Neurological diseases caused by coronavirus infection of the respiratory airways

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Neurological diseases caused by coronavirus infection of the respiratory airways

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KEYWORDS
human coronavirus, respiratory viral infection, neuroinvasion, CNS infection, neurological diseases, COVID-19

ABSTRACT
Infections of the central nervous system (CNS) infections are critical problems for public health. They are caused by several different organisms, including the respiratory coronaviruses (CoVs). CoVs usually infect the upper respiratory tract causing the common cold. However, in infants, and in elderly and immunocompromised persons, they can also affect the lower respiratory tract causing pneumonia and various syndromes of respiratory distress. CoVs also have neuroinvasive capabilities because they can spread from the respiratory tract to the CNS. Once infection begins in the CNS cells, it can cause various CNS problems such as status epilepticus, encephalitis, and long-term neurological disease. This neuroinvasive properties of CoVs may damage the CNS as a result of misdirected host immune response, which could be associated with autoimmune in susceptible individuals (virus-induced neuro-immunopathology) or associated with viral replication directly causing damage to the CNS cells (virus-induced neuropathology). In December 2019, a new disease named COVID-19 emerged which is caused by CoVs. The significant clinical symptoms of COVID-19 are related to the respiratory system, but they can also affect the CNS, causing acute cerebrovascular and intracranial infections. We describe the possible invasion routes of coronavirus in this review article, and look for the most recent findings associated with the neurological complications in the recently published literature.

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1 Introduction

Coronavirus (CoV), a member of Coronaviridae family, consists of four types of CoVs: Alpha-CoV (ACoV), Beta-CoV (BCoV), Delta-CoV (DCoV), and Gamma-CoV (GCoV) [1, 2]. This type of virus has a crown-shaped, and hence its name, “coronavirus”. They are accountable for a wide variety of respiratory and gastrointestinal diseases in multiple hosts; for example, cats, rodents, pigs, and human beings [3]. They are designed as a cluster of enveloped viruses having the largest genome among all RNA viruses. This non-segmented, 30kb, positive-strand, single-stranded polyadenylated RNA holds 4 or 5 genes that encode for the structural proteins (S, E, M, N, and HE) and some genes encode for non-structural proteins, generally covered in open reading frame (ORF) 1a and 1b. They encode two large polyproteins (pp1a and pp1ab) which are sliced by two viral proteases to produce 15–16 non-structural proteins, together with the RNA-dependent RNA polymerases (RdRp), helicase and exoribonuclease, that play a dynamic role in viral replication [4]. In a human being, different kinds of human CoV (HCoV) are labeled as pathogenic, and include HCoV-229E, HCoV-OC43, Middle East respiratory syndrome CoV (MERS-CoV), and severe acute respiratory syndrome CoV (SARS-CoV). Each one of them has a particular genotype [5]. Later in 2019, the coronavirus disease-2019 (COVID-19) epidemic known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) appeared in the city of Wuhan, China, thus attracting worldwide attention [6]. It was declared a pandemic by the World Health Organization (WHO) on March 11th, 2020 [7]. SARS-CoV-2 has a structure and infection procedure that are similar to other coronaviruses, such as SARS-CoV and MERS-CoV [8, 9]. Further classification of human CoVs with their strains and cellular receptors is shown in Table 1.

### 1.1 Methodology

The following online database/online search engine was used to conduct a comprehensive search of scientific publications (original articles related to experimental and observational studies, case series and reports, among others): PubMed, Google Scholar, Scopus, Web of Science, bioRxiv, medRxiv, CNKI, and WanFang Data (the latter are the two main databases for biomedical research within mainland China). The names or terms used to search the database were: “neurological diseases due to coronavirus”, “neurological complications of COVID-19”, “neurological manifestations of novel coronavirus 2019”, “neurological complications of COVID-19”, “neurological complications of coronavirus 2019”, “neurological complications

