9 Neuropharmacological Mechanisms of SARS-CoV-2

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INTRODUCTION

Coronavirus is mainly responsible for respiratory illness in humans. The word "corona" originated from crown-like spikes present on the surface of the virus. This virus was initially detected in bats, cats and camels. From there, it further mutated and infected other species, one of which was humans. These viruses are RNA viruses (enveloped, positive-sense, single-stranded RNA viruses that were first isolated from humans) (Tyrrell and Bynoe, 1966). They have been studied extensively for decades and found to spread diseases like severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS) and the common cold (Chowdhury and Oommen, 2020).

The virus mutated over a period of time and recently emerged as the causative agent of a novel highly contagious viral disease, which was identified in humans in Wuhan, Hubei, a city in China. The disease was declared a pandemic in March 2020, and the virus was named the "2019 novel coronavirus" (2019-nCoV) or human coronavirus 2019 (HCoV-19/hCoV-19) (Zhu *et al*., 2020). In February 2020, it was renamed "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). This name was adopted as the official name by the International Committee on Taxonomy of Viruses (ICTV). SARS-CoV-2-induced infection was recognized by the World Health Organization (WHO), and it was termed "coronavirus disease 2019" or "COVID-19," and was subsequently declared a pandemic in March 2020 (WHO, 2020).

After originating in China, the first case reported was from Thailand, which was preceded by the spread of the infection globally within a few months, except Antarctica (WHO statement on novel coronavirus in Thailand, 2020). The virus spread at an alarming rate, with high morbidity and mortality among infected patients by the end of 2020 (WHO: COVID-19 Dashboard; Ministry of Health and Family Welfare). The SARS-CoV-2 virus has a complex physiological nature, and the behaviour of this viral organism should be understood in order to comprehend its pathophysiology. The next paragraph explains the disease caused by SARS-CoV-2 (COVID-19), along with its main signs and symptoms.

SARS CoV-2 is a novel β-coronavirus capable of causing severe respiratory illness in humans (Cascella *et al*., 2022) and it is the main causative agent of COVID-19 disease. The symptomatic manifestation of COVID-19 includes fever, dry cough, breathlessness and severe infections like pneumonia (severe infection) (Wang *et al*., 2020). Initial stages of infection may be identified by the loss of sensory responses, such as loss of taste and smell in the infected patient. Other symptoms

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include diarrhoea (gastrointestinal distress), cardiovascular abnormalities, and minor symptoms such as headache, nausea, vomiting, impaired consciousness, encephalitis and acute cerebrovascular diseases (including stroke, venous sinus thrombosis and intracerebral haemorrhage) (Spudich and Nath, 2022). As the disease progresses and the patient gets proper rest and medication, the symptoms dampen, but the story doesn't end here. It comes with a number of post-disease complications. The most common and prevailing post-COVID symptoms involve respiratory diseases and neurological issues (ranging from mild headache and delirium to severe neurological disorders) in recently recovered individuals. Since the lungs were the most affected part of the body during the initial stages of the pandemic, doctors only focussed on monitoring the lung condition of the patient. The major goal of the physicians was to keep the patient alive by maintaining normal lung health. Although respiratory symptoms were maximally reported, brain-related symptoms were also observed and reported (Yu *et al*., 2020). Over time, people became more aware of the changes occurring in the brain after the COVID pandemic, and awareness about this aspect of post-COVID complications increased (Wu et al., 2020). This chapter highlights the pathophysiological changes occurring in COVID patients post-recovery.

The reported symptoms of neurological changes post-COVID (post-SARS-CoV-2 infection) range from simple delirium to brain stroke, haemorrhage, memory loss and lifelong brain damage. The main problem currently faced by physicians is the lack of information regarding the basic underlying mechanisms leading to these neurological changes post-COVID. As there are a plethora of aspects that may be the cause of these neurological changes, there is a need to study the pathology of the virus along with the different pathophysiological mechanisms related to the neurological conditions faced by the patients. This chapter gives insight into the pathology of the virus as well as the different mechanisms related to neurological changes occurring after the pandemic hit the world.

SARS-COV-2

Classification

Family: Coronaviridae. Subfamily: Coronavirinae. Genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. Genome size of CoV: 27–32 kb [a single-stranded positive-sense RNA (+ssRNA)] (Brian and Baric, 2005).

