



COVID-19: a new emerging respiratory disease from the neurological perspective

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Abstract

Coronavirus disease 2019 (COVID-19) has become a challenging public health catastrophe worldwide. The newly emerged disease spread in almost all countries and infected 100 million persons worldwide. The infection is not limited to the respiratory system but involves various body systems and may lead to multiple organ failure. Tissue degenerative changes result from direct viral invasion, indirect consequences, or through an uncontrolled immune response. [Severe acute respiratory syndrome coronavirus 2](#) (SARS-CoV-2) spreads to the brain via hematogenous and neural routes accompanied with dysfunction of the blood–brain barrier. The involvement of the central nervous system is now suspected to be among the main causes of death. The present review discusses the historical background of coronaviruses, their role in previous and ongoing pandemics, the way they escape the immune system, why they are able to spread despite all undertaken measures, in addition to the neurological manifestations, long-term consequences of the disease, and various routes of viral introduction to the CNS.

Keywords ACE2 receptors · COVID-19 · MERS · Neurological signs · SARS-CoV-2

Introduction

The sudden spread of the novel coronavirus worldwide released international panic and alarm signals. The novel SARS-CoV-2 virus responsible for the outbreak of respiratory illness was first observed in Wuhan, China, in December 2019. However, some reports refer to the earlier detection of the virus in clinical samples and sewage water in many western countries (Deslandes et al. 2020, Gemma Chavarria-Miró et al. 2020).

Many researchers discussed the reasons why coronavirus disease (COVID-19) spread, persisted, induced great economic losses, and represented a serious public health hazard, which include (1) the high contagiousness of the virus.

Although the predominant mode of transmission is via respiratory droplets, some researchers reported that SARS-CoV-2 could behave as an airborne pathogen (Jayaweera et al. 2020; Zhang et al. 2020c; John et al. 2020). (2) Its ability to utilize various types of receptors to invade the tissues which expand its virus tissue tropism (Bittmann et al. 2020). (3) The continuous adaptation of the virus to the human host via mutations to develop more contagious and more virulent variants of the virus (Becerra-Flores and Cardozo 2020; Zhang et al. 2020b). (4) The persistence of the virus for a relatively long time inside the patients even after its clearance from the nasoral cavity (Ling et al. 2020; Wang et al. 2020). (5) Its excretion in various body fluids such as urine, milk, and nasal discharges (S. Costa et al. 2020, Fei Xiao et al. 2020, Holtmann et al. 2020, Colavita et al. 2020, Sun et al. 2020). (6) Its robustness to various environmental factors and sunlight. The virus is very robust and can persist in the environment for a relatively long time and keeps its infectivity during this period. Infected persons release viral bioaerosols that remain infectious for up to 16 h in site after viral shedding and airborne transport (Fears et al. 2020). The virus can also persist on animal skin, banknotes, cloths, frozen contaminated meat, and other surfaces for up to 4 weeks, depending on the surface and the surrounding temperature (Harbourt et al. 2020). (7) Exposure of the viral antigens to antigen-

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presenting cells (APCs) as macrophages activates the production of proinflammatory cytokines set, including IL-1, IL-4, IL-6, IL-8, MCSF, CXCL-10, and TNF- α (Alquisiras-Burgos et al. 2020; Gao et al. 2020) (Fig. 1). An unbalanced response to invasion may lead to what is known as storm of cytokine (Fig. 1), which is very serious and threatens the life of the patient (Li et al. 2020a; Mahmudpour et al. 2020). (8) According to available data so far, the absence of the production of longstanding protective titer of antibodies was observed in many patients. The lifespan of the produced antibodies may not exceed 2–3 months according to the literature (Bachmann et al. 2021). This point is very serious as it hinders susceptible populations from achieving (herd immunity) status, prevents the development of an efficient protective vaccinal strategy, blocks the possibility of using plasma of recovered persons in the treatment of serious cases, and enables repeated infections of the same person (Long et al. 2020, Jiang et al. 2020, Marina Pollán et al. 2020, Lucas et al. 2020). (9) The presence of apparently healthy clinically normal shedders who harbor the virus without showing any clinical signs mostly children (Long et al. 2020; Bittmann et al. 2020). And finally, (10) its ability to escape the immune system and to develop a low titer of antibodies following infection (even no antibodies in some cases) which subjects the patients to be infected repeated times. This makes it difficult to develop a vaccine, the use of plasma in treatment and prevents the occurrence of herd immunity (Pollan et al. 2020, Marina Pollán et al. 2020).

Classification and history of coronaviruses epidemics

Coronaviruses, a Latin word for crown, were named after their characteristic crown-shaped under electron microscope. Coronaviruses (CoVs) are enveloped positive-sense RNA viruses. They are characterized by their club-like spikes (S) that project from their outer surface to facilitate adhesion to host receptors (Velavan and Meyer 2020) (Fig. 2). They own unusually large RNA genomes. Coronaviruses cause a variety of diseases in mammals and birds ranging from enteritis in cows and pigs and upper respiratory disease chickens to potentially lethal human respiratory infections. Coronaviruses (CoVs) are members of the *Coronaviridae* family. The family consists of two major subfamilies, *Coronavirinae* and *Torovirinae*. The corona members are divided in turn into four genera, *Alpha-*, *Beta-*, *Gamma-* and *Deltacoronavirus*. The viruses are characterized by enveloped positive-sense single-strand RNA particles. Their genomes are characterized by their large size (27–32 kb) (Fehr and Perlman 2015). Both Alpha and Beta coronaviruses have restricted host affinity and can infect only mammals. Meanwhile, gamma and delta members target mainly birds with some exceptional members that can infect mammals also (Woo et al. 2012).

