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COVID-19 and the central nervous system: What is the interplay?

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ABSTRACT: Since the outbreak of COVID-19 in 2019-2020, the highly contiguous disease caused by coronavirus 2 (SARS-CoV-2) spread worldwide in a short life span causing a disastrous effect and nearly 5.8 million deaths until February 2022. This global health crisis caused concerns about the disease's aetiology, epidemiology, and management. Understanding the virus's long- and short-term consequences on diverse human body organs and systems was one of the scientist's concerns despite the virus' respiratory system principal effect. Thus, after reporting neurological symptoms in approximately one-third of hospitalised patients with COVID-19, demonstrating how COVID-19 infects the central nervous system (CNS), causing neurodegenerative diseases in various patients and how the virus affects CNS function became quintessential. There are various mechanisms for COVID-19 pathophysiology, some implicating the potential virus invasion of the blood-brain barrier (BBB). Trans-synaptic and hematogenous routes are the main routes for the virus to pass through the barrier. Binding to the BBB endothelial cells is causing significant alterations in the permeability and integrity properties of the barrier, which cause an elevation of the incidence rate of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis among COVI-19 patients. COVID-19 patients developed neurological manifestations ranging from mild symptoms to severe diseases such as headache and loss of smell, encephalitis and CNS-mediated respiratory distress. However, encephalitis is not a common complication, and it has a significant mortality rate in severely ill patients due to the hyperactivation of the host immune response. Although more investigations are needed, severe COVID- 19 patients are considered at a high risk of neurodegenerative disorder as a long-term consequence of SARS-CoV-2 infection.

Keywords: COVID-19; neurodegenerative diseases; central nervous system (CNS);

1.0 INTRODUCTION

Coronavirus disease 19 (COVID-19) first broke out in Wuhan, China. In December 2019, Chinese health authorities officially announced that some patients suffered from pneumonia of unknown causes. Soon after, efforts were exerted to elucidate the genetic characterisation of the novel virus. In January 2020, Zhu et al. carried out a sequence analysis to reveal the genomic structure of the unknown virus. They have revealed that this virus is a novel coronavirus that falls into the genus beta coronavirus (Zhu et al., 2020). The novel coronavirus was formerly named 2019-nCoV, then its name was changed to SARS-CoV-2 (or COVID-19 virus). It is noteworthy that the beta coronaviruses include SARS-CoV, bat SARS-like CoV, and MERS-CoV discovered in humans, bats, and camels, respectively. Phylogenetic analysis has shown that SARS-CoV-2 exhibits ~79% identity for SARS-CoV, ~50% identity for MERS-CoV, and is closely related, with ~88% identity to the bat SARS-like CoV (Ciotti et al., 2020). A few weeks later, the COVID-19 virus spread into 18 countries other than China, urging the WHO to declare a public health emergency of international concern (PHEIC). SARS-CoV-2 spread increased dramatically over the globe, and WHO declared it a pandemic on 11 March 2020**.** Thus, until the time of writing this review in February 2022, more than 422 million confirmed cases worldwide were reported, with more than 5.8 million deaths reported worldwide (WHO, 2022).

It is well known that viruses generally undergo changes over time, which may affect virus properties and severity, hence its response to medications and vaccines. Similarly, SARS-COV-2 has been modified over time, producing several variants, some of which are reported to exhibit higher eradications for human health and threaten lives. As listed by WHO, the emergence of variants begins by the middle of 2020 (WHO, 2021b). The beta variants, β-SARS-CoV-2 (B.1.351), first emerged in South Africa in May 2020 (WHO, 2021b). The alpha variant, α-SARS-COV-2 (B.1.1.7), was first documented in the United Kingdom in September 2020. One month later, the delta variant, δ-SARS-CoV-2 (B.1.617.2), was reported in India in October 2020 (WHO, 2021b). In November 2020, the gamma variant (ɣ-SARS-CoV-2) was reported in Brazil (WHO, 2021b). A year later, a new variant, omicron (B.1.1.529), was first documented in South Africa in November 2021 (WHO, 2021a). The omicron variant is steeply spread and threatens public health more than the previous variants. This high risk of omicron compared to other variants is due to several factors (Callaway, 2021; WHO, 2021a). Omicron is highly mutated compared to the other variants. In addition, preliminary investigation proposes an increased risk of reinfection with this variant. The worst fact is that this variant might not be affected by the available COVID-19 vaccines. Thus, the omicron variant is a new health risk factor and needs further consideration.

The ongoing pandemic of COVID-19 recalls memories of similar outbreaks, such as the SARS outbreak in 2002-2004. Vellingiri et al. (2020) reported that coronaviruses are neuro-invasive, especially their beta-form such as SARS-CoV and MERS-CoV; also, they expected that the existing SARS-CoV-2 outbreak is a neuro-invasive virus as well due to the similarity between SARS-CoV-2 and SARS-CoV (Vellingiri et al., 2020). The WHO stated fever, cough, tiredness, and loss of taste and smell as the most common symptoms of COVID-19 infection, and less common symptoms are sore throat, headache, aches, pains, and diarrhoea. WHO also stated chest pain, difficulty breathing or shortness of breath, and loss of speech or mobility or confusion as severe symptoms of the disease.

Indeed, there are reports of neurological and psychiatric symptoms caused by COVID-19. Among the symptoms of COVID-19, some have been related to the CNS. Here, we discuss the possible effects of the viral infection on the central nervous system (CNS), the neurological and psychiatric symptoms of the virus, and the possibility that the neuro-invasion of COVID-19 could increase the susceptibility to develop a neurodegenerative disease in the future.

It has been reported that nearly one-third of COVID-19 patients have developed neurological and/or psychiatric symptoms (Beach et al., 2020). Mostly in the form of headache, dizziness, hyposmia, hypogeusia (Zhou et al., 2020), fatigue, confusion, and myalgia (Carod-Artal, 2020). Mao et al. (2020) found that 36.4% of hospitalised COVID-19 patients at Huazhong of Science and Technology hospital in Wuhan, China had neurological manifestations, most frequently presented

by dizziness (36 cases) and headache (28 cases) (Mao et al., 2020). There are also non-specific neurological symptoms that have been reported since the start of COVID-19, such as delirium, encephalopathy, cerebrovascular complications, neuromuscular disorders, anosmia, and ageusia (Rogers et al., 2020).

Delirium is considered the most common non-specific neurological symptom, along with agitation and altered consciousness (de Sousa Moreira et al., 2021). Beach et al. (2020) reported that three of four cases who experienced delirium had minor respiratory symptoms (Beach et al., 2020). Instead, their disease picture was a change in their mental status. It is still unclear how COVID-19 can cause these symptoms. However, it may be a primary manifestation of the viral invasion of the central nervous system or a result of encephalopathy caused by inflammation (Rogers et al., 2020). Regarding psychiatric symptoms, evidence suggests that a percentage range between 0.9% to 4% of patients with COVID-19 have developed psychotic symptoms in the form of depression or psychosis (Dinakaran et al., 2020). Among the psychiatric symptoms are mild cognitive impairment (Helms et al., 2020), mood swings (Yin et al., 2020), insomnia (Hao et al., 2020), and suicide (Valdés-Florido et al., 2020). Researchers believe that psychosis may be secondary to an infection, treatment, and increased psychosocial stress during pandemics (Brown et al., 2020). In response to infections, there are elevated levels of pro-inflammatory mediators such as interleukin-6 and C-reactive protein. These mediators have been positively correlated to the associated COVID-19 depression manifestations. Thus, psychiatric symptoms are believed to be due to the inflammatory response to the infection (Giacomelli et al., 2020).

2.0 SARS-COV-2 PATHOPHYSIOLOGY

2.1 Angiotensin system

The multi-infectious potency of SARS-CoV-2 is emphasised by its ability to invade many biological systems: respiratory, gastrointestinal, and central nervous systems. That potency can be interpreted with the expressed receptors for SARS-CoV-2 on the cellular membrane of these systems (Verkhratsky et al., 2020). The number of COVID-19 patients presented with neurodegenerative consequences is nearly 60-70 million worldwide. The estimation is expected to be duplicated within the next 20 years because of an increase in neurodegenerative risk factors (Nichols et al., 2019).

