

Review Article

Neurological Components in Coronavirus Induced Disease: A Review of the Literature Related to SARS, MERS, and COVID-19

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Background. COVID-19 has been declared the pandemic of the 21st century, causing more than 45,000 deaths worldwide. The abrupt release of SARS-CoV-2 demonstrated the potential infection, morbidity, and lethality of zoonotic viruses and human-to-human transmission. Fever, cough, and fatigue are reported as the most common symptoms of the disease, including acute respiratory distress syndrome, and also signs of severe illness, such as shock, acute cardiac injury, and renal lesions, are described. Considering the previous works related to human coronavirus and other zoonotic infections, it has been demonstrated that the neuroinvasive propensity is a common characteristic of coronaviruses, especially in SARS-CoV and MERS-CoV. **Objective.** In the present review, we analyzed the potential neurological components involved in coronavirus infections and detailed the neurological syndromes related to COVID-19. We also examined the mechanism of transmission and CNS pathology related to other viruses with similar structures such as SARS-CoV and MERS-CoV. **Methods.** A comprehensive search of different original articles and clinical, experimental, and review studies was conducted in MEDLINE/PubMed, Scopus, and Web of Science. We selected 92 articles that have been published in journals or preprints according to the search words and the inclusion and exclusion criteria. **Results.** COVID-19 patients may experience neurological symptoms such as headache, impaired mental status, confusion, dizziness, nausea and vomiting, anosmia/hyposmia, and dysgeusia/hypogeusia as initial symptoms, with more severe manifestations such as seizures or coma later on. The neurological signs shown are clinical symptoms similar to those reported for SARS-CoV and MERS-CoV. Given that both SARS-CoV and MERS-CoV have similar structures, these viruses may share comparable neurological symptoms and similar progression. Coronaviruses are linked to central nervous system dysfunction, and they are also reported as the probable cause of multiple sclerosis, encephalitis, and meningitis.

1. Introduction

Difficult days are being witnessed as the COVID-19 pandemic continues to evolve, generating uncertainty and stress throughout the world. The emergence of infectious diseases throughout the history has been the cause of suffering for

many human groups, in addition to economic instability and disruption of daily life [1]. Considering that COVID-19 is the new pandemic of the 21st century [2, 3], research has increased exponentially in recent months.

Coronaviruses were initially identified in animals, causing different diseases in the respiratory system,

gastrointestinal system, and central nervous system (CNS) [4]. In the last 18 years, various studies and clinical reports concerning epidemics caused by coronavirus with a substantial impact on human health, especially in Asiatic and Middle East countries, have been reported. These animal-to-human transmission (zoonotic transmission) and then human-to-human transmission were initially described in Guangdong, China, with the outbreak of the severe respiratory syndrome named “SARS-CoV” [5], which infected 8098 individuals with a mortality rate of 9%, across 26 countries in the world [5]. The subsequent appearance, 10 years later, of the Middle East respiratory syndrome (MERS-CoV) in Saudi Arabia [6] raised a global alarm about the possible impact on the healthcare system. Similar to SARS-CoV, patients suffered from pneumonia, followed by severe acute respiratory syndrome and kidney failure [5, 7].

Recently, a highly contagious pandemic has emerged, challenging the healthcare system of governments around the world. This severe acute respiratory syndrome, coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China, at the start of December and started spreading rapidly around the world, generating COVID-19. The transmission rate of SARS-CoV-2 is higher than that of SARS-CoV [5], and this virus rapidly spread across China and 200 countries around the world, becoming the third epidemic caused by coronavirus in the 21st century [8]. SARS-CoV-2 causes severe respiratory illness similar to fatal coronavirus infections caused by SARS-CoV and MERS-CoV [9].

SARS-CoV-2 infection produces a wide range of clinical symptoms from mild/moderate fever, cough, shortness of breath, and fatigue to more severe pneumonia and cardiorespiratory failure [10, 11]. Nonetheless, a group of patients present with nontypical symptoms like headache, conjunctivitis, diarrhea, vomiting, sputum, hemoptysis [11], anorexia [12], hyposmia/anosmia [13], and dysgeusia [14].

These symptoms may reflect the different initial niches and progression of the viral infection. Nevertheless, it is still not clear if the virus was limited to the upper respiratory tract. Since the main targets of SARS-CoV-2 are the lungs, early epidemiological reports do not mention alterations in the CNS [13, 15], and thus, its potential for opportunistic infection of the central nervous system has been underestimated [16].

Considering the previous description of neurological symptoms after the virus infection by coronaviruses (SARS-CoV and MERS-CoV) and the recent limited descriptions of clinical cases with SARS-CoV-2, this review aims to provide a summary and critical analysis of early findings on neurological symptoms and provide meaningful information for future research related to neurological disorders/syndromes by SARS-CoV-2, as well as support decision-making on strategies to handle this public health emergency.

2. Methods

An exhaustive search of different original articles and clinical, experimental, and review studies was performed in MEDLINE/PubMed, Scopus, and Web of Science, with the search words “coronavirus” or “SARS-CoV” or “MERS” or

“COVID-19” or “SARS-CoV-2” and “neurological syndrome” or “central nervous system” or “brain” or “brain infection” or “neurological disorder” (see Appendix for word combinations).

The studies were selected based on their relevance analyzing the possible neurological syndrome related to COVID-19. These articles have been published in magazines or in preprints. We found 92 articles that were organized according to the search words. The references of these selected articles were also scanned for additional studies related to human coronaviruses and CNS infection. A flowchart of the search is shown in Figure 1.