Betacoronavirus, can be divided into five subgenera (*Nobecovirus*, *Hibecovirus*, *Embecovirus*, *Sarbecovirus*, and *Merbecovirus*) with a clear zoonotic potential for the last two subgenera (such as SARS-CoV1, MERS, and SARS-CoV-2 viruses as will be discussed later) (Wong et al. 2019; Cui et al. 2019; Dong et al. 2020). The first defined

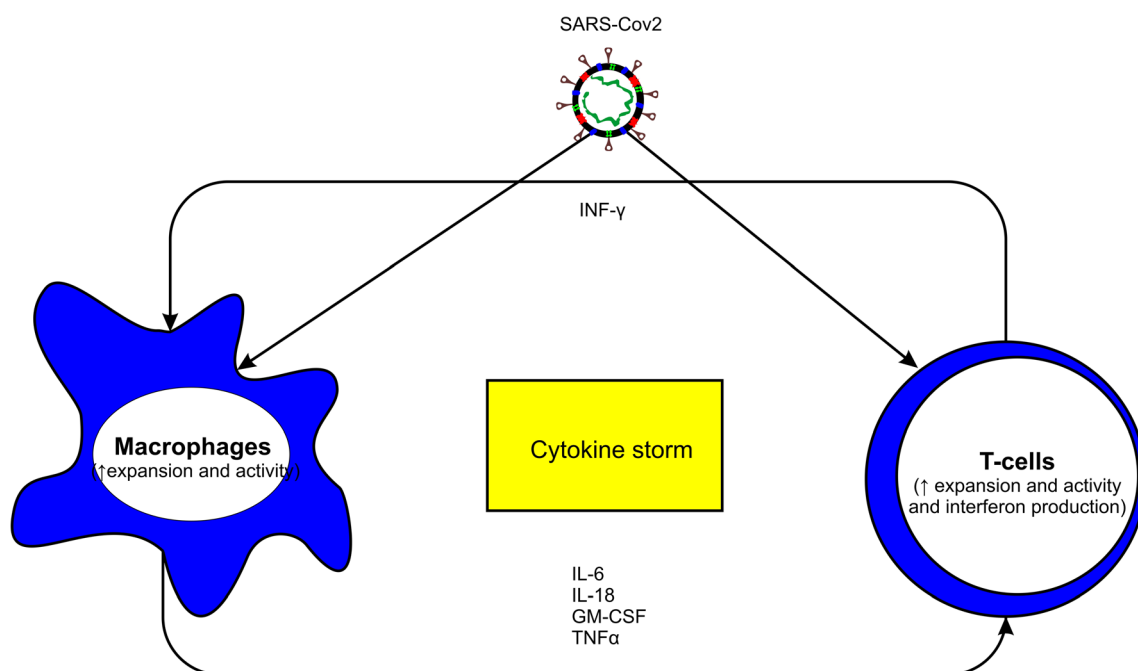


Fig. 1 Cytokine storm induced by SARS-CoV-2

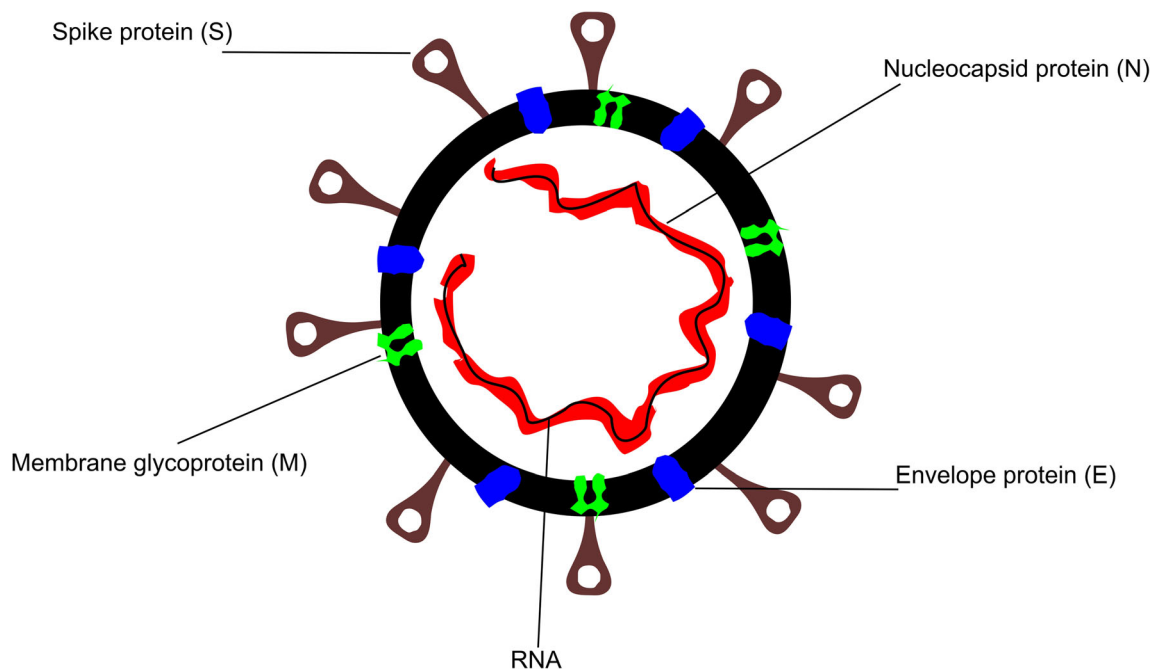


Fig. 2 Schematic diagram of SARS-CoV-2

coronavirus was the avian infectious bronchitis virus, which was isolated in 1937. This was followed by discovering another two animal pathogens in the 1940s, namely, the mouse hepatitis virus and the porcine transmissible gastroenteritis virus (Alluwaimi et al. 2020). Later on, in the 1960s, the first human coronavirus could be identified together with the porcine hemagglutinating encephalomyelitis virus. Several coronaviruses could be reported in the following decade, such as the turkey coronavirus, the bovine coronavirus, the porcine epidemic diarrhea virus, the feline coronavirus, and the canine coronavirus. In the 1980s, the swine pathogen (porcine respiratory coronavirus) was identified as the last corona member to be reported in the 20th century (SAIF 2004; Leyi 2016). With the beginning of the 21st century, coronaviruses started to induce serious human epidemics (severe acute respiratory syndrome (SARS-CoV1 and SARS-CoV-2)) in 2002 and 2019, respectively, in addition to MERS-CoV (Middle East Respiratory Syndrome) virus in 2012.

SARS-CoV-2 structure

Like other coronaviruses, the SARS-CoV-2 genome consists of 10–12 ORFs that encode both structural and nonstructural proteins. While the nonstructural proteins are needed for virus processing and replication, the structural proteins (spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins) are essential for assembly and release of the new viral particles from the infected host cells (Pooladanda et al. 2020). The structural proteins play different roles: while the (M) protein is responsible for virus assembling and shaping, the (E)

protein is required for the budding and envelop assembling; the (N) protein interacts with the viral RNA to form the helical ribonucleocapsid complex. Indeed, the spike protein (S) attracted more attention as it is responsible for viral binding to ACE2 receptors and entry to the host cells (Gheblawi et al. 2020). Moreover, the (S) proteins play a major role in SARS-CoV-2 invasion of human fetal brain during pregnancy (Varma et al. 2021) and are responsible for the olfactory, taste, and chemesthesis disorders characteristic to COVID-19 (Maaroufi 2021). In addition, they have a significant role in the induction of proinflammatory response in the brain endothelial cells which has a negative impact on the functionality of the blood-brain barrier (BBB), facilitating the passage of the virus through the BBB as reported recently (Buzhdygan et al. 2020; Rhea et al. 2020). The (S) proteins are surface-anchored glycoproteins. Therefore, they are the main target of the host neutralizing antibodies. Beside the (S) protein, anti-SARS-CoV-2 antibodies are also directed to attack the (N) protein and other epitope proteins as ORF 8 to a less extent (Schwarzkopf et al. 2021). Fortunately, the structure of (S) protein and the way it interacts with the host receptors are now understood which supports the running vaccine and antiviral development efforts (Papageorgiou and Mohsin 2020a)