The receptor-binding domain (RBD) of SARS-CoV-2 interpret its high invasion feature compared with other strain. Firstly, SARS-CoV-2 RBD binds with the host angiotensin-converting enzyme receptor (ACE2) with higher affinity than other strains. Secondly, SARS-CoV-2 evades host immunity due to hidden RBD in a mature viral spike, which needs to be activated by viral proprotein convertase (PPC) and many host protease enzymes (Kermani et al., 2021; Shang et al., 2020; Verkhratsky et al., 2020). The glycoprotein membrane of SARS-CoV-2 contains PPC motifs whose presence elucidates the virus's high pathogenicity. Shang and his research team performed an *in vitro* model for SARS-CoV-2 entry using a pseudovirus of SARS-CoV-2 infecting three cell lines (Hela, Calu-3, and MRC-5) efficiently. This model revealed the minimal contribution of transmembrane protease serine 2 (TMPRSS2) and lysosomal cathepsin (host proteases) in the viral spike cleavage process with PPC elevating the efficiency of SARS-CoV-2 entry into several host cells (Shang et al., 2020). The viral spike/ host receptor binding process is followed by endocytosis entry of the virus into the host cell through either clathrin or pH-dependent manner (Kermani et al., 2021).

2.2 Neuropilin (NRP)

The high multi-infectious potency of SARS-CoV-2 is emphasised by the availability and variability of its host receptors and co-factors on the cellular membrane of many organs (Cantuti-Castelvetri et al., 2020). Olfactory epithelial cells are neuropilin-positive cells (NRP1+). Biopsies of these cells from COVID-19 patients contain a viral load of SARS-CoV-2, proving its efficient entry through neuropilin (Cantuti-Castelvetri et al., 2020). Potent pathogenic viruses (HIV, Ebola, and SARS-CoV-2) have a polybasic furin-type cleavage site. In the case of SARS-CoV-2, this site is present at the S1/S2 boundary. When furin activates this site via proteolytic activity, a C terminal motif terminates with an arginine or lysine amino acid (R-OH). This C terminal has a high affinity to neuropilin receptors (Coutard et al., 2020). Both NRP1 and NRP2 showed a high expression level in the olfactory bulb, endothelial cells, and respiratory system, and to confirm the ability of SARS-CoV-2 to infect NRP1-positive cells, Cantuti-Castelvetri and his colleagues performed a case-control study. Specimens of olfactory epithelium were drawn from six COVID-19 patients and eight healthy controls. Co-stained specimens showed that five of six patients had infected olfactory epithelium (Cantuti-Castelvetri et al., 2020).

Neuropilin/spike interaction is revealed by Cantuti-Castelvetri and his research team using a human embryonic kidney cell line (HEK-293T) lacking both ACE2 and neuropilin receptors. This cell line was exposed to

pseudo-lentivirus containing spike protein of SARS-CoV-2. Host factors are introduced to the cell line by plasmid (ACE2+ TMRRSS2 or NRP or both). Results showed neuropilin only elevates viral entry by 40%n the presence of other host factors (Cantuti-Castelvetri et al., 2020). As shown above, many studies confirmed the entry of SARS-CoV-2 to CNS through neuropilin -host receptor expressed on the olfactory epithelial cells- in the presence of other host factors. The mechanism of entry needs to be further investigated.

2.3 Cytokine storm

Cytokines are molecules that stimulate the production of antibodies from white blood cells (B cells) or kill infected cells by T cells that, result in an immune attack, but over time, this immune activation could attack in no specified way that may be a risk factor in the development of the disease (Dewanjee et al., 2021). Acute viral infection could have an abnormal immune response. Consequently, there is a chance for the over-release of cytokines and chemokines such as IL1-β, IL-6, IL-18, IFN-γ, IP-10, CCL-2, TNF-α, IL -2, IL-7, G-CSF and MIP1α, which spread causing a cytokine storm and systemic inflammation.

SARS-CoV-2 crosses the blood-brain barrier (BBB) and causes pathological effects on CNS, including encephalopathy, acute myelitis, and other symptoms that could appear by immune and inflammatory pathways (Dąbrowska et al., 2021). Different mechanisms enhance SARS-CoV-2 BBB permeability. As a prominent example, Tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ), interleukin (IL)-2, IL-6, and IL-8, which consider pro-inflammatory mediators and effector cytokines. These mediators assist the virus in crossing BBB by activating acute innate immune response and microglial proliferation. Moreover, endothelial cell infection may damage the BBB and helps in cellular invasion (**Figure 1**) (Dąbrowska et al., 2021; Najjar et al., 2020).

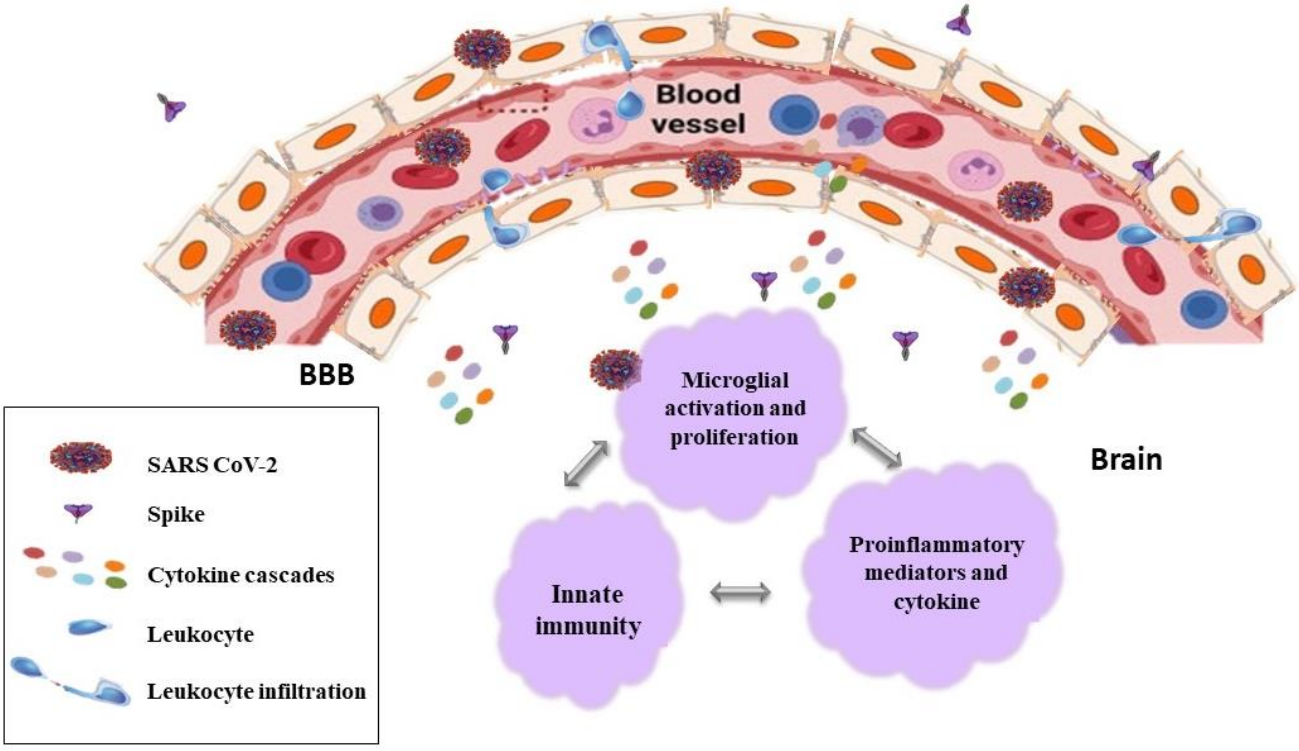

Figure 1: BBB infection and the cytokine storm. The damage to the BBB caused by the SARS-CoV2 attack results in an induction of the acute immune response, which triggers some pro-inflammatory mediators (TNF-α, IFN-ɣ, IL-2, IL-6 and IL-8). Once the microglia are activated, they induce innate immunity, pro-inflammatory mediators, and cytokines that affect the structural and functional integrity of the BBB and facilitate virus entry into the CNS.

