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REVIEW ARTICLE

Crosstalk Between Covid-19 and Associated Neurological Disorders: A Review

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Abstract: COVID-19 is a global pandemic, primarily affecting the pulmonary system but its effects on other systems are not certain. Coronavirus, the causative organism, binds with angiotensin-converting enzyme 2 (ACE2) receptors in the lungs and produces pneumonia-like symptoms. Other than lungs, ACE2 receptors are also seen in the endothelium of blood vessels. Therefore, viruses can bind to the ACE2 that is present in the endothelium of brain blood vessels and thus can invade BBB, leading to neuronal damage. It is also believed that olfactory cells rich in ACE2 receptors may act as the main route of viral spread into various parts of the brain. The reported neurological effects of SARS-CoV-2 include cerebrovascular diseases, ageusia and anosmia, Guillain Barre Syndrome, and viral encephalitis. The extent of neurological involvement in SARS-CoV-2 infection warrants the necessity of further research to systematically classify neurological complications associated with SARS-CoV-2 infection, its diagnosis, and treatment. As ACE2 receptors are present in various other organs, it is obligatory to study the effect of coronavirus on other organs also. Since the long-lasting effects of the COVID-19 are unclear, more studies should be conducted to confirm the effect of the virus on the central nervous system. This review highlights the reported neurological manifestations of SARS-CoV-2 and its mechanism.

Keywords: COVID-19, SARS-CoV-2, neurological complications, Guillain Barre syndrome, viral encephalitis, cerebrovascular diseases.

1. INTRODUCTION

As of 14th September 2020, the number of confirmed coronavirus cases crossed 29 million worldwide, and 928k deaths were reported due to this deadly pandemic. It has spread dreadfully all over the world [1]. The outbreak was initially showed up in Wuhan province of China in December 2019, reported as acute pneumonia-like symptoms. It is an infectious disease mainly spread by close contact with an infected person *via* droplets produced by coughing and sneezing. The infection's main symptoms include fever, dry cough, and fatigue associated with headache, breathing difficulty, and loss of smell sensation. A family of RNA virus, Coronaviridae, causes severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) or coronavirus disease 2019 (COVID-19). No vaccine or effective treatment is available for this disease, which makes this global pandemic more dreadful. Clinical trials are on going worldwide on antiviral drugs and other vaccines to determine an effective treatment for virus infection. Coronavirus attacks majorly on the respiratory system, and in most cases, it does not show any symptoms [2]. Even though the virus causes acute respiratory tract infections, it may also affect other body organs. The long-lasting effects of this novel virus infection on human health are still undefined. Recent studies have also emphasized that SARS-CoV-2 has a role in various comorbidities [3].

From clinical data that has emerged from the reported patients, it is evident that the virus attack can trigger neurological complications.

A retrospective study of 214 patients in Wuhan, done by Mao *et al.,* shows that 36.4% of patients suffer from neurological difficulties. Patients who are severely affected are exhibiting more neurological complications [4].

The most common complications reported so far include headache, dizziness, lost consciousness, cerebrovascular diseases, encephalitis, seizures, and loss of smell and taste. A case report in February 2020 in Wuhan confirms that the novel coronavirus causes viral encephalitis. The presence of a virus in CSF approves the role of coronavirus in neuronal complications [5]. Neurological complications of COVID-19 are widely being reported nowadays, either during infection or post-viral infection. This review highlights the crosstalk between SARS-CoV-2 and its various neurological manifestations like cerebrovascular complications, neuronal inflammation, neuromuscular interventions, ageing, and neuronal degeneration. Various mechanisms involved in these neurological complications are also discussed in this review,

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along with different diagnostic tools used in the diagnosis of SARS-CoV-2 infection.

2. STRUCTURE, SYMPTOMS, AND DIAGNOSIS OF CORONAVIRUS

2.1. Structure of SARS-CoV-2

SARS-CoV- 2 virus belongs to the family of *Coronaviridae*, a group of large, positive-stranded, enveloped RNA viruses. There are four genera, *Alpha, Beta, Gamma,* and *Deltacoronavirus* (Fig. **1**). *Alpha* and *Betacoronavirus* (β-CoVs or Beta-CoVs) infect mammals, whereas avian species get infected by Gammacoronaviruses, and Deltacoronavirus can infect both avian and mammalian species. SARS-CoV and SARS-CoV-2 belong to *Betacoronavirus*. It is a group of non-infectious as well as infectious viruses. In past years there were some coronavirus outbreaks like the Middle East respiratory syndrome (MERS CoV) and severe acute respiratory syndrome (SARS-CoV-1) [6, 7]. The structures of infectious viruses from the *Coronaviridae* family are listed in (Fig. **2**) [8].