Structure

SARS-CoV-2 has a capsid made up of nucleocapsid (N) protein and contains an envelope that is made up of three structural proteins, namely, spike (S) protein, membrane (M) protein and envelope (E) protein (Brian and Baric, 2005).

Transmission of SARS-CoV-2

S protein is the entry target of the virus responsible for binding to the host angiotensin converting enzyme 2 (ACE-2). It is the antigenic component of the virus (Figure 9.1). S protein has two subunits. One is the S_1-membrane binding subunit which binds to the host cell receptor, and the other is the S_2-membrane fusion subunit which is responsible for the fusion of viral and host-cell membranes (Huang *et al*., 2020; Letko *et al*., 2020). After binding to the ACE-2 receptor, the S protein undergoes proteolytic cleavage catalyzed by a host membrane-anchored protein. It is a type 2 transmembrane (TM) serine protease enzyme (present on the surface of the host cell), i.e., TM protease serine 2 (TMPRSS2), which is responsible for the activation of the S protein. Activation of this protein facilitates the entry of the viral contents inside the host cell as the TMPRSS2 protein

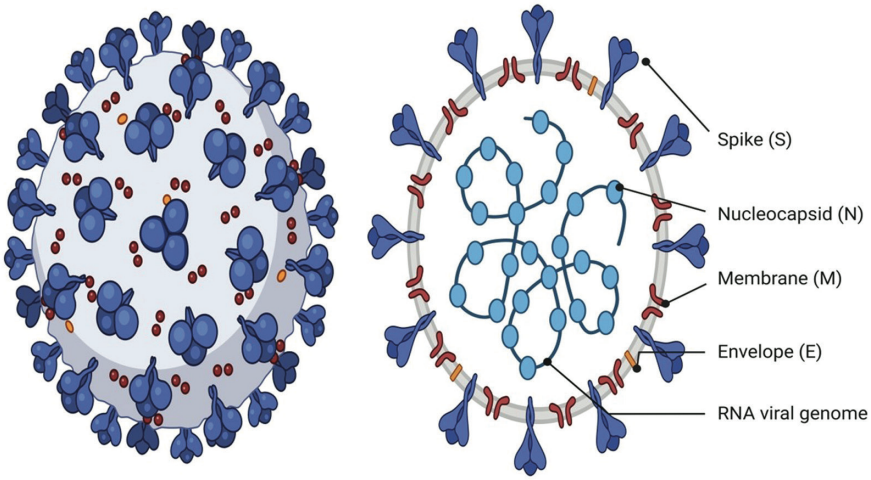


FIGURE 9.1 Structure of SARS-CoV-2: Double-layer enveloped viral genome along with nucleocapsid (N) and three membrane-bound structural proteins: spike (S) protein, membrane (M) protein and envelope (E) protein.

causes conformational changes in the structure of the S protein necessary for viral and host cell–membrane fusion (Jackson *et al*., 2022).

After fusion of the membranes, viral RNA is released inside the host cell. The RNA strands replicate and form new proteins. These new proteins are then carried to the endoplasmic reticulum (ER) by the N protein. The nucleocapsids are formed and are further transported to the lumen, and then ultimately to the Golgi vesicles. In the end, the viral content moves to the adjacent cells through exocytosis and also to the upper respiratory tract for community spread of the COVID infection (Figure 9.2).

The early phases of viral infection in the human body remain confined to the lungs and upper respiratory tract. The interaction of immune cells with the infected epithelial cells decides the extent of spread of the viral infection as the immune cells activate cytokine signalling pathways. The transcription factors activated by the immune cells in the lungs after interacting with the infected epithelial cells include interferon regulatory factors (IRFs) and the nuclear factor-κB (NFκB). IRF activation further activates interferons (IFNs)—IFN I and II and IFN genes. IFN genes are responsible for host-cell defence system activation (activation of antiviral proteins of the defence system of host cell).

NFκB activates various pro-inflammatory cytokines and chemokines, which further activate specific types of leucocytes. The virus also activates pro-inflammatory cytokines by triggering inflammasomes. These inflammasomes are multiprotein complexes containing caspase-1 protein. Caspase-1 is responsible for the cleavage of precursor molecules and activation of ILs like IL-1β and IL-18. The viral gene has certain proteins, including non-structural protein-1 (NSP-1), accessory proteins (ORF 6 and ORF 3B) and the nucleocapsid. All these proteins of the viral genome inactivate the signal transducer and activator of transcription-1 protein (STAT-1), which decreases IFN synthesis in the host cell and thus the infection prevails and spreads.