| Table 1 | Classification of human coronavirus (HCoV). |
|---------|------------------------------------------|
| Genera | Coronavirusinae | Strains | Year of origin | Receptors | Host | References |
| Alpha-coronavirus | Human aminopeptidase N (APN, or CD13) | HCoV-229E | 1966 | Bats | [10-12] |
| | Angiotensin-converting enzyme 2 (ACE2) | HCoV-NL63 | 2004 | Bats, Palm Civets | [12, 13] |
| | 9-O-acetylated sialic acid | HCoV-OC43 | 1967 | Cattle | [14, 15] |
| Beta-coronavirus | 9-O-acetylated sialic acid | HCoV-HKU1 | 2005 | Mice | [16, 17] |
| | ACE2 | SARS-CoV | 2003 | Bats | [12, 17, 18] |
| | DPP4 | MERS-CoV | 2012 | Camel | [19] |
of SARS-CoV-2", and “neurological manifestations due to respiratory viruses”. All related articles were examined in search of a likely neurological disorder associated with COVID-19. We included articles from December 2019 to April 2020, either published or in preprint form and 45 articles were categorized according to the search words and finally reviewed. These published studies were then carefully evaluated according to the following selection principles: confirmed cases of COVID-19, cases having neurological manifestations, studies including a clear description of the clinical cases, experimental studies performed in animal models, and studies on patients diagnosed with SARS-CoV-2 illness affecting the nervous system. A brief review was written based on the association between the nervous system and COVID-19.

1.2 Coronavirus as a respiratory pathogen

HCoV is primarily linked to common colds typically infecting the upper respiratory tract. However, among more exposed populations, such as newborns, children, the elderly, and immunocompromised individuals, it can spread to the lower part of the respiratory tract, where it can become associated with pneumonia, respiratory distress syndrome, exacerbations of asthma, or even SARS [20, 21]. In the late 1960s, the global medical association ignored HCoV infection in human beings; however, at the beginning of the 21st century, when a SARS outbreak occurred in Southeast Asia these innocent microorganisms rapidly became a more interesting topic for the experts. The SARS pandemic (2002–2003) is believed to have been caused by a variant of coronavirus, originating from a bat source and leading to infections in palm civets and other species kept in open shops, serving as intermediate hosts before causing disease in humans. Furthermore, 10 years after the first episode of SARS, the WHO notified the medical communities around the world that people suffering from a SARS-like illness who moved from the Arabian Headland to Britain might likely cause a rebound of this disease. Molecular sequencing techniques were used to demonstrate that this new respiratory CoV is inherently different from SARS-CoV, thus highlighting the usefulness of this technique in the diagnosis of viral disease. It is now known that the new epidemic triggered by a novel coronavirus from the class Beta-coronavirus was first named HCoV-EMC (for “Human Coronavirus-Erasmus Medical Center”), Human Beta-coronavirus 2, or nCoV (for novel coronavirus). Now it has officially been named “Middle East Respiratory Syndrome Coronavirus” (MERS-CoV) [22].

1.3 Coronavirus as a CNS pathogen

The discovery of HCoV RNA in human brain specimens has helped determine that these respiratory viruses are typically neuroinvasive in human beings, and lead to persistent CNS infections in humans [16]. HCoV was first isolated from individuals suffering from upper respiratory tract disease in the mid-1960s. OC43 and 229E (characterized by strains OC43 and 229E) were the only two serological groups recognized by the end of the 20th century, and responsible for infecting human beings. They were known as the respiratory organisms causing up to 30% of common colds [21]. Over the past decade, SARS brought new attention to coronaviruses, leading to the detection of new strains that cause infection in human beings: SARS-CoV [24, 25], HCoV-NL63 [26], HCoV-HKU1 [27], and MERS-CoV [28]. Three of these 6 CoVs, HCoV-OC43, HCoV-229E, and SARS-CoV have typical neuroinvasive properties, since

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the viral RNA can lead to an infection in the human CNS [16].