Consequently, the microglia are activated, which induces innate immunity, pro-inflammatory mediators, and cytokines. All these factors negatively affect each other and disturb the structural and functional integrity of the BBB and facilitate virus entry into the CNS. The virus might cross the BBB via three routes. (a) By infecting and deteriorating the endothelial cell itself, (b) through the disturbed junctions which are broken down as a consequence of pro-inflammation and glial activation, and/or (c) by entering with an infected leukocyte which, when infected, acts as a carrier for the virus to enter the CNS through the BBB safely.

Microglial activation and proliferation (MAP) start, in turn, to disrupt the functional and structural integrity of BBB, breaking down BBB (**Figure 1**) *and* then starting its negative effect on neurotransmission and causing glutamate-mediated neuronal excitotoxicity and damage to neurovascular endothelium leading to loss of the endothelial dynamic auto-regulatory capacity (Gupta et al., 2020). IL-17 associated with COVID-19 can also provoke cytokines (TNF-α, IL-6, and IL-1B) and chemokines (CCL2 and MIP-2) and work with (TNF-α) and IL-1B to activate IL-6 which induce T-cell apoptosis and provoke lymphocytopenia (Dąbrowska et al., 2021).

Neurodegenerative diseases such as Parkinson's, Alzheimer's, Huntington's disease, and amyotrophic lateral sclerosis consider serious risk factors as they can exacerbate the inflammatory and autoimmune reaction of COVID-19 (Najjar et al., 2020). CNS diseases are characterised by neuroinflammation, which commonly presents with microglial activation. Microglia has a pivotal role in synaptic plasticity, clearance processes, and myelination; in the aged brain, IL-6, IL-1β and IL-1α, and TNF are increased due to microglial activation as a result of neuroinflammation, which has neurogenesis-regulating properties due to this activation. During COVID-19 infection, neurons and glial cells will be negatively affected by losing their physiological function, which leads to cognitive deterioration after enhancing neurodegenerative processes (Dąbrowska et al., 2021; Tremblay et al., 2020). Fatal COVID-19 cases have a wide range of neurological and neuropsychiatric damage like encephalopathies, myalgia, and cytokine storm syndrome (CSS) (**Figure 1**), (Najjar et al., 2020), but encephalopathy consider the major cause of morbidity and mortality in COVID-19 patients which developed mainly by triggering of cytokine storm (Dąbrowska et al., 2021).

2.4 Gut-brain axis during COVID-19 pandemic infection

COVID-19 has a strange phenomenon in its ability to affect other systems rather than the pulmonary system, such as the central nervous and gastrointestinal systems (Gupta et al., 2020). Some COVID-19 patients have symptoms like vomiting, nausea, and diarrhoea. These symptoms are due to virus invasion of the gastrointestinal system through ACE2/TMPRSS2 receptors. This invasion destroys intestinal permeability and malabsorption, changing innate immunity performance and leading to increased virulence of intestinal microbes; moreover, it leads to decreased tryptophan intake (Mao et al., 2020). In general, tryptophan depletion leads to increased anxiety and irritability in humans (Moehn et al., 2012). According to the severity of the infection, the central nervous system is affected. The study performed on 214 COVID-19 patients from 16 January to 19 February 2020 showed that (36.4%) had neurological disorders (Mao et al., 2020). The gut-brain axis is an established expression of the reciprocal correlation between the gastrointestinal system and CNS affected by the last pandemic. The relationship is represented as follows; when the virus reaches the intestine, causing GIT inflammation and disturbance in monoaminergic and tryptophan absorption, an essential amino acid in serotonin biosynthesis in CNS. The malabsorption in its precursor leads to a depleted level of it; On the other hand, the level of dopamine increases, and the norepinephrine level decreases in brain tissue (Shinu et al., 2020). As a result, some psychotic events are observed as depression, delirium, and confusion (Xu et al., 2021). In addition, some disturbance in lipopolysaccharides (LPs) and cytokines performance is observed (Petruk et al., 2020).

Once the COVID-19 virus binds to the ACE receptor on the intestinal mucosa, the inflammatory cytokinesis [as; IL-6, IL-10, IL-1, and TNF-α], and the coagulation cascade is increased. The high level of inflammatory cytokines and coagulation factors lead to the formation of a thrombus. The formed thrombus may be divided into small pieces and reach the brain causing psychological disorders (Petruk et al., 2020)**.** Some lipopolysaccharides (LPs) are obtained due to the binding of the COVID-19 virus with LPs of normal microbes in GIT (Follmer, 2020)**.** As a result of increasing LPs and inflammatory processes in GIT, the aggregation of α-Syn bodies in GIT increases. Then, it reaches the brain through vagal nerves and precipitates there. The α-Syn protein, Lewy bodies, is the primary marker of Parkinson's disease (Mahalaxmi et al., 2021). In

conclusion, we must pay more attention to this pathway to improve the prognosis of psychological diseases caused by COVID-19.

2.5 Ischemia

SARS-CoV-2, like any viral lung inflammation- reduces blood oxygenation. The most negatively affected organ by hypoxia is the brain, as the thirst and nervous tissue need a constant oxygen supply. This negative effect on the brain occurs through multiple routes: 1- recruitment of respiratory alkalosis that saturates arterial blood with oxygen by only 75%, causing fragility or weakness in neuronal activity. 2- accumulated reactive oxygen species cause oxidative damage to neuronal cells. 3- hypoxia induces the production of a pro-inflammatory cascade (Mahalaxmi et al., 2021; Verkhratsky et al., 2020).

Further examination of the brain tissues of ten dead COVID-19 patients revealed a global ischemic injury with the presence of ischemic neurons in the cerebellar Purkinje cells and CA1 hippocampal subunit. Fabbri and his research team interpret their observations that the hypoxic-ischemic is a normal consequence of respiratory failure during the infection (Fabbri et al., 2021). In eighteen brain autopsies of dead COVID-19 patients, hypoxic ischemia is detected in the cerebrum and cerebellum without evidence of viral load in CNS (Solomon et al., 2020). Another case series study was conducted in Germany on forty-three postpartum COVID-19 patients, and they found that by neuropathological examination of their brain tissue, 14% of cases had ischemic lesions in several regions surrounding cerebral arteries (Matschke et al., 2020).

2.6 Autoimmunity

Antiphospholipid autoantibodies (such as NMDAR, LGI1, CASPR2, GABAB1R, GABAB2R, AMPA1, AMPA2, Ri, Yo, Ma2, CV2, Hu, and amphiphysin) have been detected in COVID-19 patients (Virhammar et al., 2021; Zhang et al., 2020). Guillain-Barré and Miller-Fisher syndromes (types of autoimmune damage in CNS) have been diagnosed in COVID-19 patients (Verkhratsky et al., 2020). After the pandemic, the incidence of many inflammatory and autoimmune diseases in CNS elevated as an immunological consequence of COVID-19 as; autoimmune encephalitis, acute disseminated encephalomyelitis (ADEM), multiple sclerosis, post-infection-acute demyelination, and neuromyelitis optica spectrum disorder (NMOSD) (Motahharynia et al., 2022; Naser Moghadasi, 2021; Novi et al., 2020). The scientific community has hypothesised that autoimmune disorders of the central nervous system linked to COVID-19 (CRAD-C) would be unique and different from disorders unrelated to COVID-19. But that hypothesis requires further long-term cohort prospective studies to be proven or rejected (Naser Moghadasi, 2021).