As all these actions have been initiated after the binding of S protein to the host cell receptor protein (ACE-2) present on the cell surface. This special type of protein is responsible for the entry of the viral content into the human body and the different sites where this protein is present, making it feasible for the virus to invade different human body systems easily.

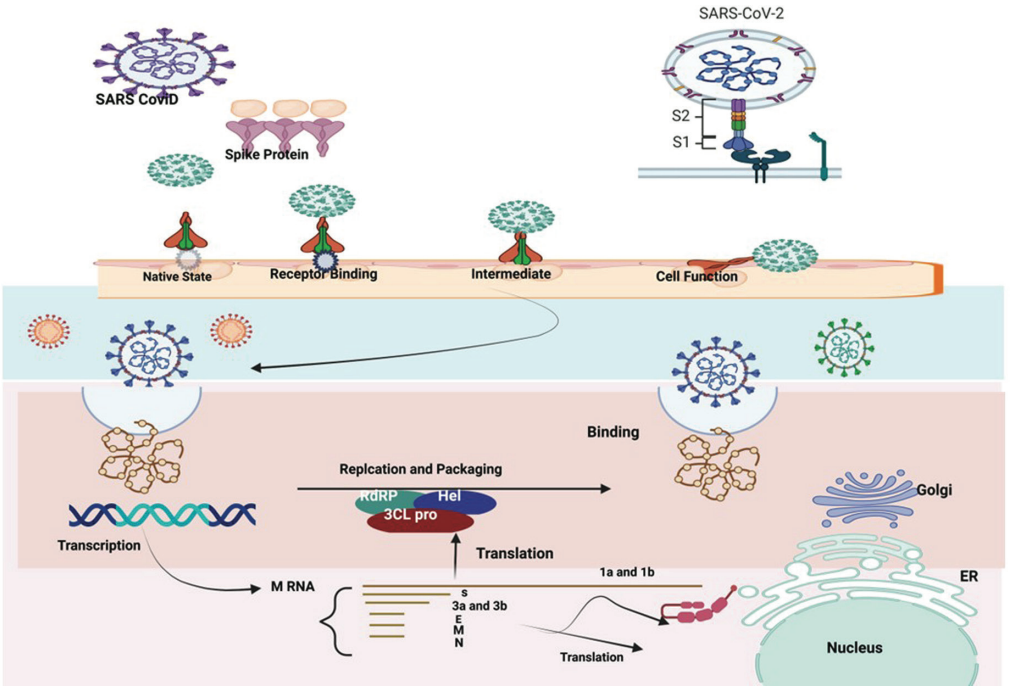


FIGURE 9.2 Transmission of SARS-CoV-2 inside the human body.

ACE-2

ACE-2 is a cell surface protein primarily expressed in the ciliated epithelium of the nasopharynx, respiratory tract (upper respiratory tract), epithelial layer of the bronchi and bronchioles, mast cells, macrophages, monocytes, and vascular endothelial cells. ACE-2 receptors are present in abundance in the lungs, followed by the brain, liver, kidney and heart (Cheng *et al.*, 2007).

These receptors are primarily present in the respiratory system, which is why lungs are the major site for infection due to COVID-19. The brain is the second most affected human body organ. This chapter includes a detailed insight into the neurological pathophysiology of SARS-CoV-2 (Zhang *et al.*, 2021).

PATHOLOGICAL ASPECTS UNDERLYING SARS-COV-2-INDUCED NEUROLOGICAL CHANGES

SARS-CoV-2 is selective in affecting the human body. It may enter the brain tissues using different mechanisms, including directly invading the CNS, by binding to the ACE-2 receptor proteins, through an outburst of ILs (hyperactivity of the immune system) by inducing hypoxia (leading to CNS invasion of the virus) and certain miscellaneous factors (Guadarrama-Ortiz *et al.*, 2020).

Direct CNS Invasion

SARS-CoV-2 virus has been reported to affect the brain directly as well as indirectly (Koyuncu *et al.*, 2013; Leber *et al.*, 2016). The direct invasion pathway includes two further types of subpathways: the haematogenous pathway (blood circulation pathway) and the neuronal pathway (olfactory pathway).