It is now clear that the (S) protein consists of two subunits called (head/S1) and (stalk/S2) subunits. While the head part is responsible for binding to ACE2 receptor, the stalk portion is essential for membrane fusion (Jaimes et al. 2020). Receptor binding was shown to take place through the interaction between the receptor binding domain (RBD) present in the S1 subunit and the peptidase domain (PD) of the host ACE2 receptors. The RBD protein is the most flexible

segment of SARS-CoV-2 and has a very high affinity to human ACE2 receptors (Hussain et al. 2020). However, to complete the infection process, cleavage of S2 subunit by the host Transmembrane Protease Serine 2 (TMPRSS2) is required as the S2 cleavage enhances the integration of HR1 and HR2 domains of S2 subunit to form a six-helix bundle structure fusion core, which enables the fusion of the virus with the cell membrane (Papageorgiou and Mohsin 2020b; Xia et al. 2020).

As the (S) protein presents on the virus's surface, it is directly exposed to the immune system. Therefore, in order to escape neutralization by the immune system, (S) protein glycosylation is carried out. The glycosylation process aims to protect receptor binding epitopes from being discovered and neutralized by the antibodies (Watanabe et al. 2020). An additional mechanism to escape the immune system includes the evolution of new mutations. In the last few months, several mutations of SARS-CoV-2 were reported in the UK, South Africa and Brazil (Mahase 2021). Mutations increase the risk of evolving more virulent and contagious strains and increase the risk of escaping virus neutralization by pre-existing antibodies produced due to previous exposure or vaccination. This, in turn, represents an obstacle to the development of antiviral preparations and vaccine design (Hie et al. 2021).

Receptors of the virus

The receptors are present in different tissues; however, the severity of the disease varies among people. While some may get the infection asymptotically, the disease can end fatally in others. This difference in disease susceptibility is attributed to age, sex, general health condition/ disease status, blood group, race, lifestyle (e.g., smoking), and genetic factors (influencing the immune response, variations in ACE receptors and even blood group) [Hussain et al. 2020; Smith et al., 2020; Scully et al., 2020; Davies et al., 2020; Bahlo, 2020 (Das et al. 2020)]. Following the introduction of the virus to the human body, the invading viral particles adhere to the cell receptors by their spike (S) protein (Fig. 3). The distribution and availability of target receptors determine both viral tissue tropism and host range. In the human body, CoV can use one or more of the following receptor: (1) ACE2 (angiotensin-converting enzyme 2/e.g., SARS-CoV 1 and 2) and HCoV-NL63 (2) DPP4 (dipeptidyl peptidase 4)/e.g., MERS-CoV. (3) aminopeptidase N by HCoV-229E and (4) 9-*O*-acetylated sialic acid by HCoV-OC43 and -HKU1 viruses. As a result, viruses that target ACE2 receptors, mainly infect type II pneumocytes and ciliated bronchial epithelial cells. Meanwhile, those target DPP4 receptors infect mainly unciliated bronchial epithelial cells based on receptor availability (Cui et al. 2019; Li et al. 2003; Yeager et al. 1992; Li et al. 2007; Wu et al. 2009; van Doremalen et al. 2014; Jeffers et al.

