation and demyelination within seven days (Wu et al., 2020). Direct entry to the CNS through the

olfactory nerve is one of the main proposed neurotropic mechanisms for COVID-19. It is hypothesized that SARS-CoV-2 may penetrate the cribriform plate, which is located near the olfactory bulb and olfactory epithelium (Yavrpour-Bali & Ghasemi-Kasman, 2020). Moreover, SARS-CoV-2 may infect the olfactory receptor neurons in the olfactory epithelium using ACE2 or TMPRSS2 receptors (Yavrpour-Bali & Ghasemi-Kasman, 2020). This results in SARS-CoV-2 uptake into the ciliated dendrites/soma, which then the virus can utilize retrograde transport along the olfactory nerve into the CNS (Yavrpour-Bali & Ghasemi-Kasman, 2020).

Research has shown that ACE2 and TMPRSS2 receptors are highly expressed in human and mouse olfactory mucosa (Meinhardt et al., 2020). This evidence is why researchers attribute the susceptibility of the olfactory tissue to SARS-CoV-2 and as a means of transportation to the CNS. In studies conducted with SARS-CoV, the "sister" virus to SARS-CoV-2, infected mice revealed pathology, determining that the virus appeared to enter the brain through the olfactory bulb and disseminated transneuronally to distally connected neurons (Cheng et al., 2020). In another study noted by Zubir et al. (2020), mice that had their olfactory neurons chemically ablated were protected from infection from HCoV-OCR43 invasion into the CNS. However, conflicting studies suggest only the olfactory epithelium expresses ACE2, not the olfactory neurons, implying that SARS-CoV-2 cannot penetrate the nerve cells (Zubair et al., 2020). Further studies using autopsy reports and murine models need to be conducted to provide further clarification.

In addition to this, it has been found that there is a potential for SARS-CoV-2 to infect the brain tissue directly. Studies have identified that ACE2 is expressed on

numerous brain structures, including the brainstem, cortex, striatum, and hypothalamus (Bougakov et al., 2020). ACE2 has also been reported to be expressed on neurons and glial cells located throughout the brain. This is important as these structures and cells become potential targets for SARS-CoV-2 infection due to their expression of ACE2 (Bougakov et al., 2020). Other receptors are also in the process of being identified as potential mediators for SARS-CoV-2 infection in the brain. One of the newly recognized receptors is CD147 or Basigin. It is currently being investigated for its role in the viral entry of SARS-CoV-2 into brain tissue and serving as another entry point for SARS-CoV-2 (Bougakov et al., 2020).

Hematogenous Pathway

For this pathway, it has been identified that SARS-CoV-2 has the potential to enter the central nervous system (CNS) by entering the bloodstream. It is important to note that there has been evidence of this mechanism of entry into the CNS by other Coronaviruses, such as MERS-CoV and SARS-CoV (Reza-Zaldivar et al., 2020). Remarkably, the most common viral entry point into the CNS from the bloodstream is through the Blood-Brain Barrier (BBB) (Reza-Zaldivar et al., 2020). First, it has been proposed that SARS-CoV-2 can enter the bloodstream by infecting and damaging the epithelial cells. SARS-CoV-2 can likely injure the epithelium barrier and pervade the bloodstream (Lima et al., 2020). Specifically, the hypothesized origin of SARS-CoV-2 infection into blood circulation is in the respiratory tract. As mentioned previously, type II pneumocytes are the population of cells that SARS-CoV-2 primarily infects, and they highly express ACE2. As a result, when these epithelial cells are infected, SARS-CoV-2 can potentially enter the bloodstream and travel to the CNS. Additionally, another

proposed entryway for SARS-CoV-2 to enter the blood circulation is through the infection of the epithelial cells of the gastrointestinal (GI) tract (Lima et al., 2020).

Once SARS-CoV-2 has invaded the bloodstream, it has the potential to disseminate and infect the brain endothelial cells through the binding of ACE2, disrupting the BBB (Lima et al., 2020). Lima et al. (2020) described that the potential consequences of SARS-CoV-2 penetrating the BBB are edema, increased intracranial hypertension, and increased promotion of virus in the CNS. Paniz-Mondolfi et al. (2020) reported that a structural analysis revealed viral-like particles of SARS-CoV-2 were observed in the endothelial cells and pericytes of brain capillaries. In addition to this, the viral-like particles were also found in the astrocytic processes and contributing to the BBB dysfunction (Paniz-Mondolfi et al., 2020). In another recent study reported by Erickson et al. (2021), the S protein component of SARS-CoV-2 was found to induce BBB leakage in primary human in vitro BBB models. These studies suggest that the hematogenous pathway is a possible means of entry for the SARS-CoV-2 virus into the CNS.