Motahharynia and his colleagues received a sudden bilateral blindness case. The case was a 96-year-old woman with previous SARS-CoV-2 infection, and MRI showed demyelination and hyperintense lesion in the white matter. They interpret the case as a COVID-19-related autoimmune disorder of the central nervous system (CRAD-C) (Motahharynia et al., 2022). An Italian 64-year-old woman had bilateral vision impairment and loss of sensation in her right leg after a month of SARS-CoV-2 infection (Novi et al., 2020). Clinical investigations of both vision disorder cases showed that COVID-19-related neuromyelitis optical differs from the atypical form of the same disorders as the absence of anti-aquaporin-4 (anti- AQ4) or antimyelin oligodendrocyte glycoprotein (anti-MOG) antibodies in the serum of COVID-19-related cases (Motahharynia et al., 2022; Novi et al., 2020).

3.0 SARS-COV-2 AND THE BRAIN

After attention was drawn to the neurological symptoms reported in nearly one-third of hospitalised patients with COVID-19 (Mao et al., 2020), some studies have screened the CNS for the existence of the virus in some cases that exhibited neurological symptoms. It was found that the cerebrospinal fluid (CSF) (Benameur et al., 2020; Moriguchi et al., 2021), neuronal and capillary endothelial cells of frontal lobe brain sections from deceased persons with the infection were infected with SARS-CoV-2 (Paniz-Mondolfi et al., 2020). Hence, a demand to investigate the gateway and mechanisms of invasion and its effect on the CNS has emerged. The situation was not easy to be evaluated, and the available studies, despite being extensive, do not provide sufficient or comprehensive evidence. This is because the studies depend on either the analysis of autopsy brains of deceased patients by the virus or a few animal models. Therefore, the invasion gateways of the CNS by SARS-CoV-2 were proposed depending on the early investigations of the CNS invasion by similar pathogens of the same beta coronaviruses family. This family includes severe acute respiratory syndrome coronaviruses (SARS-CoV) and the Middle East respiratory syndrome coronaviruses (MERS-Co V) (Ng Kee Kwong et al., 2020). Thus, they are characterised by their neurotropism and neuro-invasion potential (Zhou et al., 2020).

SARS-CoV-2 could enter a human host cell by binding the viral spike S1 protein to the angiotensin-converting enzyme 2 (ACE2) receptor (Meinhardt et al., 2021). This interaction is very similar but with a higher affinity than SARS-CoV (Baig et al., 2020). ACE2 is a membrane receptor, considered the main entry gate for some human coronaviruses. It exhibits an enzymatically active binding domain on the cell surface, to which the S1 protein of the virus binds. After binding, priming is required by the host serine protease TMPRSS2 to facilitate the virus entry inside the cell by endocytosis and translocation (Hoffmann et al., 2020; Meinhardt et al., 2021). It is noteworthy that the ACE2 is expressed in several cell types, neuronal and non-neuronal cells, and its expression increases under certain physiological conditions and upon the virus invasion (Baig et al., 2020; Lu et al., 2020; Meinhardt et al., 2021). Generally, different virus strains have been reported to invade the CNS through various methods. Two major routes have been proposed by which SARS-CoV-2 invades the CNS: the transsynaptic and hematogenous models (Zhou et al., 2020).

3.1 Trans-synaptic (Invasion through the olfactory bulb)

Previous research suggests that SARS-CoV-2 invades the CNS through the olfactory bulb trans-synaptically like SARS-CoV, due to the high similarity between the two strains (Chaudhury et al., 2021; Meinhardt et al., 2021). Therefore, it has been revealed that the olfactory route might be the pathway through which SARS-CoV-2 gains access to the CNS as a result of a study carried out on the brains of 43 deceased persons with COVID- 19, together with monitoring the olfactory dysfunction of 751 hospitalised patients (Chiesa-Estomba et al., 2020). Moreover, another study on autopsy collected from 33 COVID-19 patients who died after the infection has suggested this route (Meinhardt et al., 2021). In addition, the assessment of the SARS-CoV-2 RNA load by RT-qPCR in different body systems revealed the existence of the viral RNA in the CNS. SARS-CoV-2 RNA was found chiefly in the olfactory bulb and/or medulla (Pairo-Castineira et al., 2021). The highest level of the viral RNA and spike protein was detected in the neurons of the olfactory mucosa in about two-thirds of the tested samples. Besides, the ACE2 receptor, to which SARS-CoV-2 is binding to invade the human host cell and the gene responsible for virus priming, TMPRSS2 (Hoffmann et al., 2020), is expressed in the olfactory epithelial cells, and hence might permit the entrance of the virus into the olfactory bulb, then into the CNS (Benameur et al., 2020). Together, these have raised the possibility that the olfactory mucosa might represent a gate for the virus to enter the CNS via the neuronal-mucosal interface by retrograde axonal transport machinery (Meinhardt et al., 2021; Pairo-Castineira et al., 2021). Consequently, this possibility explains the early onset of olfactory alterations in some COVID-19 patients due to the early viral arrival into the CNS through the olfactory bulb neurons (Giacomelli et al., 2020).

3.2 Hematogenous route: a route through the Blood-Brain Barrier

Although the BBB strictly protects the brain from various pathogens, some viral strains [such as human coronaviruses] as well as bacteria [such as E- Coli and S. pneumonia], could pass through the barrier and invade the CNS and consequently inducing pro-inflammatory responses (Koyuncu et al., 2013). Pathogens could transverse the BBB, mainly by three main mechanisms (Dahm et al., 2016); transcellular, paracellular, and the "Trojan horse" machinery. Transcellular passage is a mechanism by which the pathogen invades the endothelial cells of the BBB. During the paracellular passage, viruses invade the junctions between endothelial cells of the BBB. During the "Trojan horse" mechanism, infected phagocytes, such as neutrophils and macrophages, pass through the BBB (Dahm et al., 2016). Some investigations have proposed that SARS-CoV-2 may transverse the BBB by one or more of these mechanisms (**Figure 1). H**owever, further investigations are required to get a precise picture of SARS-CoV-2 passage through the BBB.

Direct infection of the BBB has been a possible entry route by which SARS-CoV-2 might invade the CNS. By applying the viral spike S1 or S2 protein on two (a 2-D and a 3-D vessel-like) in vitro models of BBB, the properties and integrity of the barrier were significantly altered, and this alteration is dose-dependent (Koyuncu et al., 2013). It is well known that the S1 (but not S2) viral protein subunit contains a receptor-binding domain (RBD) to bind to the host ACE2 receptor (Lu et al., 2020). However, both S1 and S2 protein subunits have modified the permeability and integrity of the BBB models. Therefore, it has been proposed that the ACE2 receptor is not a major demand for SARS-CoV-2 to breach the barrier since the S2 protein, which does not bind to the ACE2 receptor, also exerts a similar deleterious effect on the BBB (Koyuncu et al., 2013). The possibility of invasion by a direct viral effect on the BBB functionality is evident (**Figure 1**), which may explain the neuropathological implications associated with COVID-19.

The question now is, how could SARS-CoV-2 cross the BBB? The possible answer to this question is when circulating SARS-CoV-2 particles through the bloodstream gain access to the cerebral circulation and BBB (Baig et al., 2020). S1 and/or S2 viral proteins bind to the BBB endothelial cells causing significant alterations in the permeability and integrity properties of the barrier (Koyuncu et al., 2013).

4.0 COVID-19 AND SPECIFIC NEUROLOGICAL DISORDERS

The world has witnessed many consequences of the COVID-19 pandemic from 2019 till now. These consequences are not limited to the infected organ but extend to many biological systems, including the nervous system. It is believed that COVID-19 is implicated in accelerating nervous cell ageing and damage. The pandemic affects many neurodegenerative diseases, the incidence rate is elevated, and the prognosis of recent cases is accelerated and more complicated. Here is a list of affected neurodegenerative diseases by the pandemic.