2004). According to newly published data, SARS-CoV-2 may utilize alternative receptors rather than the ACE2, namely, TMPRSS2, Cathepsin-L/B (CTSB and CTSL), CD-147 Receptor (Bittmann et al. 2020; Goad et al. 2020).

In addition to the cellular heparan sulfate, which forms a complex of heparan sulfate and ACE2 to facilitate viral entrance (Clausen et al. 2020), the presence of SARS-CoV-2 receptors in different tissues enables the virus from invading various organs in the body including lungs, heart, blood vessels, eyes, digestive tract, the endocrine and male reproductive systems and the central nervous system (Fig. 3) (Li et al. 2020c).

It is also proposed that the respiratory signs accompanying COVID-19 have multifactorial initiators with the direct involvement of the nervous system. For example, it has been proposed that pulmonary oedema is partially induced by the nervous system. According to this hypothesis, the SARS-CoV-2 induces inflammatory reactions in the nucleus tractus solitarius (NTS) via the axon of VII, IX, and X cranial nerves, which trigger pulmonary oedema (Anoop and Verma 2020).

Respiratory failure, the major lethal manifestation of COVID-19, could be neurogenic in origin according to some reports which linked the respiratory failure and the occurrence of Ondine curse syndrome to **dorsolateral medullary stroke** (Fiedler and Gill 2020; Li et al. 2020d).

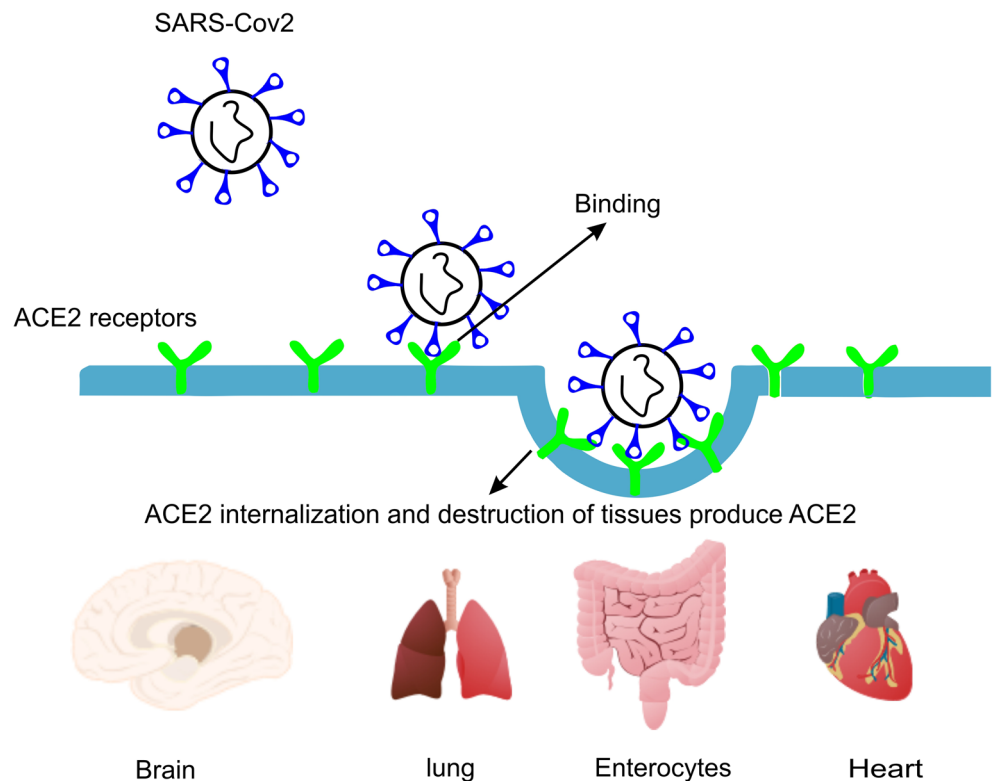
Others attributed the induction of the respiratory failure to the direct viral neuroinvasive potential to invade the cardiorespiratory regulation center in the brain stem. However, this point requires more investigation (Li et al. 2020d; Román et al. 2020; Scoppettuolo et al. 2020; Das et al. 2020; Chigr et al. 2020).

The involvement of the entire nervous system was reported in about 25–36.4% of the patients who develop variable levels of neurological symptoms. Out of these, about 84% develop neurological complications. The commonly described complaints and their prevalence included [17% (dizziness), 13% (headache), and 7% (impaired consciousness)], cerebrovascular events (62%) [ischemic strokes (46%), intracerebral hemorrhages (7%), CNS vasculitis (1%), and other cerebrovascular events (8%)], alteration of the mental status (31%) [encephalopathy (13%) & encephalitis (6%)], and finally various neuropsychiatric signs (18%) [psychosis (8%), neurocognitive (dementia-like) syndrome (5%) & affective disorders (3%)] (Ellul et al. 2020; Li et al. 2020b; Struyf et al. 2020). The present review will focus on the pathophysiological & pathopsychological effects of the SARS-CoV-2 virus on the central nervous system will be discussed in detail.

COVID-19 and the nervous system

Recent studies describe SARS-CoV-2 as a neuroinvasive, neurotropic, and neurovirulent virus (Lima et al. 2020).