There is an additional proposed mechanism for SARS-CoV-2 to enter the CNS by the hematogenous pathway, by infection of the endothelial cells of the choroid plexus, therefore penetrating the blood-cerebrospinal fluid barrier (BCSFB) (Yachou et al., 2020). This method of entry requires further investigation.

Although the virus-mediated dysfunction of the BBB could potentially be in response to direct infection by SARS-CoV-2, other indirect responses instigated by the virus may also play a prominent role. Erickson et al. (2021) reported that SARS-CoV-2

infection of endothelial cells (that overexpressed ACE2) generated the overexpression of clotting factors, adhesion molecules, and pro-inflammatory cytokines. This overexpression may be damaging to the BBB, causing it to be more permeable, and may promote viral entry into the CNS.

Immune Response and SARS-CoV-2

Both entry of SARS-CoV-2 into the CNS and nervous system damage may result from the immune system's response. As a result of SARS-CoV-2 infection, the immune system instigates a systemic inflammatory response. This response involves overproducing pro-inflammatory cytokines, chemokines, and complement (Erickson et al., 2021). This overexpression and increased inflammation produced by the immune response can have various effects on the nervous system.

First, the released factors can alter the permeability of the BBB (Yavarpour-Bali & Ghasemi-Kasman, 2020). Specifically, cytokines such as interleukin (IL)-1β, IL-6, Tumor Necrosis Factor (TNF)-α, and Interferon (IFN)- γ can disrupt the BBB by controlling transcytosis by adjusting the function of BBB transporters (Erickson et al., 2021). In addition to this, according to Erickson et al. (2021), cytokines and chemokines TNF- α, IL-1α, IL-1β, IL-1RA, IL-6, CCL2, and CCL11 serve as substrates for transport across the BBB. When production of these elevates, there is increased transport across the BBB, thus allowing the opportunity for SARS-CoV-2 to invade the CNS.

Next, it is postulated that the upregulation of the immune system in response to SARS-CoV-2 may result in inflammatory injury, leading to brain damage such as edema and even alteration of consciousness (Yavarpour-Bali & Ghasemi-Kasman, 2020). It has

also been theorized that the overexpression of the immune system due to infection may instigate a cytokine storm, which results in a systemic inflammatory response and a critical cause of ARDS (Song et al., 2020). In short, the hyper-inflammation generated by SARS-CoV-2 infection can impair neurovascular endothelial function, dysregulate the BBB, and may be a significant contributor to the CNS clinical manifestations observed in patients with COVID-19 (Najjar et al., 2020).

Finally, the last proposed mechanism of CNS damage inflicted by SARS-CoV-2 through the immune system is peripheral immune transmigration, often referred to as the "Trojan Horse" mechanism (Lima et al., 2020). This mechanism requires infected immune cells, such as leukocytes, to travel into the brain. Currently, there is speculation that SARS-CoV-2 could inflect the peripheral bloodstream leukocytes, predominantly monocytes/macrophages, and myeloid cells (Lima et al., 2020). The infection of these cells would potentially facilitate dissemination to the CNS. SARS-CoV-2 would utilize these cells as vehicles to travel across the BBB, meninges, and choroid plexus into the CNS (Reza-Zaldivar et al., 2020). It is known that SARS-CoV utilizes this mechanism by infecting lymphocytes, monocytes, and macrophages, resulting in lymphopenia, a condition that has also been reported in SARS-CoV-2 infected individuals (Lima et al., 2020). Based on this, as Lima et al. (2020) noted, researchers hypothesize that SARS-CoV-2 utilizes circulating immune cells and dendritic cells to disperse into the CNS.

Hypoxia and SARS-CoV-2

Hypoxia is another process that occurs due to SARS-CoV-2 infection and is a common clinical presentation of COVID-19. Notably, hypoxia is another method in

which SARS-CoV-2 can inflict damage on the nervous system (Yavarpour-Bali & Ghasemi-Kasman, 2020). When the virus proliferates in the cells in the lung tissue, it can produce alveolar and interstitial inflammatory exudation and edema (Wu et al., 2020). This, in turn, can lead to dysfunction of alveolar gas exchange, which eventually results in hypoxia in the CNS (Yavarpour-Bali & Ghasemi-Kasman, 2020). In response to this hypoxia, brain cells begin rapidly undergoing anaerobic metabolism, leading to the accumulation of lactic acid (Wu et al., 2020). Following this, cerebral vasodilation, interstitial edema, cerebral blood supply obstruction, and headache due to ischemia may occur (Yavarpour-Bali & Ghasemi-Kasman, 2020). If the individual infected with SARS-CoV-2 remains in a hypoxic state, brain function will continue to deteriorate as intracranial pressure increases and may result in coma or death (Wu et al., 2020). In addition to this, severe hypoxia may provoke acute cerebrovascular disease, such as an ischemic stroke (Wu et al., 2020). In essence, hypoxia-induced by SARS-CoV-2 infection may cause damage to the nervous system.