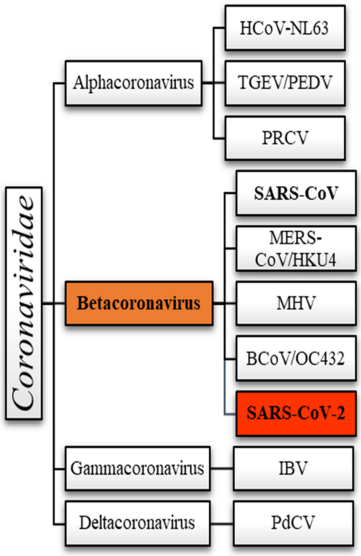

Fig. (1). Genera under *Coronaviridae*. SARS-CoV- 2 belongs to Betacoronaviruses. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Therefore, the effects of the virus in a host are long-lasting and constant. The structure of the virus has 16 non-structural proteins (Nsp1-16) and 4 structural proteins. Non-structural proteins together form a replicase/transcriptase complex (RTC) that contains several enzymes, and it interacts with different biological processes of a host like nuclear transport (Nsp7) and ribonucleoprotein biogenesis (Nsp8) [9].

Structural proteins include a nucleocapsid protein (N) bound to the genetic matter, RNA. A membrane protein (M) gives shape to the virus. An envelope protein (E) forms a viral envelope by interacting with membrane protein and spike proteins (S), which binds to the host cell receptors [10]. Spike proteins are projected out of the virus, and it gives a crown-like structure to the virus. It has 3 main segments, a transmembrane anchor, an ectodomain, and a short intracellular tail.

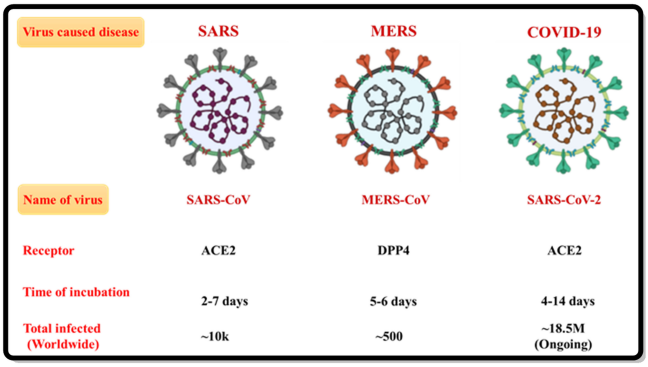

Fig. (2). Various types of coronavirus are pathogenic for humans [8]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Spike proteins in the host can modulate the metabolism of lipids. Angiotensin-converting enzyme 2 (ACE2) interacts with SARS-CoV. In (Fig. **3** and **4**) the structure of the coronavirus and its different proteins are illustrated [8].

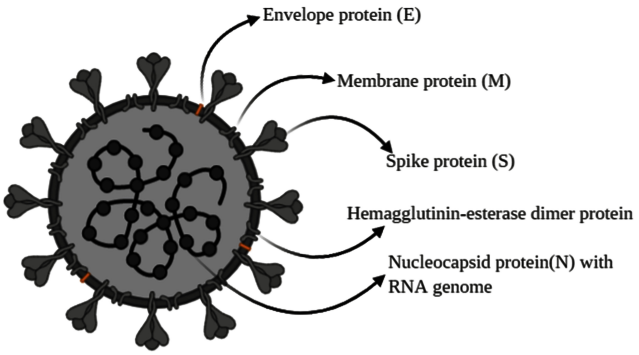

Fig. (3). Structure of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

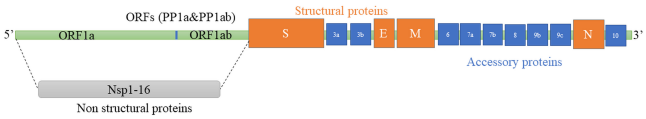

Fig. (4). Structure of SARS-CoV-2 genome. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

They are unique among RNA viruses as they have a larger genome compared to other viruses. They follow several uncommon approaches for their genome expression. There will be ribosome frameshifting during translation of their genome, and their assembly of virions are also found to be exceptional among other enveloped RNA viruses. Several

subgenomic mRNAs are produced during coronavirus transcription, which contains sequences of both ends of the genome. They are highly capable of adapting to the new environment *via* mutation and recombination, thereby altering the host range.

There are 29 known proteins in the coronavirus genome. They include two large groups of polyproteins, namely ORF1a and ORF1ab that constitute 16 non-structural proteins of SARS-CoV-2, 4 structural proteins; spike (S), envelop (E), membrane (M), and nucleocapsid (N), and 9 accessory proteins, ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF9c, and ORF10. Accessory proteins are not essential for viral replication, but they are actively involved in host pathogenesis and modulation of interferon pathways, and they are placed in between structural proteins [11].

3'- poly-A tail of viral genomic RNA can act as mRNA to translate viral polyproteins like ORF1a and ORF1ab. Both 5' and 3' end have an untranslated region (UTR), which regulates RNA replication and transcription. ORF1a and ORF1ab encode two main transcription units, replicase polyprotein 1a and 1ab (PP1a and PP1ab). The largest polyprotein PP1ab constitutes the non-structural proteins that form an intricate replicase machinery. The structural proteins and accessory proteins are translated from a set of nested subgenomic RNAs regulated by transcriptional regulatory sequences [12-15].

Spike protein of SARS-CoV-2 was found to have a key role in attaching to ACE2 receptor and thereby infection. It is a homotrimer that projects from the viral membrane. Each monomer of homotrimer has a receptor-binding domain or RBD that acts as a tool to interact with ACE2 on the surface of cells. ACE2 is mainly expressed on the surface of various cells of the host body such as lungs, heart, kidney, brain, intestine, and arteries. In the brain, ACE2 is seen in the brain stem, regions that control central blood pressure, and cardiovascular functions like the subfornical organ, nucleus of the tractus solitarius, paraventricular nucleus, and rostral ventrolateral medulla.