4.1 Encephalitis

Although SARS-CoV-2 infection affects the respiratory system mainly, about 36.4% of COVID-19 patients develop neurological manifestations. Of the patient who experienced neurological symptoms, 45.5% had severe symptoms, and 30.2% had mild symptoms (Mao et al., 2020). Neurological symptoms ranged from mild symptoms such as headache and loss of smell and taste to severe diseases like encephalitis and CNS-mediated respiratory distress (Paterson et al., 2020). A recent study categorised the COVID-19-related neurological manifestations into five main groups: encephalopathy with psychological symptoms, inflammatory CNS disease like encephalitis, peripheral neurological diseases such as Guillain-Barré syndrome, brachial plexopathy, ischemic stroke, and different central disorders (Siow et al., 2021).

Encephalitis is an inflammation of the brain tissue accompanied by mental state alterations. In COVID-19 patients, encephalitis could happen due to viral infection or host immune response (Benameur et al., 2020). Encephalitis is one of the less common neurological symptoms of COVID-19 (Maury et al., 2021), it represents 0.1% to 3% of COVID-19 patients, and it could be raised to 6% in severely ill cases, and the patients could develop encephalitis within 14 days just after getting infected with COVID-19 (Benameur et al., 2020; Mehta et al., 2020). Although encephalitis is not a common neurological complication of the SARS-CoV-2 virus infection, it has a significant morbidity and mortality rate (13.4%), especially in severe cases (Benameur et al., 2020).

The exaggerated host-immune response against SARS-CoV-2 infection is one of the most characteristic features of COVID-19, which may include the life-threatening "cytokine storm" in the severely ill patient (Poyiadji et al., 2020). computerised tomography (CT) scan and magnetic resonance imaging (MRI) reports of a female COVID-19 patient with hemorrhagic necrotising encephalopathy have shown that the hyperactivation of the host immune response could develop severe inflammation of the brain tissues (Moriguchi et al., 2021) Just after the first signs of COVID-19 and up to 34 days, neurological complications begin to occur, including alteration in consciousness, seizure, delirium, neuropsychiatric changes, abnormal movements, and focal neurological signs (Mehta et al., 2020). A recent study reported that the examination of the CSF of COVID-19 patients showed a mild pleocytosis (white blood cells WBCS ≥ 5mm^3) in 17%, raised protein level (≥ 0.4 g/L) in 26% out of the study patient's number (Mehta et al., 2020; Siow et al., 2021).

The first reported case of a COVID-19 patient with encephalitis was described by T. Moriguchi et al. 2020, and it was for a young man aged 24 years old. He developed a fever, headache, and generalised fatigue on the first day after getting infected. On the 9th day, he developed altered consciousness, generalised seizures, and a coma. His blood analysis showed an increased number of white cells, decreased lymphocytes, the dominance of neutrophils, and increased C - reactive protein. The case was clinically diagnosed with viral meningitis-encephalitis. CSF analysis using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) proved SARS-CoV-2 infection, while the nasopharyngeal swab specimen analysis using the same technique was negative, suggesting that the neuropathology of COVID-19 may have an independent mechanism. This study revealed that unconscious patients might be infected with the SARS-CoV-2 virus and then could transmit the infection to others, so the study assumed that encephalitis might be a strong early indication along with respiratory signs to diagnose COVID-19 (Moriguchi et al., 2020).

4.2 Stroke

A stroke also called a cerebrovascular accident, is considered an emergency medical situation in which an acute compromise of cerebral perfusion or vasculature occurs (Owens, 2011). COVID-19 patients have a high

incidence rate of stroke, especially ischemic stroke. The leading causes of the development of ischemic stroke are atherosclerosis and deep vein thrombosis, which become more aggressive during COVID-19 infection. In addition to atherosclerosis, deep vein thrombosis can form a small thrombus. By this time, the cerebral arteries may be occluded by this small thrombus (David Spence et al., 2020). The leading cause of thrombus formation is high coagulation in COVID-19 patients, a well-known consequence of SARS-CoV-2 infection (Saei et al., 2020). The main two biomarkers shared between COVID-19 and ischemic patients are C-reactive protein in addition, D- dimer as they are biomarkers of inflammation and coagulopathy, respectively (Abdulkadir et al., 2020). In a Catalonian multicentric prospective study, ischemic stroke/concomitant COVID-19 patients have a high severe neurological deficit and high mortality rate compared with ischemic stroke patients without COVID-19 infection (Martí-Fàbregas et al., 2021).

4.3 Parkinson's disease (PD)

Cilia and colleagues carried out a community-based case-control study on PD patients who had been infected with COVID-19, where a cohort of patients with idiopathic PD and COVID-19 were compared to control PD subjects between 1 January and 4 May 2020. The study found that COVID-19 did worsen both motor and non-motor symptoms of PD. The authors of the aforementioned work suggested changes in the pharmacokinetics of dopamine-based therapy as the absorption of the drug decreases due to diarrhoea caused by the disease or due to the systemic inflammation that boosts nerve damage (Cilia et al., 2020). However, it is still recommended to study a larger population of PD patients with further examination of the cytokine levels and viral prevalence in the cerebrospinal fluid. Moreover, the feeling of loneliness, depression, and psychological stress caused by social distancing (Umemura et al., 2014) may also reduce the efficacy of dopaminergic medications (Bhidayasiri et al., 2020).

On the other hand, PD seems to be associated with a higher risk of COVID-19 symptoms, which are influenced by age, hypertension, diabetes, and dementia but not gender (Ahorsu et al., 2020). This could be due to the respiratory muscle rigidity and the impaired cough reflex coexisting with apnea leading to further deterioration and increased COVID-19 severity (Zach et al., 2017).

4.4 Alzheimer's disease

Alzheimer's disease (AD) is a chronic neurodegenerative disorder characterised by cognitive impairments. The accumulation of extracellular Amyloid-beta protein (Aβ plaques) and intracellular neurofibrillary tangles (NFTs) (tau tangles), as well as cholinergic neuron death, are major features of AD. In addition, AD has been recognised as an immunopathological disorder due to the inflammatory cascades reported with the disease progression, including microglia excitation, cytokine storm, and other pro-inflammatory mediators (Azizi et al., 2015).

Several studies, especially those carried out on postmortem brains of COVID-19 patients with severe neurological symptoms, revealed that AD progression and COVID-19 share similarities. Therefore, the possibility that persons who have experienced severe SARS-CoV-2 infections are at high risk of developing AD as a long-term consequence is highly concerning. This is partly due to the discovery of common factors in both diseases, such as AD biomarkers in the serum of some of the patients with severe COVID-19, some common genetic factors, oxidative stress, and innate immunity activation.

Frontera et al. (2021) investigated the correlation between severe COVID-19 and AD by measuring the levels of some AD biomarkers in the serum of 251 COVID-19 patients (Frontera et al., 2021). These patients exhibited neurological complications as infection consequences but no history of dementia. Total tau, tau-181, glial fibrillary acidic protein (GFAP), neurofilament light chain (NFL), ubiquitin carboxy-terminal hydrolase L1 (UCHL1), and amyloid-beta (Aβ) have been assessed in their serum and compared with non-COVID-19 controls and with AD patients. Surprisingly, nearly similar to AD, the levels of the assessed biomarkers are elevated in COVID-19 patients (Frontera et al., 2021). Of note, the elevated level of these biomarkers correlates to the infection's severity.