As part of the selection, the following criteria were considered: extensive description of clinical cases, central nervous system infection, and neurological syndrome and studies conducted in animal models or human patients diagnosed with coronavirus. Additionally, a brief review of COVID-19 is performed, and we then explored its relationship with the CNS.

2.1. Coronaviruses and COVID-19: An Overview. Human coronaviruses are usually divided into *Alphacoronavirus* and *Betacoronavirus*, the majority of them causing common cold in humans [4, 17, 18] including HCoV-229E, HCoV-OC43, HCoVHKU1, HCoV-NL63, SARS-CoV, and MERS-CoV [19–22]. While, in some cases, opportunistic human coronaviruses may infect the CNS [23, 24], and their mechanisms of infection are not widely understood [25]. Nonetheless, the abrupt onset of SARS-CoV, MERS-CoV, and SARS-CoV-2 demonstrated the potential infection, morbidity, and lethality of zoonotic viruses and human-to-human transmission, following respiratory, enteric, and CNS infections [26].

SARS-CoV first appeared in 2002, and it has caused more than 8000 cases of infection, leading to more than 750 deaths in China, Canada, Hong Kong, Vietnam, Singapore, Ireland, Germany, and EEUU [27, 28]. On the other hand, the MERS-CoV outbreak occurred in Saudi Arabia and affected 27 countries, and 2,000 people were affected by the disease [29]. Currently, SARS-CoV-2 has spread to about 200 countries, and the WHO has reported more than 5,19,000 cases and 23,000 deaths. These coronaviruses have the potential to cause more severe disease among vulnerable people, such as the elderly or people with chronic debilitating diseases. It is important to note, however, that in the case of SARS-CoV-2, transmission and COVID-19 have also been reported in pregnancy, newborns, infants [30], and young adults.

2.2. Comparison of Characteristics of COVID-19 with SARS and MERS. Coronaviruses have the largest genome among the RNA viruses, with a nonsegmented 30 kb positive-single-stranded polyadenylated RNA possessing 4 or 5 genes encoding structural proteins (S, E, M, N, and HE) and several genes encoding nonstructural proteins [31]. The most prominent feature of coronaviruses is the club-shaped spike projections emanating from the surface of the virions. The spike proteins are believed to be a major determinant of

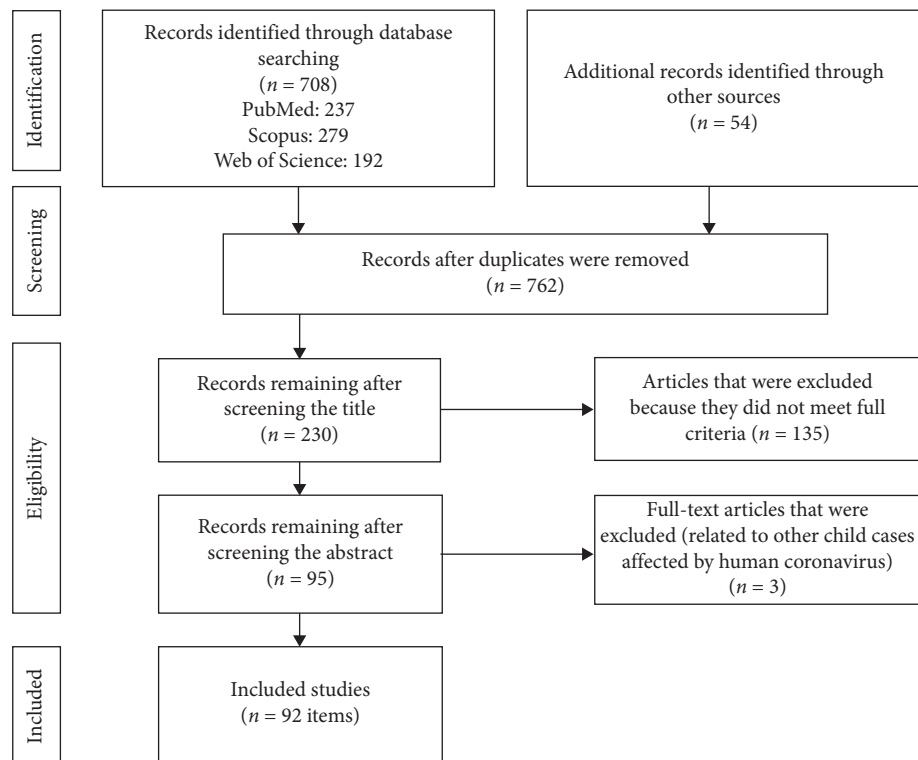


FIGURE 1: PRISMA flow diagram for the scoping review process.

the pathogenic phenotype [32], and these spikes are a defining feature of the virions and give them the appearance of a solar corona; four coronavirus genera (α , β , γ , and δ) have been identified so far [18].

Coronaviruses attach to a specific cell surface receptor and then enter the cell by fusion at the plasma membrane or after endocytosis, producing high replication of their genomic RNA [18]. These virions egress from exocytosis after vesicular transport to the cell membrane or cell membrane rupture. The human host may transmit the virions by direct transmission of respiratory secretions like nose drops and saliva. [17, 26, 33], but other transmission routes are also possible, such as contact with infected objects, aerosol transmission, human feces [26], and others probably not tears [34]; nonetheless, niche viral infection may be possible.