When compared to SARS-CoV, SARS-CoV-2 has more affinity towards ACE2, and both share 96% similarity in nucleotide sequence. SARS-CoV-2 has more positively charged spike proteins. The greater number of spike proteins can have a substantial influence on cell adhesion and BBB crossing. Most of the studies regarding the neurological effects of SARS-CoV-2 report no evidence of the virus in the brain or CSF, but demyelination of the brain can occur due to viral entry.

Interaction of spike protein with host ACE2 receptor is a two-step process. In the first step, spike protein is in a closed conformation. This step is dominated by electrostatic forces, leading to the formation of transient and nonspecific encounter complexes. In the second step, a structural rearrangement in the spike protein takes place. The RBD opens up to reveal its binding interface on the host body, ACE2, and forms a well-defined complex that is stabilized by electrostatic forces, polar and nonpolar interactions such as salt bridge, hydrogen bond, π stack, π anion, and hydrophobic interactions [16-18].

2.2. Symptoms

The disease spreads mainly by tiny droplets from the nose or mouth from person to person, which are expelled when a person with COVID-19 coughs, sneezes, or speaks.

The most frequent COVID-19 symptoms are fever, dry cough, and tiredness. Other less common symptoms that may affect some patients include aches and pains, nasal congestion, headache, conjunctivitis, sore throat diarrhea, loss of taste and smell, skin rash, and finger or toe discoloration. Typically, these symptoms are mild and begin gradually.

Most people (around 80%) recover from the disease without seeking care in the hospital. About 1 in every 5 people who get COVID-19 become seriously ill and develop breathing difficulties. Older people, and those with underlying medical issues such as high blood pressure, heart and lung problems, diabetes or cancer, are at higher risk of developing severe illness. Some of the affected people do not show any symptoms but still tested positive for the virus [19].

2.3. Diagnosis

Like other infectious diseases, coronavirus attacks also have different laboratory approaches to identify the presence of viruses in the host's body [20]. A list of diagnostic techniques are mentioned in (Fig. **5**). Samples like blood, serum, urine, stool, lower and upper respiratory tract specimens are the most accepted specimens for the analysis. Lower respiratory tract specimen analysis is strongly recommended as sometimes upper respiratory sample analysis comes negative in some severely affected cases. Different studies showed the importance of lower respiratory tract specimen analysis as it contains a high virus load than other samples [21].

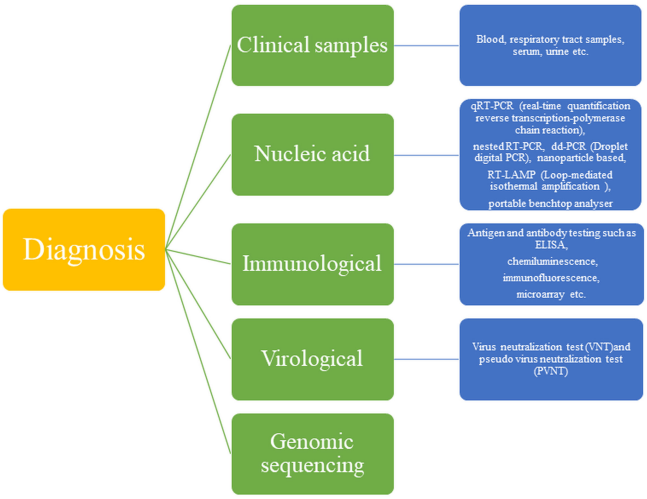

Fig. (5). Different diagnostic techniques use to detect the presence of SARS-CoV-2. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Analysis of nucleic acids is another successful approach to analyze the presence of the virus. Different probes and primers that target the SARS-CoV-2 virus genome can be useful in the laboratory investigation. The structure of the virus includes parts of nucleocapsid(N), spike protein (S), envelop (E), *etc*. can be work as a target for the lab analysis. Other than these parts, RNA polymerase (RdRP) and open reading frame1 ab (ORF1ab) are also useful as a target gene. Identification of the specific gene targets, ORF1ab and RdRP, confirms the presence of SARS-CoV-2 in the host's specimen [21].

WHO recommended and widely accepted detection technique is qRT-PCR(real-time quantification reverse transcription-polymerase chain reaction) kit for the qualitative detection of the SARS-CoV-2 virus in lower and upper respiratory tract specimens. At the same time, it is time-consuming and expensive [21, 22].

Nested RT-PCR is used in the early days of detecting the virus, which is a less expensive and time-saving type of RT-PCR. Compared to the qRT-PCR, nested RT-PCR is more sensitive and specific for the SARS-CoV-2 virus when there is a low viral load, which is in the early stages of virus attack. Nevertheless, nested RT-PCR is producing false-positive cases as there is a chance of cross-contamination from the laboratory [23-25].

Droplet digital PCR(ddPCR) has better sensitivity and specificity and less load of detection (LOD) when compared to RT-PCR. But it is expensive and needs more sophisticated types of equipment than RT-PCR [26, 27].