1.4 The neuroinvasion mechanism of coronavirus

HCoV may disrupt the nasal epithelium in human airways, where they develop and are later discharged from the apical border of the epithelial cells. A significant number of viruses are also released from the basolateral margin of epithelial cells [29, 30]. Specifically, HCoV can spread to the CNS and induce encephalitis. Often, HCoV infections are limited to the airways where they are not fully identified, resulting in the possibility of the virus passing over the epithelial barrier and reaching the circulatory or lymphatic system and possibly spreading to the CNS and other tissues of the body [3, 21, 31, 32]. Apart from HCoV, several other respiratory organisms that can reach the CNS are the influenza virus, respiratory syncytial virus, and Nipah virus. The two main routes by which the virus enters the CNS are hematogenous dissemination and neuronal dissemination [33]. To be neuroinvasive, different viral organisms, for example, SARS-CoV, HCoV-229E, and HCoV-OC43, use both entry routes from the peripheral region. The hematogenous route leads to entry of the viral organism into the bloodstream, where it can remain free for a period of time before it infects the endothelial cells of the blood–brain barrier (BBB) [34]. Furthermore, persistently infected leukocytes [32] may also act as a source and vector for neuroinvasive HCoV [16].

It has been reported that the HCoV-OC43 and HCoV-229E viruses infect human cells, especially the monocytes/macrophages [35, 36]. Murine dendritic cells infected with HCoV-229E express human aminopeptidase N [37], which is an indication that HCoVs could use them to spread into the surrounding tissues, especially into the CNS, where they would be associated with another sort of pathology. SARS-CoV has also showed the capability of infecting human monocytes/macrophages [38, 39]. HCoV-229E infection leads to the activation of human primary monocytes [35]. Later, these cells become macrophages and begin to enter the tissue, where HCoV-229E-contaminated monocytes help and promote their passage to different other tissues in the body, especially the CNS, and particularly in individuals who are immunocompromised [40].

Another course for the spread of infection to the CNS is through neuronal invasion. A specific virus starts infecting the nerve cells in the peripheral region, to gain entrance into the CNS using active transport methodology in the specified cells [33, 41]. Although the olfactory bulb is exceptionally useful in regulating neuronal invasion, many viruses follow the olfactory route to access the CNS [42, 43]. Several studies were conducted with laboratory animals, which illustrated that, after an intranasal infection, the respiratory tracts of the mice were found to be infected with HCoV-OC43 and SARS-CoV, which are neuroinvasive [44–48]. Different authors and specialists have gathered information over the years and discovered that HCoV-OC43 is naturally neuroinvasive in mice and human beings [16, 44, 46, 49, 50]. HCoV-OC43 can collect in the cell body. It can be assembled at various points of the axon employing the antergrade axonal transport mechanism to spread among cells or from neurons into glial cells. Intranasal experiments on vulnerable mice also show that once the virus has entered the CNS, it spreads to multiple areas of the brain, including the brainstem, before it finally spreads to the spinal cord [50–52]. The response of the
spinal cord injury mouse model to coronavirus was mild. After a spinal cord injury, the information and the effects of the coronavirus may not spread into the brain correctly, to initiate and bring an early response for the body. In the end, we found that HCoV-OC43 and HCoV-229E may utilize both routes, which are the transneuronal and hematogenous ones, in the direction of the CNS. The possible infection pathway used by HCoV for neuro-invasion of the CNS and its likely mechanism of neurovirulence is represented below (Fig. 1).

**2 Mechanisms of neurodegeneration caused by coronavirus and related neurological diseases**

Although no direct correlation has been observed for the onset of CNS diseases, HCoV-229E and HCoV-OC43 have been found in numerous neurological syndromes in human beings, involving Parkinson’s disease and multiple sclerosis (MS) [16]. MS represents a disease of the human nervous system, where one or more infectious agents may perform a prompting

![Fig. 1](image_url)
role, affecting immunocompromised individuals [53]. However, scientists have not found any direct association of any microorganism with MS. The relationship between coronavirus and MS was featured in numerous articles that are debated and revised elsewhere [54]. One of these reports demonstrates a steady relationship of colds and MS exacerbations. Likewise, HCoV-229E infection is significantly associated with MS patients [55]. Evidence showing a link between viral infections and MS [56] suggested that cyclical HCoV infection forms fit the observed occurrence of MS exacerbations.