AD is associated with oxidative stress due to the increased production of Reactive Oxygen Species (ROS), which are toxic to neurons and cause neuronal death. Oxidative stress has also been proposed to be strongly associated with the severity of COVID-19 (**Figure 2**). Some efforts have firmly attributed possible neuron apoptosis to oxidative stress due to severe SARS-CoV2 infection (Barciszewska, 2021). On the one hand, a cytokine storm is induced as an innate immune response to the virus infection and activates microglial cells. This microglia activation produces ROS, causing

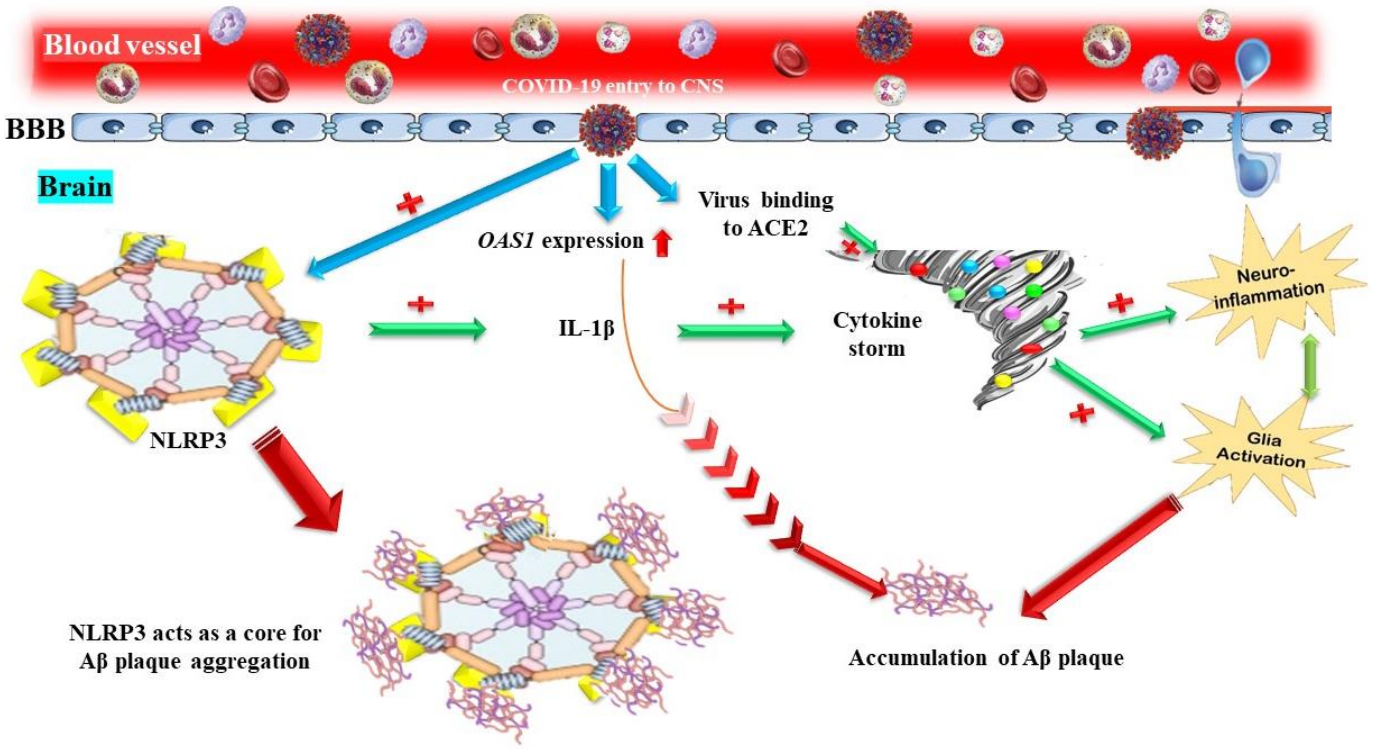

Figure 2: SARS-CoV-2 infection and the pathway of AD progression as a long-term consequence. The pathway involves (a) Entry of SARS-CoV-2 to the brain via the BBB. (b) Induction of NLRP3 as a result of breaching the CNS by the virus. (c) Triggering of innate immunity by NLRP3 and the activating IL-1β. (d) Neuroinflammation and glial activation in response to the cytokine storm. Glial activation again leads to more neuroinflammation, and then the increased neuro-inflammation over-activates the glial cell in a long-lasting mutual orchestra. (e) Upregulation of the OAS1 gene (Also known to be a genetic risk for AD). (f) Increased ACE2 receptor expression to facilitate virus binding to the cells. (g) An accumulation of Aβ plaques (a hallmark of AD) as long-term expectations of the event cascades of virus infecting the CNS.

oxidative stress**,** neurotoxicity, and neuronal apoptosis (Barciszewska, 2021).

On the other hand, it has been reported that SARS-CoV-2, when binding to the ACE2 receptor, disrupts the signalling pathway of this receptor (Ding et al., 2020) (**Figure 2**). ACE2 receptor signalling pathway is known to counteract oxidative stress, and its interruption increases oxidative stress (Alomari et al., 2020). Hence, the virus binding produces excessive oxidative stress, potentially leading to the degeneration of dopaminergic neurons or impairment of cholinergic pathways and possible AD progression (Alomari et al., 2020). In line with this, it has been revealed that the expression of the ACE2 receptor is upregulated significantly in several brain regions of COVID-19 patients and also of AD patients compared to controls of the same age and gender (**Figure 2**), suggesting that both diseases show an interrupted ACE2 receptor gene expression (Lim et al., 2020)**.**

Both diseases are immunopathological disorders which induce innate immunity and pro-inflammatory mediators. The nucleotide-binding domain and leucine-rich repeat pyrin domain-containing 3 (NLRP3) is an inflammasome known to be triggered by AD progression (Pennisi et al., 2017). Some studies on animal models have revealed that severe SARS-CoV-2 infection also induces NLRP3 (Pan et al., 2021). In AD and COVID-19 patients, it is proposed that the induced NLRP3 activates the pro-inflammatory mediator IL-1β, which in turn triggers a cytokine storm as an innate immunity response. In general, the activation of innate immunity and the induction of some pro-inflammatory mediators, such as IL-6, IL-8, IL-1β, TNF-α and chemokines, have been reported in both disorders (Wang et al., 2021)**.** The induced pro-inflammatory mediators trigger neuroinflammation; hence, a possible neuronal death is suggested (**Figure 2**).

Besides, it is strongly suggested that AD might be evolved post-COVID-19 as a long-term consequence in patients who experienced cognitive symptoms during the SARS-CoV-2 infection. Bulk work has suggested the involvement of innate immune responses in both diseases, and this is greatly supported by the investigation of common inflammatory mediators between severe COVID-19 and Alzheimer's disease. In line with this, both AD and COVID-19 patients exhibit cognitive impairments. In addition, neurodegeneration is a characteristic of the progression of both diseases.

4.5 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease known as motor neuron disease; it is deadly and characterised by muscle weakness, spasms, respiratory failure, and communication disorder, and it may also display paralysis. It shows an incidence of about 2.76 per 100,000 people and a prevalence of 9.62 cases in every 100,000 people worldwide, and this is due to degeneration of the motor neurons' function in the brain and spinal cord (Hu et al., 2021; Hulisz, 2018).

A study has reported a worsening and rapid decline in the ALSFRS-R score (Revised Amyotrophic Lateral Sclerosis Functional Rating Scale) after being positive for SARS-CoV-2 in a few months. ALSFRS-R score measures 12 aspects of physical function; speech, salivation, swallowing, handwriting, walking, climbing stairs, dyspnea, orthopnea, respiratory insufficiency, dressing, and hygiene, turning in bed and adjusting bed cloths and cutting food, with a maximum total score of 48 (normal) and minimum total score of zero (no ability), and they theorise COVID-19 ability to trigger neuroinflammation (Li & Bedlack, 2021). After the postmortem analysis of ALS patients and the detection of viral particles in the patient's serum and brain tissues, the infection could have an essential role in ALS pathology. SARS-CoV-2 demonstrates the capacity to activate microglia and reactive oxygen species (ROS) production because of activation of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) enzyme, which in turn produces superoxide anion (O^{-}_{2}) leads to excessive inflammation (Sindona et al., 2021).

COVID-19 indirectly accelerates ALS progression by interrupting rehabilitation routines such as physiotherapy and speech therapy due to the lockdown. The outpatient follow-up visits for patients have been suspended, and the management of ALS patients has become complicated because of the lack of constant medical and psychological support for months. This interruption may negatively impact the ALSFRS-R score, leading to some ALS patients increasing fatigue and declining motor skills in just two months, which results in telehealth technologies incorporated into the practice of neurology and help in some ALS patients' management (Gonçalves & Magalhães, 2021).