Loop-mediated isothermal amplification (LAMP), as the name indicates, needs a constant temperature and has a rapid amplification for the identification of coronaviruses. This technique utilizes visual or colorimetric detection methods. ORF1ab genes could be detected using this technique and practiced at home with the least instruments [28, 29].

Nanoparticle-based amplification is another technique used for the detection of the virus. Gold nanoparticles could be introduced to improve the specificity and sensitivity of the virus and analyzed by the naked eyes using the colorimetric method [30-32].

Portable benchtop-sized analyzers are the most accurate, sensitive, and powerful analyzing technique for fast detection of SARS-CoV-2, which can be used bya person who does not have any PCR training or point of care testing (testing a person in their proximity). But there are reports that this type of analyzer may produce unpredictable performances [33, 34].

Antigen tests utilize the viral proteins, specifically S and N, which are the main antigen targets for detecting the virus. The S protein can be sliced into two separate S1 and S2 subunits. S protein is essential for virus entry and can be seen on the surface of the virus, but N is the most expressed that interacts with RNA. S1 is more specific to SARS-CoV-2 detection. The nasopharyngeal swab is directly placed on viral transport media and analyzed in a laboratory setup. For the detection of this specific virus, the immunochromatographic technique is commonly used. However, it shows comparatively low sensitivity due to which newly developed biosensors are used [35-38].

Antibodies such as IgG, IgA, and IgM could be used for the identification of the virus. Immediately after the virus infestation, in 5 to 7 days, IgM is produced, and this testing can be successfully used for the identification of the virus inside the host's body. IgA could be present in the mucosal secretions and can be detected in 6 to 8 days. If the RT-PCR is failed to detect the virus and the host is still suspecting the presence of the virus, a serological analysis could work. Enzyme-linked immunosorbent assay, immunofluorescence assay, chemiluminescence immunoassay, *etc*., are considered manual laboratory-based serological analysis. Another set of analytical techniques useful in antibody detection are lateral flow assay, microarray, and microfluidic analysis [21, 39-42].

Virus culture techniques are considered the gold standard for the detection of viruses. Virus neutralization tests and pseudovirus neutralization tests are commonly used for viral culture. Viral culture is a laboratory technique that places samples of a virus in various cell lines that can be contaminated by the virus being examined. If the cells display changes, it is referred to as cytopathic effects, and the culture is positive. The serum of COVID positive patients is used for neutralization capacity, and it is evaluated whether the serum can reduce the cytopathic effects. These techniques are time-consuming and expensive [41, 43-45].

Genomic sequencing is another powerful method to analyze the evolution of viruses, the relation between genetics and disease progression, and the development of novel treatment strategies like vaccines. The main sequencing methods of SARS-CoV-2 include metatranscriptomics sequencing, hybrid capture-based sequencing, amplicon sequencing, and nanopore targeted sequencing [21, 45]. A translational research approach would be beneficial for identifying the possible CNS effects of CoV infections [46].

3. COVID-19 AND NEUROLOGICAL INVOLVEMENT

Past CoV attacks, like SARS-CoV and MERS-CoV infections, can induce neuronal damages like polyneuropathy, cerebrovascular diseases, encephalitis, ischemia, and demyelination neurons, and seizures. According to WHO reports, MERS-CoV is found to be potentially neuroinvasive. As these viruses belong to the same family *Coronaviridae,* and SARS-CoV-2 has structural and genetic similarities with other family members that can produce neural damage, SARS-CoV-2 is also expected to produce neuronal complications [47].

Clinical reports show that some patients infected with SARS-CoV-2 had neuroinvasive symptoms such as headache, seizure, loss of taste and smell, and viral encephalitis very rarely. Along with the expression of new neurological disorders, the pre-existing neurological conditions got wors-

ened in some patients. Neurological involvement of COVID-19 was reported in one-third of patients. A retrospective study done by Luigetti M *et al.* showed that from March to April, out of 213 positive cases, 64 patients had neurological involvement, including encephalopathy, seizures, headache, myalgia, encephalitis, ageusia, and anosmia [48].

SARS-CoV-2 induced neurological complications may be classified into three forms based on the parts they affect; CNS, PNS, and skeletal muscle-related. Cerebrovascular diseases (CVD) are the most common type of neurological disorder associated with this virus infection. Other CVDs related to this virus are cerebral venous thrombosis and cerebral hemorrhage. These conditions have a risk of incidence in people who have higher blood pressure, diabetes, and past CVD records. Neuromuscular complications are the second most common type in which Guillain-Barré syndrome (GBS) is a dominant complication, which is an autoimmune disease that affects neurons. The mechanism of how the virus is causing GBS is still uncertain. The possible mechanism may be either the cytokine storm produced due to infection or due to the neuronal virus invasion. The neuronal invasion may cause CNS infections and increase BBB permeability, making the brain more prone to other infections like encephalopathy. ACE2 receptors bind in the host's body, and endothelial cells, glial cells, and other related neurons rich in ACE2 receptors. Encephalitis- meningitis is another neuronal disorder associated with the neuroinvasive nature of SARS-CoV-2, which initially shows symptoms like headache, fever, fatigue, and unconsciousness [49, 50]. The role of SARS-CoV-2 in various neurodegenerative pathways is still unknown, and further studies are also needed [51, 52].