Neurological Conditions and Symptoms Associated with SARS-CoV-2

As more information continues to be discovered about SARS-CoV-2, there is increased evidence accumulating in support that the virus invades the CNS and inflicts neurological damage, as demonstrated by the clinical neurological manifestations. Various neurological complications have been reported in patients infected with SARS-CoV-2. These conditions range in severity from mild such as headache, anosmia, and ageusia, to more severe complications, including impaired consciousness,

cerebrovascular complications, encephalopathy/encephalitis, seizures, Guillain-Barré Syndrome, delirium, and psychiatric disorders (Erickson et al., 2020).

Headache

Headache has been the most common neurological symptom reported by patients who have been infected by SARS-CoV-2 (Zhou et al., 2020). Not only this, but headache was also a chief complaint of COVID-19 in general, accompanying the more classic symptoms of fever, cough, and shortness of breath (Zubair et al., 2020). The prevalence of headaches in COVID-19 patients was reported to be as high as 70% (Al-Ramadan et al., 2021). Although headache is an established indication of conditions such as meningitis, encephalitis, and intracranial hypertension, its relationship to the pathophysiology of SARS-CoV-2 is still unknown (Zubair et al., 2020). Some researchers postulate that the neuroinflammatory mechanisms that occur by cytokines and chemokines resulting from infection may contribute to the production of headaches (Zubair et al., 2020). However, it is currently understood by scientists that headache, along with the other neurologic manifestations of COVD-19, could potentially be attributed to direct infection of the virus, or secondary factors, such as the immune system (Erickson et al., 2020).

Anosmia and Ageusia

Al-Ramadan et al. (2021) reported that olfactory and gustatory impairment was a common neurological symptom of SARS-CoV-2 infection. Notably, anosmia and ageusia were reported as early manifestations of SARS-CoV-2, appearing in the first five days of illness (Zhou et al., 2020). As recognition of COVID-19 continued to improve and develop, the reported incidence of chemosensitive impairment considerably increased

from about 19.4% to 88% (Zhou et al., 2020). In a study with 417 participants diagnosed with mild to moderate COVID-19, scientists observed that the incidence of olfactory dysfunction was 85.6%, and gustatory dysfunction was 88% (Al-Ramadan et al., 2021). Notably, olfactory dysfunction was not associated with rhinitis or nasal dysfunction (Zubair et al., 2020) but was significantly linked to fever and gustatory symptoms (Al-Ramadan et al., 2021).

Impaired Consciousness

In a study conducted by Mao et al. (2020), 37% of hospitalized patients due to COVID-19 experienced impaired consciousness. Researchers suggest that the underlying reasons behind hindered consciousness due to SARS-CoV-2 may be due to several aspects, including direct infection to the brain parenchyma, encephalopathy, or seizures (Zubair et al., 2020).

Infectious Toxic Encephalopathy

Encephalopathy is a non-specific term used to describe impairment in brain function (Al-Ramadan et al., 2021). Hallmarks of encephalopathy are altered mental status or impaired consciousness, confusion, headache, lethargy, delirium, or coma (Zubair et al., 2020). Infectious toxic encephalopathy, also known as acute toxic encephalitis, is a specific type in which reversible brain dysfunction is caused by the processes of acute infection (Wu et al., 2020). These processes include severe inflammation, hypoxia, viremia, and metabolic dysfunction (Wu et al., 2020). The significant pathological change in this condition is cerebral edema, with no evidence of inflammation present in the cerebrospinal fluid (Wu et al., 2020). Due to the proposed neurotropic mechanisms and increasing evidence of brain edema in COVID-19 patients,

SARS-CoV-2 may potentially cause acute toxic encephalitis. However, more studies need to be conducted to investigate this relationship further.

Viral Encephalitis

Encephalitis is a severe condition that causes various neurological abnormalities, including headache, fever, convulsions, impaired consciousness, hallucination, confusion, aphasia, and impaired movement (Al-Ramadan et al., 2021). Wu et al. (2020) reported that encephalitis concerns the inflammatory lesions in the brain that cause neuronal damage generated by pathogens. Although some SARS-CoV-2 associated encephalitis is now being reported, such as one involving a 41-year old diabetic woman diagnosed with COVID-19 and CSF analysis consistent with viral infection (Al-Ramadan et al., 2021), more research needs to be conducted on this association.