Haematogenous Route (Blood Circulation Pathway)

Primary infection is followed by invasion of the virus into the bloodstream. It is the phase when the virus is present in the bloodstream, and it finally moves to the brain (Keyhanian *et al*., 2021).

This virus can potentially disrupt the epithelial barrier of the respiratory system and attack the bloodstream. As ACE-2 receptors are primarily housed on the surface of type II alveolar epithelial cells, these cells are the primary victims of SARS-CoV. The virus breaks through the alveolar cells and enters the blood circulation.

Gastrointestinal (GI) epithelial cells also contain ACE-2 receptors; thus, the GI tract may also play a crucial role in infecting the bloodstream with SARS-CoV-2 (Sia *et al*., 2020).

Neuronal Pathway (Olfactory Nerve Pathway)

Invasion of the nerves of different areas of the human body is the easiest way to invade the brain and thus the CNS. Olfactory neurons are directly connected to the nasal cavity (van Riel *et al*., 2015; Butowt and Bilinska, 2020) and many viruses target the brain using this very pathway, avoiding the blood–brain barrier (BBB) (Bryche *et al*., 2020).

The olfactory neuron dendrites are projected in the nasal cavity, and the axons extend up to the olfactory bulb of the brain through the lamina cribrosa (Figure 9.3) (van Riel *et al*., 2015). ACE-2 and TMPRSS2 proteins are present in the olfactory epithelial cells, thus they can also be a possible route of invasion of the virus into the CNS (Bilinska *et al*., 2020; Kanageswaran *et al*., 2015). Anosmia may be a symptom that surfaces due to the invasion of the SARS-CoV-2 virus through the olfactory pathway (Figure 9.3). The viral content has also been reported to be present in the trigeminal nerve branches (Figure 9.3).

The nerves of the nasal mucosa also connect to the trigeminal ganglion, and thus they connect to the trigeminal nerve. Viral invasion and damage to these nerves may be responsible for anosmia and headache in COVID-19 patients, and it may also lead to neuronal damage and necrosis, ultimately causing cognitive impairment (Figure 9.3).

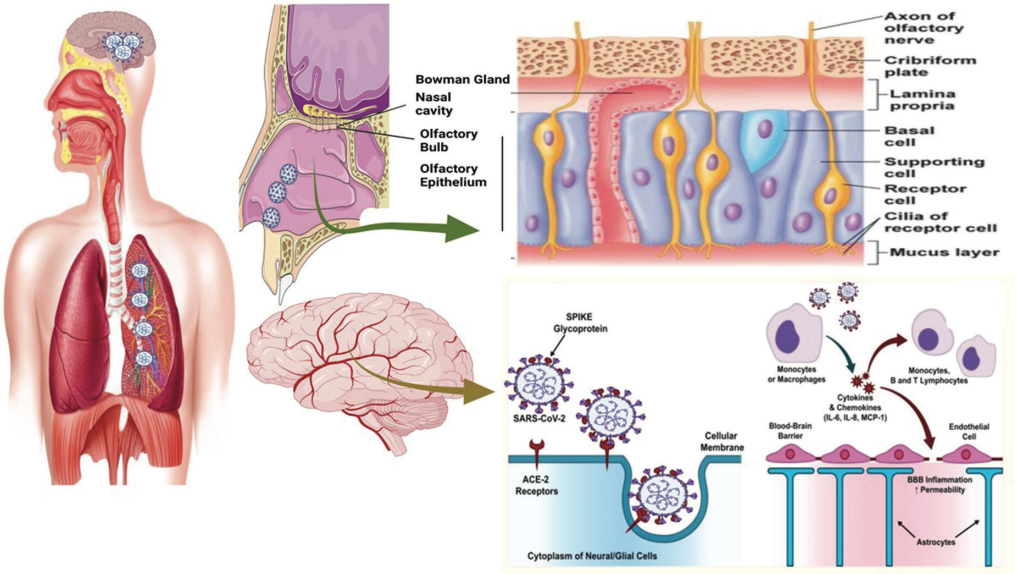


FIGURE 9.3 Different areas of the CNS affected by viral infection after invasion in the human body and the mechanism of neurological spread of the SARS-CoV-2 virus: (a) via ACE-2 receptor binding; and (b) via cytokine flood due to a hyperactive host immune system.