3.1. Cerebrovascular Complications

Cerebrovascular diseases (CVD) are reported as the most common and severe form of neurological complication in COVID-19 patients. This condition has multifaceted etiology, and it may develop after common symptoms of infection. Those with pre-existing CVD are more prone to hypoxia and thereby lower the brain's oxygenation [53, 54]. The experimental animal model confirms that the influenza virus's cytokine cascade produces ischemic brain injuries and intracranial hemorrhage [55]. In a retrospective study done in 221 SARS-CoV-2 infected patients in Wuhan, 6% of patients showed cerebrovascular complications such as ischemic stroke, intracranial hemorrhage, and cerebral venous sinus thrombosis [56]. Younger COVID-19 patients are admitted due to ischemic stroke and occlusions in large vessels [57]. All these conditions are due to the damage of the endothelium or activation of immune factors. Another possible mechanism is due to the elevated D-dimer, increased prothrombin time, C-reactive protein, and ACE2 expression [58]. The presence of the virus in CSF and brain tissues after autopsy in previous CoV attacks has been proven. CVDs could be identified by brain CT [4].

3.2. CNS Infections and Inflammations

In severely affected covid-19 patients, an increased level of cytokines was observed, termed cytokine storm or cytokine release syndrome. Cytokines such as IL-6, IL-1b, TNF, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP-10, MCP-1, and MIP1a2 were upregulated in circulation, and increased level of IL-6 and TNF in serum was also observed in critically ill patients [59]. After viral infestation, viral proteins in the blood circulation and molecular complexes such as high mobility group 1(HMGB1- a type of nuclear protein produced from damaged cells) could reach the brain *via* manipulated BBB and induce brain damage by acting as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). They can induce innate immunity by activating macrophages, pericytes, and microglia in the brain that prompt toll-like receptors (TLR, pattern recognition receptors involved in innate immunity) [60].

The main reason for the inflammation of brain parenchyma or encephalitis is either autoimmune or any kind of infection [61]. It is characterized by fever, vomiting, convulsions, and altered consciousness [62]. Encephalitis and encephalopathy are reported in SARS-CoV-2 infections very rarely. Even though the etiology of encephalitis in SARS-CoV-2 infection remains unclear, it is suspected that it may be due to cerebral inflammation caused by a viral infection. There is no evidence of the presence of a virus in CSF, but high lymphocyte levels have been documented [63].

Acute hemorrhagic necrotizing encephalopathy is another complication related to SARS-CoV-2 infection. It is a type of reversible brain dysfunction due to cytokine upsurge or damage to BBB characterized by cerebral edema and no noticeable changes in CSF [64]. Severe hypoxia in SARS-CoV-2 patients may lead to encephalopathy and develop symptoms like headache, confusion, loss of consciousness, and paralysis. CT and MRI can be used for the detection of encephalopathy. Autopsy reports of deceased SARS-CoV-2 patients indicatedthe presence of edema in the brain [5].

In a case report of 76-year-old women, the post-encephalitic seizure was reported after being infected with coronavirus, confirming the neurological involvement and seizure [65].

3.3. Ageusia and Anosmia

SARS-CoV-19 infection is highly associated with loss of sensation of smell and taste [50]. A multicenter study conducted in Europe reported that around 86% of patients develop olfactory disorder; either anosmic or hyposmic, and 89% of patients developed the gustatory disorder. Post viral anosmia leads to loss of smell sensation. The etiology behind anosmia is mucosal congestion and olfactory conduction loss due to nasal obstruction. But in the case of COVID-19, there is no noticeable runny nose or nasal congestion [66].

In COVID-19 patients, the high concentration of the virus was observed in the nose, causing inflammation of ol-

factory nerves, and damage to the receptors leads to anosmia [67]. Ageusia develops due to the binding of the virus to the ACE2 receptors that are highly expressed in the tongue, leading to damage of the taste receptors and ageusia [68].

3.4. Neuromuscular Interventions

Post COVID-19 myalgia was reported after viral shedding by a group of researchers. In a study done by Long - Quan Li *et al*. in 1995 patients, 35.8% of total subjects exhibited myalgia. Along with myalgia, elevated creatinine kinase (CK) level and rhabdomyolysis (death of muscle fibers and release of their contents to blood circulation due to direct or indirect injury to the muscles) [69], point to the fact that coronavirus is capable of producing myositis. Critically ill patients are reported with a critical illness, myopathy, or polyneuropathy (CIM or CIP), due to long term usage of non-depolarizing neuromuscular blocking agents as part of therapy [69].

Guillian Barre syndrome (GBS) is the second most common neurological disturbance that happened with SARS-CoV-2 infection. Guillain- Barre syndrome (GBS) and Miller-Fisher syndrome (MFS-a variance of GBS) were reported after 3 days to 4 weeks of COVID-19 infection and often reported in elderly patients. When compared to post-infectious GBS/MFS, para infectious GBS/MFS are most common. Typical GBS patients do not have olfactory symptoms, wherein COVID-19 related GBS, ageusia, and anosmia are common. Most of the patients were reported with lower limb areflexia (less responsive to stimuli) followed by bifacial weakness and other cranial neuropathies [70].