Table 1 describes the main biological characteristics of the new SARS-CoV-2 coronavirus, the severe acute respiratory syndrome coronavirus (SARS-CoV), and the Middle East respiratory syndrome coronavirus (MERS-CoV).

2.3. Possible Mechanism of Nervous System Infection by Coronaviruses. Different coronaviruses can outwit the immune response and infect extrarespiratory organs, including the CNS [16, 48]. Its presence in the brain tissue demonstrates the neuroinvasive and opportunistic capacity of these pathogens [49, 50]. Autopsy studies have demonstrated by in situ hybridization that coronaviruses can infect the brain, detecting viral particles [51, 52].

Furthermore, experimental studies display that coronaviruses infect the mice brain transnasally, and it seems





that the infection invades the peripheral nerve terminals and then gains access to the CNS by trans-synapse route or skips the synapse retrograde from infected tissues [16, 53], generating behavioral and cognitive impairment [49].

In patients affected with SARS-CoV, the dissemination in the systemic circulation understandably allows it to pass into the cerebral circulation. One of the factors which may facilitate the interaction of the virus spike protein with the ACE2 receptor at the endothelial could be the slow blood movement within the microcirculation. Another proposed mechanism could be the movement of the virus via the cribriform plate close to the olfactory bulb, potentially allowing brain invasion [47].

Furthermore, the haematogenic or lymphatic route may be possible [54]. By these two mechanisms, coronaviruses possess neuroinvasive and neurotropic properties; initially, they can infect the endothelial cells of the blood-brain barrier (BBB), white blood cells, glial cells, or even neurons inducing neurodegeneration and death [55, 56]. In that way, the coronaviruses contribute to an overactivation of the immune system, triggering or exacerbating the neurological symptoms [49]. There is evidence that these viral infections are possible etiological agents of demyelinating disease [57] or encephalopathy [58–60], although they underlie other brain pathologies.

Neurologic manifestations associated with SARS coronavirus infections include axonopathic polyneuropathy, myopathy, and ischemic stroke [18]. Other studies report dysphoria, vomiting, and deliria [61] and in advance stages, seizures [62]. Brain infection by MERS-CoV has shown a variety of neurologic manifestations such as ataxia, motor

TABLE 1: Comparison chart of MERS with SARS and COVID-19.

Disease	MERS: Middle East respiratory syndrome coronavirus	SARS: severe acute respiratory syndrome coronavirus	COVID-19: corona virus disease 2019
			
Virus type [31, 35–37]	MERS-CoV	SARS-CoV	SARS-CoV2
Order		Nidovirales	
Family		Coronaviridae	
Subfamily		Orthocoronavirinae	
Genus		<i>Betacoronavirus</i>	
	Subgenre C		Subgenre B
Nucleotide identity (genomic)* [25, 38]	(i) ~85% to bat (MERSr-CoV) (ii) >99% to camel (MERSr-CoV) (iii) 45–65% the S protein between bat (MERSr-CoV), human, and camel (MERSr-CoV)	(i) 78.2–97% in the S protein with bat (SARSr-CoV) (ii) Almost identical with civets (SARSr-CoV)	(i) 88–96% to bat-SL-CoVZC45 and bat-SL-CoVZXC21 (SARSr-CoV) (ii) 79.0% to SARS-CoV (iii) 51.8% to MERS-CoV
Shape		Rounded or elliptical, often pleomorphic	
Size		65–125 nm in diameter	
RNA [38]		Positive-sense RNA genome ranging from 26 to 32 kilobase in length	
Glycoprotein envelope (E) (~8–12 kDa)		Interfered with host immune response or unknown function	
Glycoprotein nucleocapsid (N)			
Structure [5, 39, 40]			
Spike protein (S)** [5, 38]	1270 aminoacids	1255 aminoacids	1273 aminoacids
Glycoproteins membrane (M) (~25–30 kDa)	Responsible for the transmembrane transport of nutrients, the bud release, and the formation of envelope		
Lipid membrane	Yes	Yes	Yes
Cellular receptor [41]	DPP4 or CD26 (dipeptidyl peptidase 4)	ACE2	ACE2***
Host-pathogen interaction [15]	Bat → camel → human	Bat → civet cat → human	Bat → snake or pangolin → human
Transmission [42]	Animal-human, human-human, zoonotic disease		
Incubation period [14]	2–10 days	2–14 days	
Organ affected [35, 43]	Unciliated bronchial epithelial cells and type II pneumocytes, epithelial cells in the kidney, small intestine, liver, prostate, and neurological system	Lymphocytes, monocytes and lymphoid tissues, ciliated bronchial epithelial cells and type II pneumocytes, intestinal mucosa, epithelium of renal distal tubules, tissue-resident macrophages, and neurons in the brain	Lung alveolar epithelial cells and enterocytes of small intestine remarkably, the kidneys and liver
Speed of spread [45]	Low	Moderate	High
Recruitment of immune cells [46]	Dendritic cells, macrophages, and T cells	Monocyte/macrophages, dendritic cells	Monocyte/macrophages, neutrophils
Immunological response [44]	Production of proinflammatory cytokines and chemokines [43]	IL-1, IL-6, IL-12, interferon γ (IFN- γ), transforming growth factor- β , CCL2, CXCL9, CXCL10, and IL-8	IL-1 β , IL-1R α , IL-6, IL-7, IL-8, IL-9, IL-10, basic FGF, GCSF, GMCSF, IFN γ , IP10, MCP1, MIP1A, MIP1B, PDGF, TNF- α , and vascular endothelial growth factor
Evades the response immune	Delayed development of the innate and adaptive immune response and prolonged virus clearance		Delayed innate immune response