ACE-2-Mediated CNS Infection

It is well known that the initial infection occurs in the lung epithelial tissues and spreads further to adjacent tissues and other organs depending on the availability of receptors (ACE-2 in the case of SARS-CoV-2) required for the binding and fusion of the virus to the host cell. Recent studies have reported that brain tissues express ACE-2 receptors on the glial cells and neurons. These receptors are most prominent in the brainstem, paraventricular nucleus (PVN) and nucleus tractus solitarius (NTS) (Xia and Lazartigues, 2010). Thus, these receptors play a crucial role in providing entry to the viral genome inside the cell, and because they are reported to be found in brain areas too, it may be a plausible reason underlying the mild to severe neurological symptoms reported by patients.

Immune Cell Hyperactivity-Induced CNS Infection

As of now, it is clear that the presence of ACE-2 is very important for the invasion of SARS-CoV-2 inside human body organs, but it is not the sole player in spreading infection in the brain tissues. Cytokine overload also plays crucial role in increasing the concentration of SARS-CoV-2 viral components inside brain tissues. This action of cytokines is due to the hyperactivity of the immune system (in response to the initial infection of the virus in the respiratory system and further in the blood circulation). This cytokine storm may lead to systemic inflammatory syndrome (SIRS) or SIRS-like phenomena (Qin *et al*., 2020).

The ILs, IL-6 and IL-8 are mainly found to be responsible for the widespread infection (Bell *et al*., 1996; Kaplanski *et al*., 1995). The monocyte chemoattractant protein-1 (MCP-1) also releases IL-6 and IL-18, and it is also involved in the transmigration of monocytes across the BBB. This may be the possible reason for inflammation of the CNS after hyperactivity of the immune system during or after COVID-19 infection (Sankowski *et al*., 2015).

Hypoxia-Induced CNS Invasion

One more factor of concern is that recent studies have found that the SARS-CoV-2 virus can also cause damage to the CNS without invading the organ, i.e., by causing hypoxemia, ultimately predisposing various neurological symptoms like brain hypoxia (with vasodilation), hyperemia and brain edema, which may further lead to serious problems like unconsciousness and coma (Abdennour *et al*., 2012).

After invasion of the CNS, the virus causes neurological changes in the brain which are diagnosed as mild to severe symptoms in patients post-COVID. This chapter further includes discussion about different neurological complications related to SARS-CoV-2.

NEUROLOGICAL COMPLICATIONS RELATED TO SARS-COV-2

The neurological manifestations due to SARS-CoV-2 infection range from minor infections to severe disease states in humans. Initial symptoms may start with mild dizziness, headache, dysgeusia or anosmia to severe disorders such as stroke, Guillain-Barré syndrome (GBS), acute haemorrhagic necrotizing encephalopathy, meningoencephalitis and cerebral venous thrombosis (Mao *et al*., 2020; Lechien *et al*., 2020; Yan *et al*., 2020; Helms *et al*., 2020). Other symptoms may include feelings of agitation and confusion, corticospinal tract signs, dysexecutive syndrome (Yan *et al*., 2020), encephalopathy, autoimmune encephalitis, acute disseminated encephalomyelitis (ADEM) and GBS. The neurological manifestations due to SARS-CoV-2 can be categorized into two major categories, i.e., acute disorders and chronic disorders.

ACUTE DISORDERS DUE TO SARS-COV-2 INFECTION

Anosmia/Ageusia

Anosmia may be defined as a decreased ability to detect any kind of smell (loss of sense of smell). It may be due to a head injury, nasal blockage and infections like COVID-19. It is one of the cardinal symptoms that occurred in COVID-positive patients just after encountering the SARS-CoV-2 virus (Agyeman *et al*., 2020). Recent reports have studied the underlying mechanism of anosmia and ageusia and concluded that these disorders occur in COVID-19 patients through the pathways of direct entry of the virus, infection and/or death of sustentacular cells (the most preferable pathway for viral entry and infection) (Butowt and Bartheld, 2021). Post-COVID, this disorder is also associated with other complications like cough, chest pain, congested nose, sore throat, GI disturbances, dysphagia, headache, insomnia, arthralgia and myalgia (Algahtani *et al*., 2022).