Previously, researchers could rule out that HCoV-229E and HCoV-OC43 have biological neuroinvasive ability in human beings. Viruses were recognized in selected control brains and in several brains originating from individuals suffering from distinctive neurological diseases, including Parkinson’s and Alzheimer’s diseases [57]. Some of them were expressively having a higher incidence of HCoV-OC43 in those patients’ brains suffering from MS [16], and in the female brain samples, as shown in Fig. 2 [58]. Even though this observation is only incidental and, more importantly, they saw that MS is more dominant in women than in men [59]. Also, these statistics correlate with the examination, that during the infection with HCoV-OC43 and HCoV-229E, autoreactive T cells have the capacity to identify both the viral and myelin antigens in individuals with MS [58]. This indicates that the person’s immune reaction may provide the induction or exacerbation of neurological disease; for example, MS in heritably or otherwise vulnerable sick patients [58]. Furthermore, even the use of cyclosporin A, an immunosuppressant drug used in mice infected with HCoV-OC43, led to a more rapid onset of inflammation in the brain (encephalitis), indicating the responsibility of T cells used for the survival and clearance of the virus without any appropriate immunopathology [19]. It was also noted that encephalitis caused by HCoV-OC43

![Fig. 2](http://bja.tsinghua.com/)

**Fig. 2** Recognition of coronavirus RNA in human CNS and HCoV-myelin antigen cross-reactive T cells in MS patients. (A) Double-blind examination of 90 human brain post-mortem trials showed the occurrence of HCoV-229E and HCoV-OC43 RNA in healthy controls, patients with other neurological disorders (OND), and patients with MS. The percentage of brain specimens from MS patients having HCoV-OC43 RNA was clearly higher than that of OND and healthy controls. RNA taken from both HCoV was seen more frequently in female brains compared to male brains. (B) Additional monospecific T-cell clones were isolated from MS patients in comparison to healthy controls, and cross-reactive T-cell clones were isolated only from MS patients. Reproduced with permission from Ref. [3]. Elsevier Sci Ltd, 2014.
might be somewhat facilitated by the reaction of T cells to contamination in recombination activation gene knock-out rats [46].

The contribution of different forms of T cells has been shown to play a vital role in demyelinating CNS diseases produced by the murine CoV, specifically for mouse hepatitis virus, strain JHM (MHV-JHM) [60]. In the CNS of mice, expressing mouse hepatitis virus is used as an experimental model that causes chronic demyelinating infections. In recent studies, this murine coronavirus has caused partial oxidative tissue injury, which was noticed in MS individuals [61], highlighting that longstanding diseases of the nervous system caused by CoVs could generate MS-like lesions. Patients can also be checked for the persistence of HCoV viral RNA in the CNS [16]. In some cases, this may be associated with the beginning or worsening of different neurological diseases, including MS.

Experts determined that the HCoV-OC43 virus initiates the process of immune cell infiltration and cytokine assembling inside the mouse CNS, by experimenting with alternative mouse models. The immune response was expressively expanded subsequently due to the infection caused by the virus variations, which harbor alterations on the top of viral glycoprotein (S), resulting from the viral infection of human nerve cells [51] which induce glutamate excitotoxicity [52, 62]. The increase in cytokine production after S-mutant virus infection might initiate neuronal injury [63] causing disturbance in glutamate homeostasis by downregulating the glutamate transporter GLT-1 receptors on astrocytes,

![Diagram](image)

**Fig. 3** HCoV infection causes an increase in the production of pro-inflammatory cytokines and neuronal degeneration as an outcome of glutamate excitotoxicity. In a physical state, glutamate is mainly produced by neurons and discharged in the synaptic cleft, which is a junctional point between two neurons, as a primary excitatory neurotransmitter of the nervous system that starts the ligand-dependent receptor AMPAr (alpha-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid receptor). This allows the entry of sodium ions and the passage of the nerve impulse in the post-synaptic neuron, leading to activation of the N-methyl-D-aspartate receptor that permits the entrance of calcium ions. During infection of neurons caused by HCoV-OC43, microglial cells spot the existence of virus and produce pro-inflammatory cytokines (TNF-α, IL-1β) and IL-6 which downregulate the astrocytic receptor glutamate transporter 1 (GLT-1) and avoid the efficient recapture of glutamate. This condition interrupts the control of glutamate homeostasis and due to the overproduction of this neurotransmitter in the synaptic cleft leads to excitotoxicity with a massive entrance of calcium which ultimately leads to nerve cell degeneration and loss. Reproduced with permission from Ref. [3], Elsevier Sci Ltd, 2014.
which can bring back the additional amount of glutamate, and produce glutamate excitotoxicity [64]. As a result, neuronal degeneration occurs, as shown in Fig. 3 [52], which may be related to hind-limb paralysis and possibly CNS damage [65]. The result of the experimental neuronal collapse may ultimately lead to the death of these innate cells.