Seizure

Seizures linked to SARS-CoV-2 infection have been reported in about 10% of COVID-19 patients (Zubair et al., 2020). It is also important to note that seizures have been reported in other coronavirus infections. Additionally, Zubair et al. (2020) reported that patients who have a primary seizure disorder and contract COVID-19 are at a higher risk for seizure and status epilepticus. Al-Ramadan et al. (2021) stated that non-epileptic seizures have also been described; however, further investigation into these cases is needed.

Cerebrovascular Complications

Occlusion or rupture of the blood vessels that comprise the cerebrovascular system can potentially halt blood perfusion in the brain, leading to a

stroke (Al-Ramadan et al., 2021). In addition to this, an ischemic brain injury that is induced by the inflammatory response due to SARS-CoV-2 may also cause an acute cerebrovascular complication (Wu et al., 2020). It has been found that patients with severe COVD-19 disease often present with elevated D-dimer levels and significantly decreased platelet reduction, which also may induce a cerebrovascular complication (Wu et al., 2020). Many cases are emerging reporting COVID-19 patients who experienced a stroke. It is important to note that most of these patients were: significantly older, had more cardiovascular risk factors, had higher levels of D-dimer and C-reactive protein, indicative of a hypercoagulative state (Zubair et al., 2020). However, a recent study in New York observed that COVID-19 patients younger than 50 years old also experienced large-vessel strokes (Zubair et al., 2020). Thus, more studies need to be conducted.

Guillain-Barré Syndrome

Guillain-Barré Syndrome or acute inflammatory demyelinating polyneuropathy (AIDP) is a condition that has been slowly emerging in patients with COVID-19. Guillain-Barré Syndrome is known to develop following a gastrointestinal or respiratory illness. The disorder, using a mimicry mechanism in order to bind to the peripheral nervous system, results in neuronal dysfunction (Zubair et al., 2020). A study reported 5 cases of Guillain-Barré Syndrome in Italy following a COVID-19 infection. In most cases, the patients presented with paresthesia and lower-extremity weakness (Zubair et al., 2020). Al-Ramadan et al. (2021) stated that another study potentially found 24 cases of Guillain-Barré Syndrome associated with COVID-19. The emergence of these cases indicates Guillain-Barré Syndrome is a complication of COVID-19; however, more research needs to be done.

Psychiatric Disorders

The COVID-19 pandemic in itself has served as a significant psychological stressor. Depression, anxiety, insomnia, and trauma-related disorders have been reported due to the SARS-CoV-2 pandemic. The current data conveys that the frequency and severity of psychiatric symptoms are associated with proximity to COVID-19 patients (Troyer et al., 2020). In addition to the psychological conditions people are experiencing due to the global pandemic, neurotropic mechanisms of SARS-CoV-2 may promote the onset of psychiatric symptoms (Orsini et al., 2020). Researchers speculate the association between SARS-CoV-2 infection and psychiatric symptoms may be attributable to the systemic inflammatory response that occurs due to infection (Orsini et al., 2020). Common psychiatric conditions emerging are depression, delirium, and psychosis (Orsini et al., 2020). In order to fully comprehend the association between SARS-CoV-2 and psychological symptoms, more studies need to be conducted.

RECOMMENDATIONS FOR FUTURE STUDIES

SARS-CoV-2 infection and its proposed ability to invade the CNS only continue to grow in strength with the emerging evidence. As scientists continue to study the various mechanisms of SARS-CoV-2, there will be more definitive answers regarding how the virus functions and the damage it executes. Researchers across the globe have been working to gain insight into SARS-CoV-2's neurotropic methods by using available information on previous coronaviruses and attempting to begin data collection. As research on COVID-19 continues, scientists can specifically test the proposed mechanisms and the associated neurological conditions that have surfaced.

Understanding the mechanism through which SARS-CoV-2 can enter the CNS is imperative, as it will provide the information necessary to decipher why the specific neurological conditions are occurring. In addition to this, it is also crucial for scientists to continue investigating the neurological disorders associated with COVID-19 to assess the strength in their correlation. Studying and being cognizant of these severe neurological conditions may lead to early detection and better outcomes with severely ill patients. Finally, long-term assessments of COVID-19 patients are critical to understanding the chronic effects of this disease.

RESEARCH STRATEGIES

An in-depth analysis of multiple sources conducted in this review. To obtain sufficient information on the subject of Coronaviruses, numerous reputable databases were used, such as ScienceDirect, Google Scholar, MEDLINE, ResearchGate, PubMed Central, JSTOR, and the New England Journal of Medicine. In addition to searching for published articles directly for research, cited articles were also utilized.

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