Ageusia is defined as the loss of sense of taste. ACE-2 receptors are found to be distributed throughout the nasal and oral cavities. The tongue is mainly involved in the sensation of taste, which is lost because of the inhibition of the ACE-2 receptors by the SARS-CoV-2 virus in the oral cavity. This may be the principal mechanism of the induction of ageusia during COVID-19 infection in humans (Zhou *et al*., 2020). Post-COVID, this disorder is also associated with other complications, including persistent anosmia, dyspnoea, chest pain, headache and hearing difficulties (Algahtani *et al*., 2022).

Stroke

Increased risk of acute ischemic stroke was also being reported in COVID-19 patients, which also has a long-term effect on the human body. This risk is multifactorial as it activates a number of inflammatory as well as coagulation cascades, resulting in raised levels of different underlying factors such as erythrocyte sedimentation rate (ESR) levels, lymphopenia and increased fibrin D-dimer levels in the human body. The mechanism behind ischemic stroke may be endothelial cell damage and/or hypercoagulability of blood (Qureshi *et al*., 2021).

Three main mechanisms appear to be responsible for the occurrence of ischemic strokes in COVID-19 (Oxley *et al*., 2020; Beyrouti *et al*., 2020): a hypercoagulable state, vasculitis and cardiomyopathy. As ACE-2 receptors are present in the endothelial layer (Hamming *et al*., 2004) of the heart, binding of these receptors to the SARS-CoV-2 viral proteins may lead to severe inflammatory responses predisposing thrombotic complications like vasculitis (Varga *et al*., 2020; Spence *et al*., 2020).

Encephalitis

Encephalitis was reported to be a major complication in severely ill COVID-19 patients (Paterson *et al*., 2020). It was reported during the infection period as well as a post-infection complication (Umapathi *et al*., 2020; Pilotto *et al*., 2020). The mechanism behind this disorder may be viral neuroinvasion, a disrupted BBB or activation of autoimmunity. Older patient groups are at higher risk of encephalitis as they also suffer from other diseases along with COVID-19 (Dogan *et al*., 2020; Cao *et al*., 2020). This disorder has also been reported to be present in patients with asymptomatic conditions of COVID-19 (Radmard *et al*., 2020). Young children are found to be at higher risk of developing encephalitis after COVID-19 infection (Langley *et al*., 2020; Zhang *et al*., 2020). The cause of neuronal infection in children is multifactorial, as all the mechanisms have been reported in different cases of neurological changes in children's brains. The main causes include direct viral invasion (haematogenous pathway) (Pezzini and Padovani, 2020), autoimmune response activation post-COVID-19 infection and indirect viral attack, i.e., cytokine storm activation (Aghagoli *et al*., 2021).

Encephalopathy

Encephalopathy is defined as any disease or disorder of the brain which alters the function or structure of the brain. It may be manifested as confusion, delirium and deep coma (Elkind, 2022). It may occur due to any infection (viral, bacterial, etc.), cellular malfunction (mitochondrial dysfunction), metabolic disorder, any kind of tumorous growth in the brain, increased pressure in the brain, elemental intoxication (exposure to toxic chemicals, solvents, drugs, radiation, paints, etc.), traumatic conditions, brain hypoxia, ischemia, etc. This condition may lead to altered brain activity and the mental state of the patient. It causes loss of memory and cognition, which may further lead to lethargic behaviour, concentration problems and other related issues (Akimoto *et al*., 2022). Older COVID-19 patients are more prone to encephalopathy as there are other comorbidities associated with their health like Parkinson's disease, stroke and prior use of antipsychotic drugs. This may cause decreased immunity and allow invasion of the virus easier and infection more drastic (Elkind, 2022). Encephalopathy in children has been reported as a case of altered consciousness (the hallmark of encephalopathy in children) along with other alterations in brain scans (Elkind, 2022).

Peripheral Neuropathy

Peripheral neuropathy (PN) is a result of damage to the peripheral nerves, which can manifest as weakness, and pain in head and feet regions of the body. It also extends to other systems of the body, such as the gastrointestinal tract, urinary system and circulation. Post-COVID, PN has been reported as a common neurological complication. It is observed mostly in patients with comorbidities like diabetes since it affects the immune system. This disease may be caused by the side effects of COVID medications given to patients. The mechanism of PN is found to involve retrograde neuronal transmission through damaged or infected neurons. These neurons may be part of the olfactory system or the vascular endothelial system (Zubair *et al*., 2020; Algahtani *et al*., 2016).