Even though HCoV has the capability of infecting the CNS, back in 1980, its presence in human CNS-related models was characterized. This virus was first noticed in a post-mortem of patients with MS [65]. Since then, several reports have confirmed the existence of the virus in specimens obtained from MS patients by performing different procedures [66, 67]. In 2000, a study was conducted in which post-mortem specimens were taken from individuals suffering from several neuro pathologies (among them MS was generally predominant) demonstrated that 67% were found to be positive for HCoV (with HCoV-229E being twice as regular as HCoV-OC43 [16]. Furthermore, the predominance of HCoV-OC43 in MS specimens was statistically more considerable than that of control individuals, which was the primary statement to provide an essential indicator of the neurotropic capacity of these respiratory organisms [68]. The first incident of SARS-CoV infection-causing neurological signs and symptoms was accounted back in 2003, in a 59-year-old female [69]. This woman was initially admitted to the hospital with a history of fluctuation in fever, chills, cough, and diarrhea, ultimately leading to limb twitching, convulsions, and continuous requirement of oxygen supply [69]. Later, infection of SARS-CoV was diagnosed in the tracheal aspiration sample and in the cerebrospinal fluid (CSF) samples, which were treated with ribavirin, but still, seizure duration did not improve.

Furthermore, some additional treatments were performed after which no episode of seizures was noticed, and later she was sent home three weeks after being admitted to the hospital [69]. The next year, one more case of SARS-CoV infection was observed in a 32-year-old woman where the genetic substance was found in the CSF samples as the pathway is shown in Fig. 4 [70].

![Fig. 4](https://example.com/fig4.jpg)

**Fig. 4** CoV flows into the nervous system via the olfactory bulb, producing inflammation and demyelination. Upon nasal infection, HCoV can enter the CNS through the olfactory bulb, as ablation of this portion of the brain limits its neurotropic capacities in mouse models. After the infection is ready, the virus can extend to the whole brain, including CSF in less than a week. Therefore, it has been explained that this virus can cause demyelination. Similarly, primary glial cultures have been found to secrete IL-6, IL-12p40, IL-15, TNF-α, CXCL9, and CXCL10 upon viral infection. Reproduced with the permission from Ref. [25], Frontiers in Cellular Neuroscience, 2018.

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Fecal specimens and peritoneal fluid tests were also positive. The patient was admitted at 26 weeks of pregnancy and required mechanical ventilation 7 days after admission. On day 8, she showed signs of acute kidney failure which lead to the termination of the pregnancy via cesarean section, and a newborn girl was born with no additional complications [70]. Later, after three weeks, the patient was put under anesthesia, and mechanical ventilation was performed. Finally, on the 27th day, the endotracheal tube (ETT) was removed with no episodes of seizures [70]. Organ transmission of SARS-CoV in post-mortem specimens of individuals who passed away from the infection was revealed. The post-mortem statement specifies that the discovery of SARS-CoV-N protein and viral RNA in the gastrointestinal tract, kidney, sweat glands, parathyroid, pituitary gland, liver and cerebrum, proves that this virus can cause systemic infection [71].

Another report of HCoV-OC43 was spotted in samples from CSF and nasopharyngeal area taken from a teenager back in 2004 [72]. Later, the kid displayed acute diffuse encephalomyelitis, a low-endemic nervous system infection that can cause demyelination, which is indicated as the first case associated with HCoV. No other infectious organisms were found in other specimens [73]. Therefore, a detailed description of the cytokine profile in the nervous system, brought by SARS-CoV infectivity, was advertised. Hence, the researchers revealed that these two chemokines induced by IFN-γ (CXCL9, a CXC chemokines family member) and IFN-γ-inducible protein 10 (CXCL10) were significantly produced in brain specimens from a sick individual as shown in Fig. 4 [74]. Still, many reports showed a more significant amount of CXCL10 in SARS-CoV-infected persons, showing no neurological signs and symptoms. As a result, researchers believe that CXCL9 might be strongly associated with CNS illness [74].