4.6 Multiple sclerosis

Multiple Sclerosis (MS) is a persistent immunological demyelination disease that affects CNS (Dolati et al., 2018). It may lead to a range of potential symptoms, such as movement (tremors and shaking) (Hatteb & Daoudi, 2018), vision (Sanchez-Dalmau et al., 2018), and balance (Tona et al., 2018). The MS diagnosis depends mainly on magnetic resonance imaging (MRI) which detects the foci in the white matter of MS patients. There are also many biomarkers for MS diagnosis, such as the CSF level of oligoclonal bands (OCB) (Arneth & Kraus, 2022). It has been shown in many reports of COVID-19 in MS patients that clinical characteristics do not differ greatly in COVID-19 patients with MS from non-infected MS patients (Louapre et al., 2020; Moss et al., 2020; Safavi et al., 2020; Sormani, 2020).

Few studies have shown a link between MS treatment and the emergence of COVID-19, but it has been found that most disease-modifying therapies (DMTs) have little to no effect on the innate immune system, which is responsible for the body's first line of defence against infections, and thus do not increase susceptibility to SARS-CoV-2 (Baker et al., 2020). No clear association of COVID-19 with immunotherapy or with the use of low or high-efficacy therapies was found, which is consistent with some of the reported experiences in MS and other autoimmune diseases (Montero-Escribano et al., 2020). However, some studies suggest that amongst anti-CD20-treated patients, COVID-19 susceptibility was higher in patients treated for a more extended period (median duration 2.8 years in COVID-19 vs. 1.2 years in non-COVID-19); moreover, some of the MS patients present low IgG levels, and it is known that IgG hypogammaglobulinemia is more frequent with repeated infusions, which could potentially contribute to the infection susceptibility (Luna et al., 2020).

4.7 Creutzfeldt- Jakob disease (CJD)

CJD is one of the rare ageing diseases. Its incidence is 1:1000,000 worldwide, but the highly complicated interaction between COVID-19 disease and neurological symptoms predicts a rise in neurodegenerative diseases (Nasiri et al., 2021). 90% of CJD patients die through the first year of disease occurrence (Young et al., 2020). The pathophysiological causation of CJD is the recruitment

of an unusual isoform folded abnormally of prion protein (sialoglycoprotein) (Nasiri et al., 2021; Young et al., 2020). This disease is characterised by an elevated lactate dehydrogenase level in CSF, a common factor with COVID-19 (Nasiri et al., 2021).

During the COVID-19 pandemic, two cases were diagnosed with both diseases (COVID-19 and CJD); however, they were healthy individuals before the COVID-19 infection. Nasiri (2021), Young (2020), and their research team anticipated the occurrence of these cases due to the recruitment of inflammatory cascades, including IL-1, TNF-α, and complement component (C1q) as an immune response to COVID-19. These cascades' abundance leads to activating a neurotoxic A1 astrocyte, the epicentre of an accumulated abnormal form of prion protein- subsequently forming a neuroinflammatory phenotype feature propagating CJD (Nasiri et al., 2021; Young et al., 2020).

4.8 Guillain- Barré syndrome (GBS)

Guillain- Barré syndrome is an autoimmune disease that attacks peripheral cells in the central nervous system (Trujillo Gittermann et al., 2020). The major symptoms of this syndrome are ascending weakness, loss of deep tendon reflexes, and sensory deficits. Acute flabby palsy is one of the consequences of Guillain- Barré syndrome. The major biomarker of this syndrome is an elevated level of dissociated cytological albumin in CSF (Abu-Rumeileh et al., 2021). Many pathologic bacteria and viruses are involved in GBS incidence as Epstein–Barr virus, cytomegalovirus, varicella-zoster virus, and Mycoplasma pneumonia. (Costello & Dalakas, 2020). About 67% of cases suffer from respiratory and gastrointestinal infections before GBS (Yuki & Hartung, 2012). According to SARS-CoV-2, Fantini and his research team used structural and molecular modelling approaches to prove an interaction between the N-terminal of spike and gangliosides (Fantini et al., 2020). These facts increase the possible role of COVID-19 in GBS.

The most accepted hypothesis of the pathophysiology of GBS depends on the analogy between ganglioside (one of the peripheral nerve components) and lipopolysaccharide (the main component of the infectious agent). This analogy perturbs the host immune system to attack gangliosides rather than infectious agents (Dalakas, 2020; Yuki & Hartung, 2012).

Paybast and his colleagues examined 2 cases (38-years old man and his 14-years old daughter) suffering from GBS symptoms after recovery from COVID-19 (Paybast et al., 2020). In a case report published by Sedaghat and her colleague, 63-years old male COVID-19 patient showed manifestation of GBS after two weeks of infection (Sedaghat & Karimi, 2020). A case series of five COVID-19 patients followed by GBS were declared by Toscano (Toscano et al., 2020). In a retrospective multicentered study conducted by Filosto and his research team, 30 GBS patients with positive COVID-19 were diagnosed in different regions in Italy. This study concluded a significant elevation in GBS incidence over one year by 2.6-fold (Filosto et al., 2021). Gigli et al. revealed that the incidence of GBS elevated during the pandemic by 5.41-fold in 2020 (Gigli et al., 2021).

A systematic review included 52 studies that incorporate a total of 73 patients presented with GBS with varying severity of COVID-19, albuminocytological dissociation was detected in CSF in about 71% of cases. The primary form of GBS associated with COVID-19 is acute inflammatory demyelinating polyneuropathy (AIDP). But this review failed to determine the time of GBS incidence if it precedes or simultaneously COVID-19 infection (Abu-Rumeileh et al., 2021). The feature of GBS differs significantly after the pandemic. The damage in cranial nerves associated with a demyelinating in peripheral nerves was not commonly manifest in GBS cases before the pandemic, but it only appeared in 5% of cases. On the other hand, during the COVID-19 pandemic, the cranial nerve damage was detected in 47% of the patients (Trujillo Gittermann et al., 2020). So, COVID-19-associated GBS cases have a com high level of demyelination and thus are in more advanced stages than non-COVID-19 GBS ones (Filosto et al., 2021). Only one study rejects the presence of a significant causative relation between COVID-19 and GBS. Their results may be due to the high GBS treatment rate and high level of precautionary level measures against COVID-19 in the UK (Country of study) (Keddie et al., 2021).

5.0 HOW TO DIAGNOSE CNS INVASION BY COVID-19?

CNS injury biomarkers can be detected in COVID-19 patients, confirming a correlation between SARS-COV-2 infection and neurodegeneration. These findings motivate the recommendation to use these markers as indicators of the stage of SARS-COV-2 infection and its further complication in the brain. Many observational and prospective studies were performed to detect CNS injury during COVID-19 infection; Johan Virhammer and his research team prospectively studied nineteen COVID-19 patients with neurological symptoms and estimated the CSF level of several CNS injury biomarkers (neurofilament light chain [NfL] protein, glial fibrillary

Table 1: Summary of biomarkers that can be used to detect neurodegenerative consequences in COVID-19 patients