^oImages adapted from Cui et al. 2018 [47]. *The genome comprises the 5'-untranslated region (5'-UTR), open reading frame (ORF), 1a/b encoding nonstructural proteins (NSPs) for replication, and structural proteins including S, E, M, and N and accessory proteins (studies have indicated notable variations in SARS-CoV and SARS-CoV2 such as the absence of 8a protein and fluctuation in the number of amino acids in 8b and 3c protein in SARS-CoV2). **Envelope spike protein (S) is functionally divided into the S1 domain, responsible for receptor binding, and the S2 domain, responsible for cell membrane fusion. ***ACE2: human angiotensin-converting enzyme 2. SARS-CoV2 has 14 binding residues that interact with the ACE2 receptor and is 10- to 20-folds higher than that of SARS-CoV.

deficits, and altered mental state from confusion to coma [63] or headache, nausea, and vomiting [54]. The rapid infection and replication of MERS-CoV in human dendritic cells, macrophages, and primary T cells aggravate the infection and production of proinflammatory cytokine/chemokine [64], worsening the response and inducing massive apoptosis [65].

Perhaps, the neuroinvasive potential by SARS-CoV-2 needs some more elucidation. Taking the previous work with human coronavirus and other zoonotic infections as reference, neuroinvasive propensity has been demonstrated as a common feature of coronaviruses [53, 66], especially between SARS-CoV and SARS-CoV-2 [67]. Other studies show that the human brain cell lines are capable of or have been infected by coronaviruses [68], including astrocytoma, neuroblastoma, and oligodendrocytes cell lines [61].

Recently, the presence of the ACE2 receptor has been demonstrated on glial cells and neurons. The COVID-19 virus uses a protein S1 that interacts with the ACE2 receptor and allows the binding of the virions to the target cell membrane [47]. Even the peak proteins of the three coronaviruses are similar, not identical, which explains the greater affinity of the COVID-19 peak protein with the human ACE2 receptor.

2.4. Neurological Syndrome by Coronaviruses. SARS-CoV and MERS-CoV are zoonotic diseases that can infect both humans and animals. Both viruses have a very similar structure. Infection by these viruses in humans produce typical clinical characteristics such as fever, myalgia, cough, and dyspnea, which typically proceed to shortness of breath and pneumonia. Other clinical characteristics consider nontypical symptoms like diarrhea, anorexia, anosmia, and hyposmia. Furthermore, it seems that SARS, MERS, and COVID-19 have similar incubation periods [69].

Different studies point out that, before and after virus confirmation by reverse transcriptase polymerase chain reaction in the respiratory sample, neurologic symptoms would be present and may have been underdiagnosed previously. These symptoms included dizziness, headache, vomiting, and confusion. It may also include weakness in the upper and lower limbs, altered reflexes, or ataxia. More severe symptoms may range from generalized tonic-clonic seizures, loss of consciousness, coma, and death. A review of different studies is shown in Table 2.

Given the progression of those symptoms, changes in the immune response were manifested [81], especially macrophage activation, increased lymphocytes, and expression of chemokine receptors on activated T cells. [58], which are usually analyzed in a blood sample or CFS, and also cytopathic effects are observed. Neuroimaging methods such as tomography and MRI showed inconclusive results, with some patients showing normal values and others displaying hypodensity and hyperintensity in different areas of the brain, including stroke [62].

In addition, the human respiratory epithelium is highly susceptible to SARS-CoV and MERS-CoV which may support productive viral replication, as shown in the first

case. Most patients had three or more damaged organs or systems after exposure to SARS-CoV-2 [9], and it is possible to define, additionally, the first symptoms associated with the infection of the CNS.

2.5. Clinical Symptoms in Neurological COVID-19 Patients.

At present, there are some reports referring to the neurological symptoms of COVID-19 patients. These studies indicate that neurological signs, such as headache, nausea, and vomiting, are the initial symptoms. Some other documents indicate a diminished sense of smell, diminished sensation of taste, or even anosmia (Table 2). The reported neurologic signs are clinical symptoms similar to those informed in SARS-CoV and MERS-CoV. Considering that SARS-CoV and MERS-CoV have a similar structure and as several reports point out, comparable neurological symptoms are notable which indicates that the progression would be similar. Different coronaviruses are linked to CNS dysfunction, and they are reported as the probable cause of multiple sclerosis, encephalitis, and meningitis [82–84]. Hence, viruses could be another potential source of brain dysfunction even in the absence of a lung with low respiratory tract infection.

Well-defined mechanisms of transmission between the lower and upper respiratory tracts of the CNS remain unknown. From other studies on coronaviruses, however, we could suggest that transmission begins even in the upper or lower respiratory tract, forming different viral niches with the possibility of altering the respiratory epithelium, reaching the bloodstream or lymph and spreading to the CNS [49, 85], and crossing the BBB and infecting the brain neurons such as glial cells or neurons, for example [84], the latter being more susceptible to infection by coronaviruses [46] (Figure 2). Another variant of infection would be by axonal transport, retrograde transmission from the respiratory organs, or even the enteric nervous system as do other coronaviruses [85–89].

Examination of the data suggests that coronavirus may reach the CNS and induce the disease in the short term, but it is not known whether it can persist in resident human CNS cells and may become a factor or cofactor in neuropathogenesis associated with a long-term neurological syndrome or sequel in vulnerable populations with other comorbidities, children [90] or elderly populations.