Studies prove that virus entry to the central nervous system is *via* the olfactory pathway, blood-brain barrier, or infected immune cells' infiltration. Hypothalamus and cortex of covid-19 infected patients were detected with neuronal damages [70]. The underlying pathophysiological processes may be secondary to the neuroinvasive nature of the ravaging virus demyelination or viral infection, which produces an inflammatory environment that causes an aberrant immune system reaction, resulting in peripheral demyelination [71]. Due to this virus invasion, there will be overactivation of macrophages, neutrophils, and natural killer cells, leading to cytokine releasing syndrome (CRS) such as IL-1β, IL-6, IL-12, and TNF-α. This upsurge may cause tissue and peripheral nervous system damage [71].

3.5. Aging and Neuronal Degeneration

Comorbidities like cerebrovascular diseases, diabetes, and chronic obstructive pulmonary disease can worsen the condition of COVID-19 patients [72]. Neurological manifestations of coronaviruses are already established earlier duringthe time of MERS-CoV infections [73, 74].

When SARS-CoV spike proteins enter the host body, their pro-inflammatory effects are meditated by TLR on human macrophages *via* NF-kB, which may lead to an upsurge of cytokine production and thereby brain injury and impaired brain function. Animal studies reveal that viral infection leads to increased levels of IFNa/b, followed by activation of interferon receptors (IFNR1) on cerebral endothelium and cognitive impairment [59].

Recent studies confirm the interaction of viral proteins with human proteins in different age-related pathways, which influences the brain's health and eventually is associated with the development of AD [74]. For example, viral proteins such as Nsp6, Nsp10, Nsp 13, Orf3a, Orf 8, *etc*., interact with vesicle trafficking (an age-related pathway). Nucleocapsid protein (N) interacts with host proteins such as G3BP1 (involved in the induction of innate immunity), and this complex inhibits the formation of stress granules (SG), which can manipulate RNA biology and protein synthesis in the host cell [75]. The virus's nucleocapsid protein also interacts with LARP1 (mTOR translational repressor; involved in different biological processes) and regulates protein synthesis [76]. The role of mTOR in aging is already proven in several studies [77]. When the spike protein of the virus binds with the ACE receptor, it can modify the host's cellular mechanism like protein homeostasis, leading to impaired protein translation, folding, and clearance. These manipulations can affect several aging hallmarks, such as increased endoplasmic reticulum stress, and inhibit the ubiquitin-proteasome system, leading to protein misfolding. Further effects include mitochondrial dysfunction and an increase in the ROS level and can affect the host's innate immunity. Virus infection alters the control over the host's Hsp90 (a chaperone protein involved in the proper folding of other proteins and stabilizes proteins against stress) by increasing RNA polymerase enzyme, facilitating caspase activation and inducing apoptosis [78, 79].

A cohort study conducted by UK Biobank (UKB) demonstrates the relationship between COVID-19 and APOE4. In adults aged over 65, pre-existing dementia is the main risk factor, and it is a common comorbidity associated with COVID-19. APOE4 allele relates to dementia, and people with double copies of APOE4 possess a higher risk. In the study, they used genetic data of around 338,000 people of European descent from the UK Biobank to analyze the role of APOE4 in AD. Out of which more than 9,000 people carried two copies of APOE4. This data is cross-checked with people who tested positive for COVID 19. The resulting observation proposes that people possessed APOE4 homozygous genotype and were associated with twice the risk of severe disease than people who possess another variant like APOE3. They concluded, however, that the APOE4 allele raises the risk of serious infection with COVID-19. It affects lipoprotein function and manipulates macrophage pro/anti-inflammatory phenotypes. APOE is highly expressed as a co-existing gene in the lungs' alveolar cells, along with the ACE receptor [80].

Possession of one or two copies of APOE4 leads to enhanced innate immunity levels and cytokines [81]. Reports from previous studies assure the role of APOE4 in the parasite, bacterial, and viral infections [82]. An *in vitro* study demonstrated the influence of APOE4 in viral infections; cells that possess two copies of APOE4 alleles showed a rapid progression of HIV disease. Also, APOE4 is associated with

comorbid risk factors connected with severe coronavirus infection such as atherosclerosis and body vitals like blood pressure [83, 84]. ACE2 is highly expressed in alveolar tissues, and a high concentration of APOE4 is more dangerous in asthmatics as they activate immune mediators like cytokines and interleukin-6. Thus the possession of two copies of APOE4 increases the severity of coronavirus infection [85].

4. MECHANISMS OF NEURONAL DAMAGE BY CORONAVIRUS

The mechanism by which SARS-CoV-2 produces neurological damage is still unknown. The pathways that cause neurological damage are explained in light of past CoV infections and new reports based on SARS-CoV-2 infection [86].

4.1. Direct Invasion

Direct invasion of the virus to the nervous system causes neuronal damage *via* the blood-brain barrier or neuronal pathway. ACE2 is highly expressed in the lungs produces pneumonia-like symptoms. Along with the lungs, ACE2 receptors are seen in the endothelium of blood vessels. The virus can bind to the ACE2 endothelium of brain blood vessels and thereby invade BBB and finally neuronal damage. Another possible way of BBB breaching is found to be high levels of pro-inflammatory cytokines that can produce structural and functional damage to the BBB. In both ways, there will be damage to the BBB, and invasion of the virus made it easier.