Biomarker	Sample type	Observation	References
Neurofilament light chain (NfL)[a] (As axonal injury evidence)	CSF plasma	• Elevated in COVID-19 cases • Their elevation in COVID-19 is related to many factors • There is a higher level in 20% of COVID-19/ encephalitis cases	(Edén et al., 2021; Frithiof et al., 2021; Kanberg et al., 2020) (Virhammar et al., 2021) (Pilotto et al., 2021)
Glial fibirally acidic protein (GFAP) (Astrocytic injury biomarker)	Plasma	• There is a higher level in 16% of cases • Present at a higher level in 40% of COVID-19/ encephalitis cases	(Frithiof et al., 2021; Kanberg et al., 2020; Virhammar et al., 2021) (Pilotto et al., 2021)
Total Tau	CSF plasma	• Elevated in COVID-19 cases • A higher level was found in 37% of cases • Nearly the level is higher in 16% of COVID-19/ encephalitis cases	(Frithiof et al., 2021) (Virhammar et al., 2021) (Pilotto et al., 2021)
Neopterin (Microglia and astrocytes activation biomarker)	Serum CSF	• Elevated in COVID-19 cases	(Edén et al., 2021)
β2-microglobulin (β2M) [b]	CSF	• Elevated in COVID-19 infection	(Edén et al., 2021; Pilotto et al., 2021)
Interleukin 8 (IL8)	CSF	• Elevated in COVID-19/ encephalitis cases	(Pilotto et al., 2021)
Tumor necrosis factor-α (TNF- α)	CSF	• Elevated in COVID-19/ encephalitis cases	(Pilotto et al., 2021)
Triggering Receptor Expressed on Myeloid cells 2 (TREM-2) (Microglia activation biomarker)	CSF	• Nealy higher in 13% of COVID-19/ encephalitis cases	(Pilotto et al., 2021)
Human cartilage glycoprotein-39 (HC-gp39) (also called chitinase-3-like-1 (CHI3L1) and (YKL-40) [c]	CSF	• YKL-4 presented at an abnormal level in CSF of COVID-19/Enc cases	(Pilotto et al., 2021)
Spike protein [d]	CSF brain tissues	• By Immunohistochemistry, the viral spike can be detected.	(Kumari et al., 2021; Matschke et al., 2020; Virhammar et al., 2021)
Viral load	Olfactory bulbs and brain tissue Autopsy samples	• After (5-6) days of COVID-19 infection by inhalation in mice, a high level of viral load was detected • SARS-CoV-2 was detected in the brain of 53% of total autopsy samples	(Kumari et al., 2021) (Matschke et al., 2020)

(a) Neurofilament light chain (NfL): Structural component of myelinated axons.
(b) β2-microglobulin (β2M): One of the histocompatibility complex class I molecules.
(c) Human cartilage glycoprotein-39 (HC-gp39): astrocytes and microglia produce this glycoprotein in case of neuroinflammation and encephalitis.
(d) Spike protein: Viral protein responsible for receptor recognition and cell membrane fusion process.

Table 2: Host genetic predispositions to neurodegenerative disease

Gene	Variants	Effect	References
oligoadenylate synthetase 1 (OAS1)	rs1131454 rs10735079 rs4766676 rs6489867	OAS1 variants are involved in the high incidence of Alzheimer's disease and severe stage of COVID-19 by mediating the myeloid cells' pro-inflammation state.	(Magusali et al., 2021; Singh et al., 2021)
IL6	rs140764737 rs142164099 rs2069849, rs142759801 rs190436077 rs148171375 rs13306435	implicated in many neural pathogenic mechanisms associated with COVID-19	(Singh et al., 2021; Strafella et al., 2020)
IL6R	rs2228144 rs2229237 rs2228145 rs28730735 rs143810642		
ApoE	*ApoE e4*	ApoE e4 (homozygous form) is significantly correlated with cognitive symptoms during COVID-19 infection	(Goldstein et al., 2020; Kuo et al., 2020; Williams et al., 2020)
Exosomal transcription factors	*(LITAF, IRF2, IRF9, PHF11, ZNF385A, MIER1, SP140L, BCL3, STAT4, NFKBID, TRIM22, JUND, STAT1, BLOC1S1, SP110, TRIM38, MXD1, SP140, and HESX1)*	Exosomal transcription factors regulating neurodegenerative genes during COVID-19 infection	(Ahmed et al., 2021)
ACE	rs4646994 (289 bp insertion/ Deletion)	This deletion variant is considered a protective factor against COVID-19 as it leads to a reduction in *ACE2* expression	(Delanghe et al., 2020)

acidic protein (GFAP), and total tau). They found that the elevation in CSF level of NfL occurs in 63% of cases depending on the severity of COVID-19 infection and level of consciousness. CSF level of total tau elevates in 37% of cases with GFAP elevated in 16% of cases (Virhammar et al., 2021). Arvid Edén and his colleagues performed case series on six COVID-19 patients with neurological symptoms. They detected the CSF level of the following parameters: NfL, Neopterin, and β-microglobulin. They found that NfL CSF level is elevated in half of the cases. On the other hand, Neopterin and β-microglobulin levels are elevated in the serum and CSF in all cases (Edén et al., 2021). Robert Frithiof and his neuroscientist team conducted a cohort observational study on eleven COVID-19 patients with critical illness polyneuropathy/myopathy (CIN/CIM) in a care unit compared to seven COVID-19 patients without CIN/CIM. They concluded that the plasma level of NfL, GFAp, and total tau is significantly elevated in CIN/CIM COVID-19 patients group compared with COVID-19 patients without CIN/CIM (Frithiof et al., 2021). Nelly Kanberg and her research team conducted an observational study on different stages of COVID-19 disease; (severe n=18, moderate n=9, and mild n=20) compared with 33 age-matched controls. They found that there is a slow increase in plasma level of NfL through the follow-up of cases, so it can be considered an indicator of the consequences of CNS injury as the axonal injury is a progressed later step. Their results concluded that the Early peak of GFAP concentration in plasma, followed by a decrease in it, indicates early astrocytic injury (Kanberg et al., 2020). Andrea Pilotto's research team (2021) designed an observational study as follows; three study groups; COVID-19 with encephalitis cases (COVID-19/Enc) (n=30), encephalitis cases (n=21), and healthy control group (n=18). This study aimed to determine the level of many cytokines and neuroinflammatory biomarkers in CSF cases (Pilotto et al., 2021). All findings and significant results of the aforementioned studies are summarised in **Table 1.**

6.0 GENETIC INSIGHT

The susceptibility and the outcome of many diseases are a manifestation of many genetic factors. It implies that

genetic polymorphisms between individuals can affect diseases' progression, including SARS-CoV-2 and neurodegenerative diseases. Genetically corresponding COVID-19 patients have the same prognostic consequences (Sang et al., 2021)**.** Many immunogenetic factors have been studied to reveal their contribution to the neural consequences of COVID-19 and are summarised in **Table 2**. (Magusali et al., 2021; Pairo-Castineira et al., 2021)**.**

7.0 CONCLUSION AND PERSPECTIVES

SARS-CoV-2 has become a fruitful field of study for neuroscientists and neurologists. Neurological symptoms manifestations in a large proportion of COVID-19 patients have been questioned for the emergency intrusion of neuroscientific research to elucidate the possible explanations of the matter. An early explanation of the issue was dependent on the fact that SARS-CoV-2 is very similar to the other strain of SARS-CoV; therefore, it has been believed that SARS-CoV-2 is neuro-invasive like SARS-CoV and that SARS-CoV-2 could enter the host cell by binding its spike S1 protein to ACE2 receptor on the host cell with the aid of TMPRSS2 for priming. Dependently, possible routes of the virus entry into the CNS have been investigated.

When SARS-CoV-2 crosses BBB and enters the CNS, it induces an innate immune response. Consequently, cytokine storms, as well as reactive glia, are triggered. As a result, pro-inflammatory mediators are induced and may have a deleterious effect on the neurons by further activating glial cells, hence, neuronal toxicity and apoptosis. Thus, it has been accepted that severe COVID-19 patients are at high risk of neurodegenerative disorder, especially AD, as a long-term consequence of SARS-CoV-2 severe infection.

The likelihood of post-COVID-19 progression of neurodegenerative disorders has been explained by evaluating the shared factors between neurodegenerative diseases and severe COVID-19. However, more investigations are needed, and some questions must be answered. To our knowledge, few investigations have been carried out to elucidate the transcription factors and/or genes that might be implicated in post-COVID neurodegeneration. Moreover, it is unknown which comes first and is considered the primary filament for neurodegeneration; neuroinflammation or neuronal infection.

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