3. Discussion

The aim of this review was to elucidate the possible neurological component by coronavirus infections, specifically SARS-CoV, MERS-CoV, and SARS-CoV-2. Considering the recent descriptions of neurological symptoms after SARS-CoV-2 infection, we reviewed more than 90 papers in the last 20 years related to coronavirus brain infection and included different human, clinic, and experimental studies. We detail a neurologic syndrome related to COVID-19 and review the transmission mechanism and CNS pathology related to another virus with the similar structure (SARS/MERS).

Despite many other coronaviruses being discovered before SARS-CoV outbreak [91], different researches took

TABLE 2: Neurologic findings reported in SARS, MERS, and COVID-19.

Reference	Title	Type of study	Virus	Virus confirmation	Host	Age	Comorbidities	Initial clinical manifestation	Neurologic symptoms/findings	Neurological clinical test/techniques	Disease type/final conclusion
[70]	Possible central nervous system infection by SARS coronavirus	Clinic case report	SARS-CoV	RT-PCR of CSF	Humans (n = 1)	32	—	Myalgia, fever, chills and rigor for 2 days, and unproductive cough	Generalized tonic-clonic convulsion loss of consciousness	CSF test, EEG, and RMI showed no abnormalities	The results suggest that the central nervous system (CNS) is affected by SARS-CoV
[51]	Detection of severe acute respiratory coronavirus in the brain: potential role of the chemokine MIG in pathogenesis	Clinic case report/experimental study	SARS-CoV	RT-PCR	Humans (n = 1)	39	—	Fever, chills, malaise, headache, dizziness, and myalgia	Headache, dizziness	isolation and identification of SARS-CoV	Brain tissue revealed necrosis of neuron cells and broad hyperplasia of gliocytes Immunostaining demonstrated that monokine induced by interferon-gamma (MIG) was expressed in gliocytes with the infiltration of CD68+ monocytes/macrophages and CD3+ T lymphocytes in the brain The cytokine/chemokine assay revealed that levels of interferon-gamma inducible protein 10 and MIG in the blood were highly elevated, although the levels of other cytokines and chemokines were close to normal

TABLE 2: Continued.

Reference	Title	Type of study	Virus	Virus confirmation	Host	Age	Comorbidities	Initial clinical manifestation	Neurologic symptoms/findings	Neurological clinical test/techniques	Disease type/final conclusion
[52]	Organ distribution of severe acute respiratory syndrome- (SARS-) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways	Histopathological examination/autopsy study	SARS-CoV	RT-PCR of tissue selected	Human experimental group (n = 4)	Mean: 45.5 SD: 17.13	—	The initial symptoms were related to pyrexia, followed by chills, generalized aching pains, nonproductive cough, and sputum with a small quantity of blood (in one case)	—	IHC RT-PCR ISH Transmission electron microscopy	SARS-CoV was found in the brain and other tissues. The pathological changes in these organs may be caused directly by the cytopathic effect mediated by local replication of SARS-CoV
[71]	Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection	Review	SARS-CoV	—	Transgenic mice expressing hACE2 (K18-hACE2) Transgenic mice expressing hACE2 (AC70)	—	—	Weight loss by 3–5 DPI and died by 7 DPI; infection begins in airway epithelia with subsequent alveolar involvement and extrapulmonary virus; developed acute wasting syndrome and died within 4–8 DPI	Macrophage and lymphocyte infiltration into the lungs and upregulation of proinflammatory cytokines and chemokines in both the lung and the brain	Histological and immunohistochemical analyses	Extensive involvement of the central nervous system likely contributed to the death of mice; even though viral pneumonia was present, transgenic mice expressing human ACE2 receptors also developed fatal disease, with extrapulmonary dissemination to many organs including the brain
[72]	Pathogenesis of severe acute respiratory syndrome	Review	SARS-CoV	—	Various	—	—	Patients present with flu-like symptoms including fever, chills, cough, and malaise	IHC, ISH, and EM have confirmed the viral infection of neurons.13, 15, and 42; gliocytes have also been found infected by SARS-CoV	IHC ISH CT Genomic sequences in cerebral spinal fluid and in brain tissue specimens	Edema and degeneration of neurons and several neurons in situ hybridization showed positive results

TABLE 2: Continued.

Reference	Title	Type of study	Virus confirmation	Host	Age	Comorbidities	Initial clinical manifestation	Neurologic symptoms/findings	Neurological clinical test/techniques	Disease type/final conclusion
[63]	Severe neurologic syndrome associated with Middle East respiratory syndrome corona virus (MERS-CoV)	Clinic case report	MERS-CoV Tracheal aspirate tested positive for MERS-CoV	Humans (n = 3)	C1: 73 C2: 57 C3: 43	Case 1: diabetes, hypertension, and dyslipidemia Case 2: diabetes and hypertension Case 3: diabetic and hypertensive with chronic kidney disease and ischemic heart disease	C1: Fever C2: Acute myocardial ischemia with pulmonary edema C3: 10-day history of productive cough, dyspnea, rigors, fever, and diarrhea	C1: ataxia, vomiting, and confusion Also, dysmetria and decreased motor power on the left side Case 2: at HD 4, the patient was unresponsive and hypotensive with left-sided facial paralysis	C1: brain CT, brain MR, and CSF test C2: brain CT and CT angiography C3: MRI and CSF	Altered level of consciousness ranging from confusion to coma, ataxia, and focal Motor deficit MERS-CoV infection may be responsible for the extensive CNS injury observed in our patients C1: multiorgan failure and signs of irreversible brain stem dysfunction C2: axonal polyneuropathy
[54]	Neurological complications of Middle East respiratory syndrome coronavirus: a report of two cases and review of the literature	Clinic case report	MERS-CoV RT-PCR of sputum	Human postmortem (n = 2)	C1: 34 C2: 28	C1: diabetes mellitus C2: does not report any comorbidities	C1: fever C2: fever, generalized myalgia, dizziness, productive cough, and then development of bronchitis	C1: severe headache, nausea, and vomiting C2: weakness in both legs and inability to walk with numbness and tingling in stocking distribution	C1: chest imaging and brain CT C2: MRI and CSF tests were normal	C1: multiorgan failure and signs of irreversible brain stem dysfunction C2: axonal polyneuropathy

TABLE 2: Continued.