Guillain-Barré syndrome is a type of peripheral neuropathy, as it is a disorder of inflamed neurons in the peripheral nervous system due to any kind of viral or bacterial infection of neurons (Levin, 2004). Manifestations related to GBS range from muscular paralysis (ascending) to sensory as well as autonomic neuronal disturbances/dysfunction and respiratory failure (Willison *et al*., 2016). This disease may be caused by a number of microbes, with SARS-CoV-2 as the newest addition to the list. This disease is more prevalent post-COVID as the nervous system is damaged due to the COVID-19 infection in patients (Jacobs *et al*., 1998). In children, post-COVID GBS has been reported as a severe complication with a common mechanism as in adults (Dugue *et al*., 2020; El Mezzeoui *et al*., 2021).

Myositis

Myositis is defined as inflammation of muscles, more precisely the musculoskeletal system. It is manifested as pain, swelling, tenderness and weakness of the muscles. This disease is more commonly reported in children with multisystem inflammatory syndrome (MIS) (Lindan *et al*., 2021; Sánchez-Morales *et al*., 2021). Myositis of the neck and face has been reported in children in the later phases of COVID infection as a complication. The underlying mechanism of the disease post-COVID involves either bioenergetic dysfunction or autoimmune inflammatory damage of the muscles (Mohkhedkar *et al*., 2021).

Different muscles have been found to be affected post-COVID. Types of myositis include acute viral myositis, rhabdomyolysis, dermatomyositis and paraspinal myositis (Saud *et al*., 2021).

CHRONIC DISORDERS DUE TO SARS-COV-2 INFECTION

Fatigue

Fatigue is the most prevalent symptom reported in patients recovering from COVID infection. It is a common and enervating sign in patients with post-COVID neurological complications. As fatigue doesn't have any specific cause, its mechanism is not clearly distinguished. Underlying causes of fatigue may be attributed to changes in concentration of neurotransmitters in the nervous system, inflammatory changes in the body, neurological disorders, psychological issues, cognitive impairment and issues with substrate metabolism. Respiratory and cardiac damage may also be counted as predisposing factors precipitating fatigue as a post-COVID complication (Rudroff *et al*., 2020; de Medeiros Carvalho et al., 2020; Rogers et al., 2020).

Cognitive Impairment

Cognitive impairment is defined as improper functioning of the brain, thus affecting the activities related to the cognitive power of the brain. It is a complication that persists even after six months in patients recovered from COVID-19. The cases are found to be more severe in patients with psychological and cognition-related comorbidities. The pathophysiology underlying cognitive impairment includes microglial inflammation (leading to Alzheimer's disease) (Mandrekar-Colucci and Landreth, 2010) and cardiovascular changes (cognitive impairment and dementia) (Pendlebury and Rothwell, 2019; Solomon *et al*., 2020).

Depression/Altered Mood

Depression, anxiety and insomnia are some of the most common post-COVID complications reported in the long COVID phase. These complications may occur as a result of psychological changes due to coronavirus invasion in the brain directly, or indirectly by activating immunomodulatory pathways in the body (Khubchandani *et al*., 2022). Certain stressors like fear of illness, loneliness, future uncertainty, stigma and trauma due to long and drastic diseased conditions play a significant role in defining the underlying mechanism of direct activation of psychological illness, i.e., depression and mood swings. Old age and related comorbidities lead to more severe post-COVID stress-induced depression as well as anxiety in patients (Cucinotta and Vanelli, 2020).

CONCLUSION

SARS-CoV-2-induced COVID-19 infection is a life-threatening infection that caused severe infection in humans and was declared a pandemic by the WHO in 2020. This disease has been found to be associated with severe respiratory infection along with devastating effects on different organ systems of the human body. As the symptoms of COVID-19 included anosmia and/or ageusia, the role of neurological infection came into view, which was not highlighted and was neglected in the initial phase of the pandemic. The current chapter has highlighted the neuropathological aspects of SARS-CoV-2 infection, keeping in mind the different age groups and the severity of infection, either acute or chronic. From this data, it can be concluded that the neurological effects of SARS-CoV-2 are not only restricted to the acute phase of the disease but are also precipitating even after the recovery of the patient, which has been termed as post-COVID consequences or more precisely, long-COVID complications.

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