Another direct invasion is through the nerve endings. In the case of SARS-CoV-1, intranasal inoculation of the mice showed the viral spread to the different parts of the brain, and the removal of the olfactory bulb in mice resulted in less spread of the virus in the brain. The olfactory nerve bulb was the main route of viral spread by this method, and a high degree of neuronal damage was observed. Recent findings point out that olfactory cells are rich in ACE2 receptors [87-90].

4.2. Hypoxia

Hypoxia is another mechanism that lies behind neurological damage in coronavirus infection. The binding of the virus to the ACE2 receptors leads to impaired functioning of normal gas exchange between cells, which further causes hypoxia in the brain and other parts of the CNS, leading to increased anaerobic metabolism in the brain mitochondria. Solomon *et al.* conducted a study, an autopsy of 18 deceased SARS-CoV-2 patients, showed hypoxic changes in the cerebellum and cerebrum and neuronal damage in the cerebral cortex and hippocampus. Hypoxia leads to edema, ischemia, cerebral vasodilation, and obstructed cerebral blood flow that eventually leads to headaches [91, 92].

4.3. Immune-mediated Pathology

Recognition of the virus in the host's body results in the activation of innate immune responses like interferons and natural killer cells. Due to viral infection, there will be an excessive defense mechanism called systemic inflammatory response syndrome (SIRS). It happens to avoid the noxious effect of the foreign material that invaded the host's body. As a part of SIRS, a cytokine storm may lead to multiple organ dysfunction. The same happens in the case of SARS-CoV-2 infection, and it affects macrophages, microglial cells, and astrocytes in CNS. Due to the effects on microglial cells, pro-inflammatory agents such as interleukin-6 (IL-6) will be the main member of the cytokine storm. Other than IL-6, there will be an overproduction of other interleukins as well as TNF-α. This activation or cytokine storm results in neuronal damage, even death [93-96].

4.4. ACE2

The lungs are the major organ involved in the pathophysiology of COVID-19 infection since ACE2 receptors are highly expressed in the lungs. ACE2 is present in other organs such as the nervous system, skeletal muscles, and vascular endothelium, and it leads to elevated blood pressure and eventually results in cerebral hemorrhage. As mentioned earlier, vascular endothelium is rich in ACE2 receptors through which the virus may damage BBB and thereby neurons [67, 97, 98].

5. INVOLVEMENT OF AGE AND SEX IN COVID-19 INFECTION

Neurological effects like ischemic or hemorrhagic stroke of SARS-CoV-2 infection is commonly reported in middle-aged or elderly. Various studies on neurological interventions of SARS-CoV-2 pointed out the same. In a study done by Mao *et al*., out of 214 patients, 40.7% were men, and 88 were severely infected with SARS-CoV-2, and 64% of them were above 50 years of age. 78% of overall had neurological symptoms. Those who were severely infected had more serious neurological symptoms [73]. In another study of 153 patients infected with SARS-CoV-2, male patients (48%) were reported to develop neurological symptoms, and the median age of the patients was 71 years. These patients had cerebrovascular symptoms, altered mental status, and PNS symptoms [99]. Males and females have a different immune response to the virus, and males are suspected of having a lower immune power than females. Studies showed that in males, viral clearance is delayed. A recent study pointed out that the testis can act as a port for the virus. Other than this, sex hormones play a role in the immune responses as estrogen is an immunoenhancing agent, but testosterone is immunosuppressive [100]. Age is another main factor in the severity of virus infection. As age increases, the number of ACE2 in the lungs decreases, and this decrease is more in males than females. Virus attack increases the decline of ACE2, thereby increasing the number of ACE1. As a result, there will be a generation of more angiotensin II, and it can damage endothelial cells in different organs such as the lungs and brain [101].

6. MEDICATIONS USED FOR THE TREATMENT AND THEIR NEUROLOGICAL EFFECTS

There is no proper cure for the disease to date. Only supportive treatments are available globally. For further preven-

tion of virus spreading, the infected should be isolated and protected. Humans infected with the virus should be treated with supportive care such as bed rest, maintain internal homeostasis, frequent monitoring of vitals like heart rate, pulse rate, respiratory rate, blood pressure, *etc*. Different therapies used in the treatment are listed below in Table (**1**). The latest clinical trial of dexamethasone shows a reduction in the mortality rate of ventilated patients or severely ill patients. In patients with mild symptoms, it is not found to be very effective [102]. Recently, Favipiravir, another antiviral drug that inhibits RNA dependent RNA polymerase (RdRp), was found to be effective in COVID-19 [103]. Supplementary studies should be done to know the exact mechanism behind the effect.

Table 1. Therapies used in the treatment of COVID-19*(Different classes of drugs and their mechanism of action)*.