Reference	Title	Type of study	Virus	Virus confirmation	Host	Age	Comorbidities	Initial clinical manifestation	Neurologic symptoms/findings	Neurological clinical test/techniques	Disease type/final conclusion
[73]	Neurological complications during treatment of Middle East respiratory syndrome	Clinic case report	MERS-CoV	RT-PCR of sputum	Humans (n=4)	Mean: 45.5 SD:7.14	C1: atrial fibrillation, diabetes mellitus, hypertension, chronic kidney disease, hypothyroidism, and tuberculosis C2: no underlying medical problems	C1: cough, dyspnea, and chest discomfort C2: severe myalgia, chills, fever, cough, and headache; after a week, the patient presented with gastrointestinal symptoms, including nausea, vomiting, and anorexia C3: fever, coughing, chest discomfort, dyspnea, and stool loss	C1: complete external ophthalmoplegia and mild limb ataxia; suspected weakness in all four limbs C2: deep tendon reflexes were mildly diminished in both legs; tingling and pain in the four distal limbs were also present C3: tingling present in the distal parts of the patient's hands and feet; also, reflexes were decreased in both knees but were normal in both upper extremities	C1: MRI and CSF was normal; EEG exhibited diffuse slow-wave activity; RT-PCR of CSF was negative C2: EMG and evoked potential studies were normal	C1: BBE overlapping with GBS C2: ICU-acquired weakness or GBS C3: infectious or toxic polyneuropathy and the patient's sensory symptoms gradually improved over 6 months C4: acute sensory neuropathy caused by a toxin or infection
[74]	Histopathology of Middle East respiratory syndrome coronavirus (MERS-CoV) infection: clinicopathological and ultrastructural study	Histopathological examination/case report	MERS-CoV	RT-PCR of sputum	Humans (n=1)	33	T-cell lymphoma, thrombocytopenia, and neutropenia	Fever and productive cough with new infiltrate on chest radiograph	No significant inflammatory infiltrate	Light microscopy, electron microscopy (EM), and immunohistochemistry	The brain was histologically unremarkable

TABLE 2: Continued.

Reference	Title	Type of study	Virus	Virus confirmation	Host	Age	Comorbidities	Initial clinical manifestation	Neurologic symptoms/findings	Neurological clinical test/techniques	Disease type/final conclusion
[75]	Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4	Experimental study	MERS-CoV	Real-time quantitative PCR	Transgenic mice DPP4	—	—	MERS-CoV: infected lungs revealed mononuclear cell infiltration, alveolar edema, and microvascular thrombosis, with airways generally unaffected	—	Histologic and immunohistochemical analyses; infection of human cell lines; and primary porcine astrocytes	Brain disease was observed, with the greatest involvement noted in the thalamus and brain stem; animals immunized with a vaccine candidate were uniformly protected from lethal infection
[9]	Clinical characteristics of 82 death cases with COVID-19	Clinic case report	SARS-CoV-2	—	Humans (n = 82)	66 of 82 (80.5%) of patients were older than 60 years median age: 72.5 years.	Comorbidities (75.6%) including hypertension (56.1%), heart disease (20.7%), diabetes (18.3%), cerebrovascular disease (12.2%), and cancer (7.3%)	Fever, cough, and fatigue; the great proportion of them were diagnosed with severe illness when admitted; incubation period: 3–7 days	A majority of patients (75.6%) had 3 or more damaged organs or systems following the infection with SARS-CoV-2	Laboratory analyses: blood count, liver function, renal function, electrolyte test, coagulation function, C-reactive protein, lactate dehydrogenase, myocardial enzymes, procalcitonin, and status of other virus infection; radiological analyses: X-ray and computed tomography	A majority of patients (75.6%) had 3 or more damaged organs or systems following the infection with SARS-CoV-2; CNS not mentioned
[76]	COVID-19-associated acute hemorrhagic necrotizing encephalopathy: CT and MRI features	Clinic case report	SARS-CoV-2	Real-time quantitative PCR	Humans (n = 1)	Young female	No mention	3-day history of cough, fever, and altered mental status	aCT angiogram demonstrates normal appearance of the basilar artery and proximal posterior cerebral arteries; CT demonstrates symmetric hypoattenuation within the bilateral medial thalami	aCT CT CSF analysis RT-PCR	Acute necrotizing encephalopathy

TABLE 2: Continued.