Fig. 3 Binding and internalization of SARS-CoV-2 via ACE2 receptors and destruction of ACE2-producing tissues



and many other organs and cells as endothelial cells,

Following the entry of the virus, it remains in the oro-nasal cavity for a short time before binding to cells expressing ACE2 receptors such as the olfactory epithelial support cells, stem cells, in addition to the nasal respiratory epithelium, that can express both ACE2 and TMPRSS2 receptors. The virus enters the cells by fusion with the cell membrane. Although SARS-CoV-2 stands for severe acute respiratory syndrome, the virus affects various body organs and systems with a variable degree of severity. Among the greatly affected systems in the body is the nervous system leading to the emergence of neurological and neuropsychiatric signs (Alquisiras-Burgos et al. 2020). The first signs of COVID-19 infection include fever, myalgia or arthralgia, fatigue, and headache, which are the COVID-19 infection alarm/red flags (Li et al. 2020b, Struyf et al. 2020). The neurological symptoms develop in about one-third of the patients due to direct and indirect involvement of the nervous system during the course of the disease. Unfortunately, the used ACE2 receptors represent a cardio-cerebral vascular protection element which play a major role in regulating blood pressure and exert an anti-atherosclerosis mechanism. SARS-CoV-2 binding to the receptors results in the elevation of the blood pressure and increases the risk of a cerebral hemorrhage. Meanwhile, antibodies against the virus antigens can attack human self-antigens in the cerebral vascular endothelial cells leading to

the BBB disruption (Scoppettuolo et al. 2020). Moreover, SARS-CoV2 can affect the integrity of the BBB by various mechanisms, trigger severe and prolonged neuroinflammatory reactions, capable of invading the brain tissue via different routes and exerts cytotoxic effects resulting in degenerative changes in infected tissues (Alquisiras-Burgos et al. 2020). The damage of the BBB may also result from the direct interaction between the S protein and the ACE2 receptors, which are highly expressed in the CNS vessels and capillary endothelium, according to some reports. The resulting damage of the BBB enables the passage of the virus to the brain (Wu et al. 2020; Scoppettuolo et al. 2020).

According to the available data, the involvement of the central nervous system can be achieved via a dual pathway (Fig. 4), directly via the transsynaptic route (olfactory bulb, the only part of the CNS not protected by dura), indirectly through hematogenous dissemination (Huang et al. 2020; Chigr et al. 2020; Das et al. 2020), through neuronal retrograde dissemination or the trans-cerebral route (Baig and Sanders 2020), through the trigeminal nerve, peripheral nerves, the CSF or via the nerve ending in gastro-intestinal tract (gut–brain axis). All these routes were proposed based on current evidences (Satarker and Nampootheri 2020; Tremblay et al. 2020; Lima et al. 2020; Jakhmola et al. 2020). The second pathway is the hematogenous dissemination; this, in

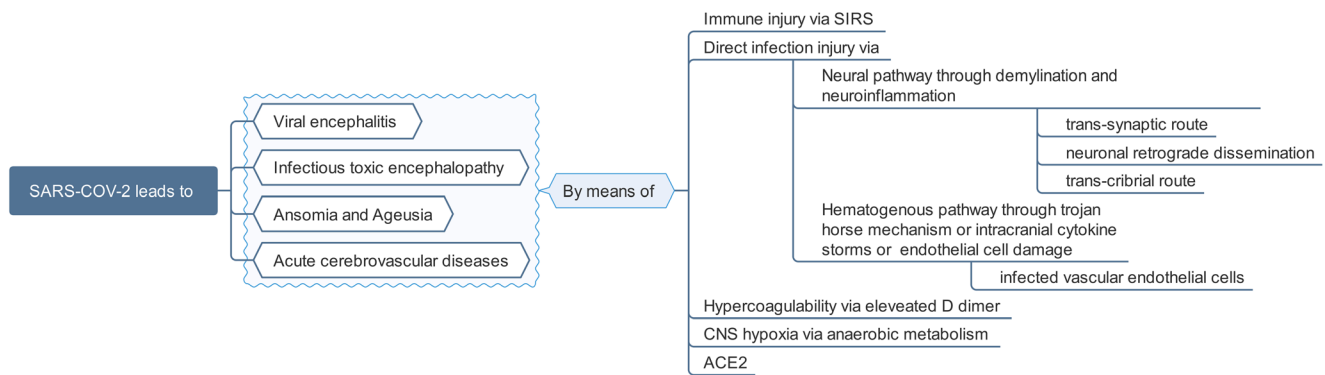


Fig. 4 Postulated mechanisms of effect of SARS-CoV-2 on nervous system

turn, takes place via different possibilities: (1) Transported to CNS through infected vascular endothelial cells, which normally express ACE2 receptors. The virus could be detected in brain samples from the capillary endothelial and neurons of a frontal lobe specimen (Paniz-Mondolfi et al. 2020). (2) Using the Trojan horse mechanism (i.e., introduction of the virus to the CNS with infected WBCs which pass through the BBB) which is also used by several other viruses (Park 2020; Jakhmola et al. 2020; Kamel et al. 2020; Desforges et al. 2019). And finally, (3) hematogenous route through the compromised BBB as a result of intracranial cytokine storms (Zubair et al. 2020; Poyiadji et al. 2020; Garg 2020). These findings were confirmed by the direct detection of viral particles in the CSF of many patients (Ellul et al. 2020). Unfortunately, once the virus enters the CNS, viral clearance is not possible as the immune response in the CNS is limited to cytotoxic T lymphocytes alone due to the lack of major histocompatibility antigens in the CNS. The infection of the brain tissues and the resulting inflammation could be responsible for the occurrence of most of the nervous signs (Sheraton et al. 2020). On the other hand, although the glial cells (e.g., astrocytes and microglia) are principally involved in the neuroinflammatory process of the brain, their role becomes restricted upon infections by neurotropic viruses. Recent reports discussing the neurotropism of SARS-CoV-2 suggested implications of glial cells as targets of SARS-CoV-2 leading to glial cell dysfunctions (Vargas et al. 2020). Moreover, the migration of SARS-CoV-2 infected microglia across healthy brain regions may spread and exaggerate the neuroinflammation process (Tremblay et al. 2020).