Drug Class	Therapies Used for the Treatment of COVID-19	References
Antivirals	• **Interferon-alpha (INF-α)** o Promotes innate and adaptive immunity, inhibits replication of the virus • **Lopinavir/Ritonavir** o Protease inhibitor inhibits protein synthesis in virus • **Ribavirin** o Nucleoside analogue prevents replication of the virus • **Arbidol** o Anti-influenza drug, potent inhibitor and reduce reproduction of the virus • **Remdesivir** o Nucleoside analogue inhibits SARS-CoV and MERS-CoV	[106] [107] [108] [109] [110]
Antimalarials	• **Chloroquine and Hydroxychloroquine** • Potential broad-spectrum antiviral	[111]
Cellular therapy	• **Natural killer cells (NK cells)** o Immune cells for defense mechanism • **Mesenchymal cells** o Strong immunomodulatory and anti-inflammatory action	[112] [113]
Immunotherapy	• **Convalescent plasma therapy** o Treatment using antiviral antibodies separated from the plasma of recovered patients • **Monoclonal antibodies** o Prevention of virus entering to host cells by targeting spike proteins using monoclonal antibodies	[114] [115]

Some of these drugs show neurological effects, and some of them possess drug interaction with other lifesaving drugs such as antihypertensives, anticoagulants, and statins. Neurocognitive effects are associated with antivirals such as ritonavir and lopinavir when used for a longer period. Interferon α and ribavirin may produce neuropsychiatric effects. Antimalarials like chloroquine and hydroxychloroquine are producing neuropsychiatric adverse effects [47, 104, 105].

7. LIMITATIONS AND CURRENT SCENARIO

SARS-CoV-2 has spread globally and is considered a global pandemic. It has affected every aspect of human life. However, there is no proper treatment available to date, and the disease is still spreading from one person to another. Research works are going on for better treatments. Another matter of concern is the mutation of SARS-CoV, resulting in the emergence of new strains, making the treatment more complicated. Some affected people are not having any symptoms that make the infection more dreadful.

More clinical research needs to be conducted to classify neurological problems and their pathophysiology. Still, the long-term effects of the virus attack are unknown. Along with standard tests, CSF should be tested to understand the neurological impact of the virus.

Those who have been severely affected show high levels of cytokines due to an altered immune system, as theyare pro-inflammatory agents, which may exacerbate an existing cognitive deficit or may result in de novo cognitive impairment. Cytokines and other related chemokines such as IL-1β, IL-2, C-reactive protein, TNF-α, *etc*., are mediated in neuronal inflammation and resulted in neuronal damage. It is necessary to do cerebrospinal fluid investigations to assess the virus infiltration and predict the possible long-term effects of the virus attack.

8. FUTURE PERSPECTIVES

The impact of SARS-CoV-2 on the nervous system is very complicated and dangerous. Aged people who already suffer from neurological disorders such as CVD, stroke, and Alzheimer's are more prone to severe neurological complications due to SARS-CoV-2. Examining nasopharyngeal swabs or other respiratory specimens will not be enough to detect the virus if it is present in the nervous system. For detection of neurological involvement of virus infection, proper investigative approaches should be used for better diagnosis. It is also necessary to develop a systematic approach in treating neurological complications associated with SARS-CoV-2.

CONCLUSION

SARS-CoV-2 infection can manipulate the host's neurological homeostasis and produce unwanted effects such as headache, dizziness, loss of consciousness, and some other severe symptoms such as seizure, ischemia, hypoxia, inflammation, and encephalitis, *etc*. Along with dreadful respiratory effects, COVID-19 may affect other systems and organs. Furthermore, pre-existing disease conditions can worsen. In this review, we tried to demonstrate different diagnostic techniques, neurological effects, and their mechanisms in detail. Timely assessment of symptoms and CSF evaluation may help to manage neuronal complications of virus infection. Further clinical research is warranted to classify neurologi-

cal complications associated with SARS-CoV-2 and its treatment systematically.

LIST OF ABBREVIATIONS

SARS-CoV-2	=	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	=	Coronavirus Disease 2019
RNA	=	Ribonucleic Acid
MERS CoV	=	Middle East Respiratory Syndrome Coronavirus
SARS-CoV-1	=	Severe Acute Respiratory Syndrome Coronavirus 1
Nsp	=	Non-structural proteins
RTC	=	Replicase/transcriptase Complex
ACE2	=	Angiotensin-converting Enzyme 2
ORF1ab	=	Open Reading Frame1 ab
RdRP	=	RNA Polymerase
qRT-PCR	=	Real-time quantification Reverse Transcription-polymerase Chain Reaction
ddPCR	=	Droplet digital PCR
LOD	=	Load of Detection
IgG	=	Immunoglobulin G
IgM	=	Immunoglobulin M
IgA	=	Immunoglobulin A
ELISA	=	Enzyme-linked Immunosorbent Assay
WHO	=	World Health Organization
CNS	=	Central Nervous System
PNS	=	Peripheral Nervous System
CVD	=	Cerebrovascular Disease
GBS	=	Guillain-Barré Syndrome
BBB	=	Blood-brain Barrier
CSF	=	Cerebrospinal Fluid
CoV	=	Coronavirus
CT	=	Computerized Tomography
MRI	=	Magnetic Resonance Imaging
CRS	=	Cytokine Releasing Syndrome
IL	=	Interleukins
TNF-α	=	Tumor Necrosing Factor-alpha
G3BP1	=	Ras GTPase-activating Protein-binding Protein 1
SG	=	Stress Granules
mTOR	=	Mammalian Target of Rapamycin
UKB	=	UK Biobank
APOE	=	Apolipoprotein E
SIRS	=	Systemic Inflammatory Response Syndrome
INF-α	=	Interferon alpha
NK cells	=	Natural Killer cells

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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