A new report published in 2016 describes several characteristics of HCoV infectivity in the nervous system and respiratory infections. Starting with the 183 kids suspected of being admitted in hospital with acute encephalitis, out of which 22 patients showing HCoV infections were positive, with nausea/vomiting, headache, and having high temperature as the most common manifestations. Usually, they specified that peripheral blood lymphocytes and eosinophils counts in CNS-HCoV-infected individuals were lower in contrast with respiratory-HCoV-infected patients. Simultaneously, the immune cells might be linked to the immune reaction provoked by the virus—it is either respiratory-restrained or displays neurotropism capabilities [75].

The capability of the nervous system afterward, the nasal infection has been explained formerly in mice models, especially for HCoV-OC43 [47]. Another researcher reported that three days after infection, viral antigens were detected in OBs. At the same time, the virus was not found in peripheral blood cells or anywhere else in the brain. Later, after one week, the viral organism was identified in whole brain tissue, suggesting that once established in the CNS, it could spread rapidly. This replication resulted in the death of acute encephalitis in sick mice. Strikingly, the excision of olfactory bulbs prevents transmission of the MHV after nasal contamination [76]. For that reason, HCoV has the inherent ability to infect nerve cells and disseminated from the nervous system into the surrounding environment through a trans neural pathway, which can also be seen in the MHV [76, 77].

As described so far, CoVs are respiratory viruses with neurotropic capabilities that not just empower them to accomplish expectancy and maintain a strategic distance from host
immune response, yet additionally have neurological importance and could worsen the infection-related diseases. Although its methods and pathway to arrive at the CNS have not been resolved, the recognition of viral proteins or genetic material in this issue has been systematically proven, dividing the researcher’s aims into obtaining new knowledge in regards to this subject. Up until now, epidemiological reports have made it possible to accomplish this. Still, further investigation is required in creature models to thoroughly understand the systems utilized by coronaviruses to enter the CNS and to come after more appropriate medications to put an end to this viral infection with no aggravated disease.

3 COVID-19

Coronavirus is a single and positive-stranded RNA virus without fragments. The coronavirus family is separated into four different genera α, β, γ, and δ. It is a pathogen that mainly targets lungs and intestinal area causing respiratory and intestinal diseases. SARS-CoV-2 belongs to the new Beta-type coronavirus, with a total of nearly 29,000 nucleotide bases. These bases hold genetic instructions for reproduction and are one of the viruses that exist in the form of RNA. SARS-CoV-2 genomic sequence analysis has been published in various academic journals. A recent study found that the SARS-CoV-2 virus sequence is very similar to bat coronavirus, the overall genome sequence identity is 96.2%, and there is 79.5% sequence homology with SARS coronavirus [78]. SARS-CoV-2 has a unique recognition protein marker known as “spike proteins” that lies on the surface of the cell membrane. This spike protein allows the coronavirus to recognize angiotensin-converting enzyme 2 (ACE2) and enter the mucosal epithelium. Still, research is ongoing to determine whether this virus can infect T cells or any other cells, which has been detected the expression for this virus. A research center recently proposed that pangolins may be an intermediate host [79], but it may be too early to confirm. Still, there is a long way to find a source of the virus. A study was conducted in 214 patients to find the neurological manifestations of COVID-19; out of these 214 patients, 78 patients show the neurological events with a percentage of 36.4%, which suggests that COVID-19 has the potential and robust neurotrophic effect.

3.1 Mode of transmission

The main routes for the transmission of the SARS-CoV-2 are via respiratory droplets and contact transmission [80]. Although this new virus also belongs to the SARS and MERS coronaviruses family, the main thing that makes it different is the “genetic characteristics”. There is also some evidence of the virus's detection in the stools that leads us to speculate that the digestive tract can also be the source for transmission through aerosol, but it is not yet identified [81].