As mentioned before, SARS-CoV-2 is a multitropic virus. The virus has an affinity to various body systems such as the respiratory system, digestive system, endothelial cells, and nervous system. The neurological signs accompanying infection with SARS-CoV-2 may result from direct viral infection to the nervous system or develop in response to multiple organ failure, hypoxia, inflammation or sepsis. The increase in inflammatory mediators and C-reactive protein (CRP) levels accompanied with lymphopenia were reported. In addition, in some patients, cytokine storm syndrome characterized by

secondary hemophagocytic lymphohistiocytosis may occur, requiring regular monitoring of ferritin level during the course of the disease (Mehta et al. 2020). Therefore, to reduce the risk of acute cerebrovascular complications, early targeting of anti-inflammatory pathways is recommended (Jha et al. 2021). The combined use of corticosteroids, anti-IL-6 antibody (tocilizumab), or anti-IL-1 therapy (anakinra) was successfully applied to reduce the mortality rate (Narain et al. 2020).

The appearance of nervous signs may even precede the occurrence of fever and respiratory manifestations. Symptoms like the loss of smell and taste may even represent the only clinical signs in some patients (Hjelmæsæth and Skaare 2020; Carrillo-Larco and Altez-Fernandez 2020). In general, the reported neurological symptoms can be divided into three different categories: symptoms related to the involvement of the central nervous system, such as (headache, ataxia, dizziness, epilepsy, impaired consciousness, and acute cerebrovascular disease), symptoms attributed to the involvement of the peripheral nervous system (including loss of taste, loss of smell, hypoplasia, and neuralgia), and finally musculoskeletal symptoms (Mao et al. 2020b).

The involvement of nervous system results in serious damages which may persist even after the complete recovery of other body systems, the damages include encephalopathy (in absence of direct CNS invasion), and encephalitis (induced by a direct viral invasion of the CNS) (Fig. 4). The nervous manifestations begin usually with headache, the loss or perturbation of taste (dysgeusia or ageusia) and loss of smell (anosmia or hyposmia) in most cases. The impairment of smell and taste was noticed in 81% and 94%, respectively. Additional signs like dizziness, impaired consciousness (ranging from mild confusion, delirium, up to deep coma) ischemic stroke occurred in (17%, 13%, 7.5% and 0.9%), respectively. Meanwhile, visual disturbances and neuralgia were noticed in 2.3% and 1.4%, respectively. Other manifestations as paresthesia, hallucinations, and seizures were reported with a lower prevalence (Yaghi et al. 2020; Sheraton et al. 2020; Passali and Bentivoglio 2020; Lechien et al. 2020). In another meta-analysis, the most common neurologic sign was the myalgia (19.2%), followed by headache (10.9%), dizziness

(8.7%), and underlying cerebrovascular disease (8.5%) and followed to less extent by nausea, concurrent cerebrovascular disease, and impaired consciousness in 3.8%, 4.6%, and 4.4%, respectively (Pinzon et al. 2020a). Other signs were noticed on patients during their ICU stay such as confusion, agitation, signs of upper motor neuron syndrome as hyperreflexia with clonus and positive Babinski's sign, and dysexecutive syndrome. These signs were reported in 65%, 69%, 69%, and 33% of the studied cases, respectively (Sheraton et al. 2020).

As previously mentioned, the virus exerts its effect on both central and peripheral nervous systems via multiple pathological pathways, including formation of microthrombi, induction of acute infarctions due to hypoxic-ischemic reactions, ischemic strokes, and local inflammation of the brain tissue accompanied with parenchymal infiltrates of T-lymphocytes (Koralnik and Tyler 2020b; Kantonen et al. 2020; Koralnik and Tyler 2020a). Other serious nervous signs which are less frequent but could be life-threatening are encephalopathy, acute necrotizing hemorrhagic encephalopathy, meningoencephalitis, posterior reversible encephalopathy syndrome, or nerve root enhancement, post-COVID-19 CNS demyelination, brainstem, and cortical autoimmune encephalitis and Guillain Barré Syndrome (GBS). The prevalence of the acute cerebrovascular diseases was higher in elderly patients and those suffering from chronic diseases as type 2 diabetes (Poyiadji et al. 2020; Koralnik and Tyler 2020a; Paterson et al. 2020b; Mao et al. 2020a).

In addition to the harmful effects resulting from the direct viral invasion of the neurons, additional damage may occur due to the undesired adaptative immune response in which anti-SARS-CoV-2 antibodies produced by the immune system exert cross-reaction with the PNS and the brain microvascular endothelial cells to induce BBB dysfunction, neuronal dysfunction (such as acute motor axonal neuropathy (AMAN), Miller-Fisher-variant, and GBS). The most common neurological signs are summarized in Table 1 (Gutiérrez-Ortiz et al. 2020; Sedaghat and Karimi 2020; Ellul et al. 2020; Alquisiras-Burgos et al. 2020).