Reference	Title	Type of study	Virus	Virus confirmation	Host	Age	Comorbidities	Initial clinical manifestation	Neurologic symptoms/findings	Neurological clinical test/techniques	Disease type/final conclusion
[77]	Coincidence of COVID-19 epidemic and olfactory dysfunction outbreak	Cross-sectional study	SARS-CoV-2	Only online form	Humans (n = 10069)	32.5 ± 8.6 (7-78) years	No mention	Fever, cough, and dyspnea were less common in the participants with anosmia/hyposmia complaint in some period of time in the last four weeks	Sudden onset of anosmia: 76.24%; decreased sense of smell was constant: 60.90%; decreased taste sensation in association with anosmia: 83.38%	Online checklist, which was distributed in social networks	Postviral epidemic olfactory dysfunction
[12]	Neurological manifestations of hospitalized patients with COVID-19 in Wuhan, China: a Retrospective case series study	Retrospective case series	SARS-CoV-2	RT-PCR	Humans (n = 214)	Average age: 52.7 ± 15.5	83 (38.8%) had at least one disorder: hypertension (51, 23.8%), diabetes (30, 14.0%), cardiovascular disease (15, 7.0%), and malignancy (13, 6.1%)	Fever (132, 61.7%), dry cough (107, 50%), anorexia (68, 31.8%)	78 patients had nervous system symptoms: CNS: dizziness (16, 8%); headache (13.1%); PNS: hypogeusia (5.6%), hyposmia (5.1%); common in severe cases	Positive result to real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay	Cerebrovascular disease impairment consciousness and muscle injury
[78]	Metabolic disturbances and inflammatory dysfunction predict severity of coronavirus disease 2019 (COVID-19): a Retrospective study	Retrospective study	SARS-CoV-2	RT-PCR	Humans (n = 97)	Median age: 39 years (range 23-82 years) Mild group: 37 years (29-55) Severe group: 58 years (47-67)	Mild group: hypertension (5, 6.9%), diabetes (2, 8%), cardiovascular disease (2, 8%), and cerebrovascular disease (2, 8%) Severe group: hypertension (10, 40%), diabetes (3, 4.2%), cardiovascular disease (0, 0%), and cerebrovascular disease (1, 1.4%)	Fever (58.8%), cough (55.7%), fatigue (33%), sputum production (15.5%), vomiting and diarrhea (12.4%), and nasal congestion (10.3%)	Dizziness and headache (7.2%)	Positive results for fluorescence reverse transcription polymerase chain reaction (RT-PCR) chest computed tomography with COVID-19	Metabolic immune-inflammatory dysfunction were found in patients with COVID-19
[79]	Retrospective analysis of clinical features in 101 death cases with COVID-19	Retrospective study	SARS-CoV-2	RT-PCR	Humans (n = 101)	Average age: 65.46 years. 24-83 years	Hypertension (42.57%), diabetes (22.77%), neurological disease (9.90%), malignant tumor (4.95%), and respiratory disease (4.95%)	Fever (90.10%), cough (68.32%), dyspnea (74.26%), white sputum (30.69%), myalgia, general weakness, dizziness, headache, and nausea and vomiting (85.15%)	Dizziness and headache	Positive RT-PCR or highly homologous gene sequencing with known coronavirus	Fatal respiratory distress syndrome and multiple-organ failure; The heart may be the second damaged organ; the median time from onset to death was 21.00 days; CNS not mentioned

TABLE 2: Continued.

Reference	Title	Type of study	Virus	Virus confirmation	Host	Age	Comorbidities	Initial clinical manifestation	Neurologic symptoms/findings	Neurological clinical test/techniques	Disease type/final conclusion
[80]	Understanding COVID-19 new diagnostic guidelines: a message of reassurance from an internal medicine doctor in Shanghai	Review	SARS-CoV-2	—	Humans	—	—	(1) Fever and/or respiratory symptoms; (2) chest CT features of multiple small patchy shadows and interstitial changes and obvious extrapulmonary bands (early stage); multiple ground glass infiltrations and infiltrates in both lungs (later stages). (3) Early stage of the disease: Total white blood cell count is normal or decreased, or the lymphocyte count is decreased	—	(1) Real-time fluorescent RT-PCR detected a nucleic acid of novel coronavirus in respiratory or blood samples or (2) sequencing of virus genes in respiratory or blood samples, highly homologous with SARS-CoV-2	Pneumonia syndrome and other symptoms
[53]	The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients	Review	SARS-CoV-2	—	—	—	—	—	Patients with COVID-19 also showed neurologic signs, such as headache, nausea, and vomiting	—	Patients with COVID-19 display clinical symptoms similar to those reported for SARS-CoV and MERS-CoV; the infection of SARS-CoV has been reported in the brains from both patients and experimental animals, where the brainstem was heavily infected

aCT: computer tomography angiogram; CT: computer tomography; MRI: magnetic resonance imaging; BBE: Bickerstaff's encephalitis; GBS: Guillain-Barré syndrome; ICU: intensive care unit; HD: hospital day; RT-PCR: reverse transcriptase polymerase chain reaction; IHC: immunohistochemistry; ISH: in situ hybridization; EM: electron microscopy.