3.2 Clinical findings

COVID-19 is highly contagious and has a very long incubation period. The incubation period is generally 3–14 days, and the most prolonged period is 24 days. In Table 2, the symptoms associated with COVID-19 are summarized [81, 82]. The COVID-19 first affects the respiratory system, and from there, it spreads into the CNS. It affects the lungs by decreasing its stretching ability and causing lung fibrosis. The clinical data of 214 patients hospitalized with COVID-19 in three different designated nursing hospitals in Wuhan was collected to assess the presence of neurological symptoms. Among all these patients, 36.4% showed major neurological manifestations.
However, these neurological manifestations were more common in people with severe illness, including acute cerebrovascular symptoms, impaired consciousness, and skeletal muscle symptoms.

3.3 Mechanisms of COVID-19 infection in cerebral system

As previously described in patients suffering from acute respiratory failure, the COVID-19 virus can pass into the brain via a transcribral route. At the beginning phase of COVID-19 infection, the virus may enter the cerebral circulation, and slow down the movement of blood in the microvessels, which might be one of the reasons that can advance the interaction between COVID-19 spike protein and ACE2 receptor expressions in the capillary endothelium. Therefore, virus fragments sprouting out from the capillary endothelium and damaging the endothelial layer can promote the access of the virus into the CNS. Once it is in the neuronal environment, its interaction with the ACE2 receptor expression can start the viral bud cycle, which is joined by neuronal impairment, with no production of any substantial inflammation.

COVID-19 might increase the chance of arterial and venous thrombo-embolism disorders, causing inflammation, hypoxia, and diffuse intravascular coagulation. Until now, the clinical cases of stroke and its association with COVID-19 are few [83–85]. A study was performed among 214 COVID-19 patients at Wuhan, out of which 36.4% patients shows the neurological symptoms. Neurological manifestations were seen in many patients, especially in the critical case group. Computed tomography was obtained, which showed few patients with ischemic stroke and intracerebral bleeding. The patients with stroke were older and showed a few typical signs and symptoms of COVID-19 having co-morbidities such as hypertension [83]. Another study was conducted in the USA where more than 350 patients with COVID-19 were examined, but there was no confirmation of cerebrovascular disease. However, in younger people having relatively mild signs and symptoms of COVID-19, stroke was reported arising from the blockage of the large vessel [86].

Many countries around the world have published stroke instructions and guidelines during this COVID-19 pandemic. In Singapore, when the first patient suffering from COVID-19 was admitted to the hospital, early investigation and treatment of stroke were performed in individuals suffering from SARS-CoV-2 using endovascular therapy (EVT) and intravenous thrombolysis (TPA) [80, 87].

Ischemic stroke and hemorrhagic stroke are known to be possible neurological complications of COVID-19 [88]. Intracerebral hemorrhage and subarachnoid hemorrhage might be associated with arterial hypertension stimulated by joining of SARS-CoV-2 to ACE2 receptors and decrease in the platelet counts [82, 89]. It is necessary to state here that, before the proposed expected

| Table 2: Clinical features associated with COVID-19 |
|-----------------------------------------------|
| Major clinical manifestations                  |
| Fever                                         |
| Dry cough                                     |
| Shortness of breath                           |
| Fatigue                                       |
| Pharyngalgia                                  |
| Abdominal pain                                |
| Diarrhea                                      |
| Conjunctivitis                                |
| Neurological symptoms                         |
| Acute cerebrovascular symptoms                |
| Sudden slurred speech                         |
| Paralysis of limbs                            |
| Intracranial infection                        |
| Headache                                      |
| Seizures                                      |
| Unconsciousness                               |
| Muscle disorder symptoms                      |
| Soreness and weakness                         |
| Other symptoms                                |
| Neuralgia                                     |
| Paresthesia                                   |
| Sphincter dysfunction                         |

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neuronal damage, rupture of brain capillary endothelium leading to the bleeding in the brain tissue may have lethal consequences for patients with COVID-19 infection.

3.4 Differences between the neurological complications associated with SARS-CoV, MERS-CoV and SARS-CoV-2 infection

As we know that HCoV could spread into the CNS because of its neuroinvasion capabilities, which can form different neurological complications [90]. Here, we present a table showing the difference among the neurological complications between different coronaviruses.