Understanding the disease pathogenesis provides an explanation for COVID 19 associated neurological signs. Animal experiments showed that the loss of smell and taste is believed to be a result of direct nerve invasion by the virus (Netland et al. 2008; Meppiel et al. 2020; Scheidl et al. 2020b). According to the majority of the reports, the most common nervous sign of COVID-19 is the severe headache (Rodríguez-Morales et al. 2020; Pleasure et al. 2020). Headache is also a common sign of encephalitis, meningitis, intracranial hypertension, and vasculitis. However, the characteristic severe headache accompanying COVID-19 infections is attributed most probably to metabolic acidosis. Lung affection results in generalized oxygen deficiency, which, in turn, results in a state of CNS hypoxia. The hypoxia results, in

addition, from the direct viral invasion of the cardiorespiratory centers in the medulla (Netland et al. 2008, Meppiel et al. 2020, Scheidl et al. 2020b). The performance of anaerobic metabolism due to oxygen deficiency leads to the accumulation of lactic acid in the tissues (Chhetri et al. 2020). The metabolic acidosis induces cerebral vasodilation and interstitial edema in addition to a swelling of brain cells, and finally, obstruction of cerebral blood flow occurs. The congestion and ischemia are the main inducers of severe pain and headache (Mao et al. 2020a; Pinzon et al. 2020b). Additional causes for the headache were also reported where the headache was linked to the neurotropic affinity of the virus, following invading the brain and activating the glial cells, a severe proinflammatory state will be invoked. The severe inflammation results similarly in edema and swelling of the brain tissues, which, in turn, strengthens the headache. (Pinzon et al. 2020a).

The occurrence of cerebrovascular disease is attributed to the induced coagulopathy due to the damage of the endothelial cells by the virus, which leads to the activation of the inflammatory and thrombotic pathways (Zhang et al. 2020a). On the other hand, the induction of acute ischemic stroke may be triggered by the early inflammatory process, which follows acute infection. This, in turn, results in destabilizing the carotid plaques or generating atrial fibrillation (Ellul et al. 2020). While the occurrence of anosmia (loss of smell) and the olfactory dysfunction as one of the earliest signs of the diseases can now be explained. This is attributed to the elevated ACE2 expression in the olfactory neuroepithelium. Higher receptor expression in upper respiratory epithelium than in lower respiratory and alveolar epithelium confirms the previously published data referring to the upper respiratory epithelium as the main site of SARS-CoV-2 entry to the body. The virus particle copy number could be detected in nasal swabs (~200 fold) of that in pharyngeal swabs or bronchoalveolar lavage (Chen et al. 2020a, b). Meanwhile, the impairment of consciousness, seizures, encephalopathy and meningitis are all consequences of the direct adhesion of the SARS-CoV-2 to the ACE2 receptors in the brain tissues (Moriguchi et al. 2020; Poyiadji et al. 2020).

In addition to the previously listed nervous signs, several psychiatric and neuropsychiatric disorders were also reported in association with COVID-19, including confusion, depression, anxiety, impaired memory, and insomnia at variable levels. In addition, steroid-induced mania and psychosis irritability, and fatigue were also reported (Rogers et al. 2020). Many of these psychotic symptoms can persist for a long time such as the aggressive behaviour, auditory hallucinations, Capgras delusion, persecutory delusions, and complex systematized delusional misperceptions (Poyiadji et al. 2020; Koralnik and Tyler 2020a; Paterson et al. 2020a). The explanation of the occurrence of neuropsychiatric signs is the combined effect of hypoxia and the induced neuroinflammation,

Table 1 List of the most commonly reported neurological symptoms in association with COVID-19 epidemic. The major COVID-19 neurological abnormalities which were reported in medical publications

SARS-CoV-2 induces	Resulting in:	As a consequence/manifested by:	Reference
Systemic infection	Multiple organ failure	Headache Encephalitis and encephalopathy (hypoxic and metabolic forms) accompanied by CNS dysfunction Altered sensorium (agitation, delirium, and coma)	(Garg et al. 2020)
	Coagulopathy and acute cerebrovascular disease	Ischemic and hemorrhagic cerebrovascular accident (CVA) Large-vessel Ischemic stroke Multiple infarcts, cerebral venous thrombosis Intracerebral hemorrhage and subarachnoid hemorrhage Multiple vascular territories manifested by focal motor and sensory disorders, acute intracranial vasculopathy Multiinfarct dementia	(Zhang et al. 2020d, Sharifi-Razavi et al. 2020, Coolen et al. 2020, Román et al. 2020)
	Severe inflammatory reactions (storm of cytokines)	Kawasaki like (in children), antiphospholipid antibodies, SIRS-like syndrome (systemic inflammatory response syndrome) Inflammatory encephalopathy and encephalitis Infectious toxic encephalopathy and encephalitis accompanied with altered mental status Seizures Dysexecutive syndrome Meningitis	(Zhang et al. 2020e, Mehta et al. 2020, Wu et al. 2020, Jha et al. 2021)
	Targeting ACE2 receptors	Cerebral hemorrhage, damage of BBB	(Wu et al. 2020)
Abnormalities due to invasion of the PNS	Neuroinfection and dysfunction (branches of facial nerve) and/or other cranial nerves (e.g., optic nerve).	Dysgeusia and ageusia/anosmia and hyposmia Acute myelitis Visual disturbances Neuralgia Polyneuritis cranialis Direct affection of muscles (atonia and paresis) Amblyopia (lazy eye syndrome), acute flaccid myelitis in some cases	(Oxley et al. 2020, Eliezer et al. 2020, Wei et al. 2020, Edwards et al. 2020, Korálnik and Tyler 2020a, Carrillo-Larco and Altez-Fernandez 2020)
	Neuropathy and muscular injury (myalgia)	Facial muscle weakness may affect the functionality of the eyelids and lacrimal system Manifested by loss of smell, taste and muscular weakness/pain. The infection may extend to the cardiorespiratory center.	
Abnormalities due to invasion of the CNS (mostly inflammation--mediated)	Corticospinal tract dysfunction	Meningoencephalitis, Subarachnoid invasion responsible for the characteristic headache and nuchal rigidity, Endothelialitis The signs occur due to the direct viral invasion and the resulting inflammation Central hypopnea respiratory failure due to the involvement of brain stem. Alteration of mental status (AMS) ataxia	(Bernard-Valnet et al. 2020, Li et al. 2020d, Román et al. 2020)
Abnormalities due to post-infection	Immune-mediated reactions	Acute disseminated encephalomyelitis, (ADEM) manifested by headache. Acute necrotizing encephalopathy (ANE). Immune-mediated inflammatory encephalitis. Guillain Barré syndrome (GBS also known as acute inflammatory demyelinating polyneuropathy (AIDP)) manifested by muscular flaccidity, myopathy, and multilimb weakness Acute hemorrhagic necrotizing encephalopathy (AHNE) CNS-demyelinating lesions Miller-Fisher syndrome (MFS)	(Dixon et al. 2020, McArthur 2020, Pleasure et al. 2020, Zanin et al. 2020, Gutiérrez-Ortiz et al. 2020, Li et al. 2020b, Román et al. 2020, Ellul et al. 2020, Jha et al. 2021)