3.5 Neurological findings and precautions during COVID-19 treatment

Most patients affected by the virus are middle-aged and older, or critically ill. These patients may have had an acute ischemic stroke and are more prone to embolic vascular events, having abnormally increased D-dimers [81, 82, 110]. The neurologist should take different treatment measures, especially in patients with a cerebrovascular disease where anticoagulation therapy is recommended for stroke [111, 112]. As the SARS-CoV-2 virus binds to ACE2 receptors [73], some patients with hypertension and COVID-19 infection may show an abnormal increase in blood pressure and increase the risk of cerebral hemorrhage and ischemic stroke. For the sequel of ischemic stroke, few treatment options have been successful in restoring the brain function in current clinical studies except comprehensive cell-based therapy, which indicates that special attention and precautionary measures need to be taken in stroke patients infected with COVID-19 [113–115]. Different studies have shown that the antihypertensive drugs ACE inhibitor (ACEI) and angiotensin II receptor blockers may increase the receptor expressions for ACE2. To avoid aggravating symptoms, these drugs should be stopped in these patients and switched to other hypertensive medications like calcium channel blockers diuretics, and hypertensive medicines. Furthermore, some patients may have intracranial infections that could lead to symptoms like headache, epilepsy, and unconsciousness. Many patients with higher levels of neurological injuries may require a nasal catheter to support breathing. In that case, doctors must pay attention to keep the patient’s nasal catheter clear and sterile because it may provide a route for transmission for COVID-19 to enter into the brain. It requires great attention

**Table 3 Differences between the neurological complications among different coronaviruses.**

| Type of coronavirus | Neurological complications | References |
|---------------------|---------------------------|------------|
| SARS-CoV            | Epilepsy (Status epilepticus and generalized tonic clonic seizures) | [69, 70, 91–99] |
|                     | Neuromuscular disorders (myopathy & polyneuropathy) | |
|                     | Oditory neuropathy | |
|                     | Stroke | |
|                     | Chronic post SARS Syndrome | |
|                     | Autonomic dysfunction | |
|                     | Acute disseminated encephalomyelitis (ADEM) | |
|                     | Acute bilaterally non-occlusive stroke | [100–102] |
|                     | Right frontal lobe intracerebral hemorrhage | |
|                     | Polynepathy | |
|                     | Guillain-Barré syndrome | |
| MERS-CoV            | Critical illness polyneuropathy | [103–109] |
| SARS-CoV-2          | Ischemic stroke | |
|                     | Intracerebral hemorrhage | |
|                     | Cerebral venous sinus thrombosis | |
on the part of neurologists to perform investigations like magnetic resonance imaging scans and lumbar punctures if the patient is willing to rule out the presence of SARS-CoV-2 viral nucleic acid in the CSF. The SARS-CoV-2 may enter the CNS through the cribriform plate near the olfactory bulb and affect the brain. Furthermore, patients with early COVID-19 without complications should be thoroughly examined for olfactory changes or hyponatremia through CNS interventions. Here, physicians need to combine the principles of diagnosis and treatment of intracranial infection, as well as COVID-19 treatment guidelines, for brain protection, epilepsy, and other antipsychotic symptoms.

4 Conclusion

Respiratory viruses are the primary cause for pneumonia and bronchiolitis worldwide, affecting individuals of different ages but posing a greater threat to young teenagers, and elderly and immunodeficient individuals. The dominant respiratory viruses responsible for these illnesses are HCoV, hRSV, and IV. Of all these, HCoV is a significant concern due to the specific pathways (i.e., trans neural and hematogenous) followed when causing extrapulmonary complications in the CNS, such as febrile seizures, syncope, convulsions, status epilepticus, limb paralisis, encephalitis, and MS, among others. However, the exact mechanism responsible for transmitting this neurotropic virus to the CNS has not been accurately determined. COVID-19, a new disease caused by a type of coronavirus, also leads to significant neurological symptoms, thus leading researchers to direct more efforts toward evaluating it. To date, several mouse models for CoV have been set up, making it possible to acquire new data and understand their neurotropic capacities and neurological signs and symptoms. Thus, new epidemiological data need to be broadly compiled to establish an increasingly significant and straightforward connection between coronaviruses and human CNS infections, in order to rule out specific mechanisms of virus transmission to the CNS. However, additional research is still needed, as various characteristics of these CNS diseases are yet to be identified.

Conflict of interests

The authors declare that they have no conflict of interests.

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