which damages the hippocampal and cortical areas resulting in neuropsychiatric signs (Steardo et al. 2020).

Little data are available through brain changes in autopsies of deceased cases suffered from COVID-19. Such data is important to clarify the neuroinfection track of COVID-19 in order to establish appropriate measures (Das et al. 2020).

The reported autopsy findings included edema of the brain tissue (Xu et al. 2020). Cerebral and dotted subarachnoid hemorrhages, signs of ischemic necrosis, encephalopathy, broad gliocyte hyperplasia and diffuse vascular congestion (Chen et al. 2020b; Ellul et al. 2020; Huang et al. 2020; Vasquez-Bonilla et al. 2020). In addition, generalized hypoxic changes

in the cerebellum and cerebrum accompanied by neuronal loss in the hippocampus, cerebral cortex, and in the cerebellar Purkinje cell layer were also reported (Aghagoli et al. 2020). Meanwhile, immunohistochemical staining of autopsy materials revealed clear infiltration of monocytes and macrophages plus T cells accompanied by increased expression of the cytokine and monokine induced by gamma interferon (Ellul et al. 2020).

However, molecular examination of autopsy brain materials using quantitative RT-PCR (qRT-PCR) identified SARS-CoV-2 RNA in microvascular endothelial cells of the frontal lobe (Alquisiras-Burgos et al. 2020).

These findings are supported by Paniz-Mondolfi and his team who reported the presence of pleomorphic spherical viral particles in frontal lobe tissue and endothelial cell samples following their examination with electron microscope. These findings confirmed previous reports describing SARS-CoV-2 transcellular penetration across the brain microvascular endothelial cells (Paniz-Mondolfi et al. 2020). Conversely, immunohistochemical and histopathological examination of brain tissues of 18 patients could not reveal any cytoplasmic viral staining on positive results. A complete absence of any specific brain changes referable to SARS-CoV-2 was noticed (Solomon et al. 2020).

Long-term effects of coronavirus infection on the brain and its consequences

Neurological complications resulting from COVID-19 infection results not only in short term nervous signs but persist in the form of long term consequences such as insomnia (in 26%), myalgia (63%), anxiety and depression (23%) of the cases in addition to headache, dizziness, and seizures (Huang et al. 2021). The loss of smell and taste may partially or completely persist in some patients after the recovery of the patients (Netland et al. 2008; Meppiel et al. 2020; Scheidl et al. 2020b).

Serious neurological long term consequences were also reported including encephalopathy, encephalitis, stroke, and acute peripheral nerve diseases. Moreover, patients suffering from demyelination and axonal type of GBS, Miller-Fisher syndrome, and Kawasaki-like multisystem inflammatory syndromes in children and teenagers were also reported. These serious neurological damages develop as consequences of brain damage due to direct viral infection (encephalitis), due to intravascular coagulation and endothelial dysfunction / cerebrovascular ischemia (strokes), or as a result of severe immunological response and cytokine storm leading to autoimmune events (e.g., acute demyelinating inflammatory polyneuropathy/GBS, Parkinson's disease, multiple sclerosis and narcolepsy) (Scheidl et al. 2020a; Heneka et al. 2020; Varatharaj et al. 2020).

On the contrary, other reports suggest that the neurodegenerative disorder such as Parkinson's disease in COVID-19 patients may result from direct viral invasion to the brain via the olfactory tracts and spread towards the brain rather than being a consequence of severe immune response. This hypothesis is supported by neuropathological evidence showing that the Lewy bodies accumulate and are localized first in the olfactory pathway before extending to other parts of the brain. (Schirinzi et al. 2020)

It is worthy to mention that neuropsychiatric aspects of COVID-19, even in healthy individuals, must be taken into consideration. Such disorders can occur due to prolonged stressful situations (e.g., the fear of infection, social distancing, and economic pressure) that may induce post-traumatic stress disorder and other neuropsychiatric syndromes (Bossù et al. 2020).

Conclusion

COVID-19 is a highly contagious disease which infected almost 100 million persons worldwide within its first year. The high contagiousness of the diseases beside its high fatality rates makes it one of the worst epidemics in the last decades. The involvement of the nervous system, among other body systems, during the course of the disease and its major role in the elevation of mortality rate is now well documented. The virus can reach the central nervous system via various routes, inducing BBB dysfunction and initiating different degenerative neurological changes through direct and indirect mechanisms. Therefore, even recovered patients may continue to suffer from persisting neurological and psychological disorders. It is very important to deeply examine CSF and P.M. brain samples to clear the exact role of the involvement of the nervous system and possible disease pathogenesis. The collected data will aid in the development of better diagnostic tools and therapeutic approaches, which will increase the survival rate of the patients and improve the life quality of the recovered persons.

Availability of data and materials Not applicable.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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