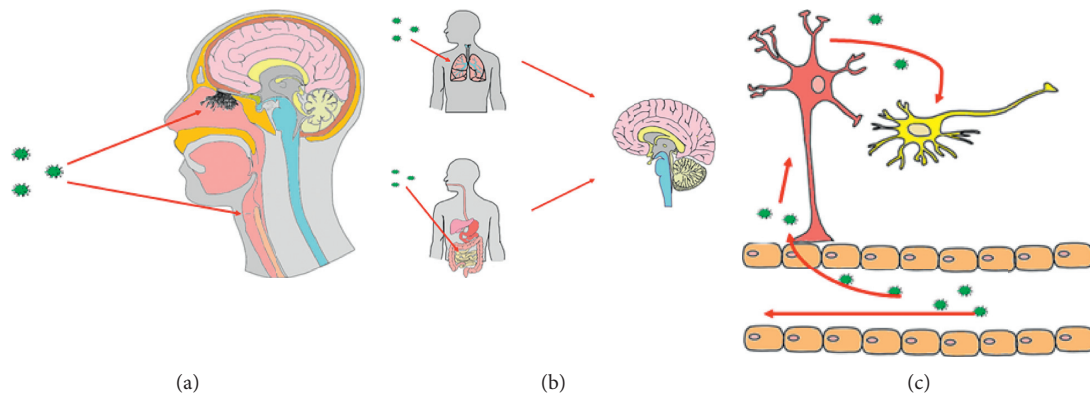


FIGURE 2: Possible mechanisms of brain infection. (a) The SARS-CoV-2 virus infects the nasal epithelium and throat. (b) Through infection of the lower respiratory tracts or enteric system, the viruses could use the homogenous or lymphatic route to reach the brain. (c) Rupture of BBB may cause glial cell infection as well as neuronal infection.

place involving the mechanisms of infection, transmission, etc. The appearance of epidemics by novel viruses of the same family displays the coronavirus as a fast-evolving virus [7] and particularly important for the investigation of its extensive contagious properties, its spread in several countries, morbidity and mortality.

Similar to other viruses, the SARS-CoV-2 virus spread rapidly through human-to-human transmission. Insufficient awareness of infection control in hospitals and international air travels facilitated the rapid global spread [71]. Today, more than 200 countries around the world have reported patients with COVID-19, and there have been more than 25 000 deaths. Although there are a high number of recovered patients, no follow-up studies on the nonrespiratory symptoms have been reported. In this paper, we focus on the symptoms and infections of the central nervous system caused by coronaviruses (SARS-CoV, MERS-CoV, and SARS-CoV-2).

The incubation period of COVID-19 is from 2 to 14 days [8, 14]. Different reports mention several symptoms, including fever, cough, and fatigue assumed as the most common symptoms [80]. In addition to these aforementioned signs, acute respiratory distress syndrome, shock, acute cardiac injury, and acute kidney injury are reported, with 20% to 30% of cases developing serious illness [78].

Previous studies demonstrated that coronaviruses contain neuroinvasive, neurotropic, and neurovirulent properties regardless of the pulmonary infection, as it has been shown in some cases. The presence of SARS-CoV and MERS-CoV viruses was usually confirmed by RT-PCR, immunohistochemistry, and in situ hybridization in post-mortem studies [52]. Other clinical approaches may include CT, MRI, and cerebrospinal fluid (CSF) test, to check SARS-CoV-2 by reverse transcriptase polymerase chain reaction. Analysis of the data suggests that a significant percentage of patients infected with COVID-19 may have neurological complications that may last longer than the lung infection itself. Initial neurological symptoms are diverse and include deterioration of mental status, confusion or coma, dizziness, headache, nausea and vomiting, anosmia/hyposmia, dysgeusia/hypogeusia, and seizures.

Further studies are urged to be performed to distinguish between opportunistic and disease-associated viral presence in the human brain [25] and also to describe the key mediator mechanism in brain damage induced by SARS-CoV-2 infection.

There have been some suggested mechanisms through which this virus affects the central nervous system, pointing to neuroinvasive characteristics similar to other human coronaviruses [31]. Because the exact mechanism is not thoroughly understood, autopsy studies are needed to further understand the mechanism [54]. It is possible that the neuroinvasive potential includes different routes such as hematogenous, lymphatic routes, olfactory tract [46], and optic nerve. Therefore, the advent of neurological symptoms should be monitored and analyzed more intensively. Surveillance should be maintained promptly, identifying other nonrespiratory symptoms, along with the follow-up of recovered patients and asymptomatic COVID-19-positive individuals [83].

The incubation period may vary for the infection of the lungs and other tissues, depending on the viral niche accumulation. A confirmative test is always recommended in the respiratory tract and CSF if a patient presents neurologic symptoms. Those are important to exploit the knowledge of neuroinvasion and dissemination of other similar coronaviruses to increase the ability to control the viral infection, detection of symptoms, and research focus on the possible mechanisms of neuropathogenesis.

The recent appearance and discovery of COVID-19, in addition to the ease of its transmission, has made SARS-CoV-2 a virus with a great impact on the public health worldwide. The profiling of the condition and the understanding of the affected organs, in particular the central nervous system whose condition could have sequelae over time, are of vital importance. Therefore, the establishment of an adequate profile of the disease will also favor the adoption of health measures.

3.1. Limitations. This study has potential limitations. First, a few reported cases of neurological symptoms caused by COVID-19, observations of the process, and prognosis of the

neurologic disease are needed. Second, this paper mainly uses the descriptive analysis to review and summarize the clinical cases.

4. Conclusion

Recent findings in COVID-19 are closely related to those reported in SARS and MERS. Specifically, here, we review those related with the neurologic syndromes. The structural homology and nucleotide identity are higher than 51% in MERS and 79% in SARS [25]. In both epidemics cases, reports regarding neurologic syndrome were investigated.

To our concern, there have been no follow-up studies related to the CNS. Now, with the global pandemic, COVID-19, case reports suggest similar CNS infection by the SARS-CoV-2 opportunistic virus [92]. Coronaviruses are a rapidly evolving virus that can disrupt the human life, infect many organs such as the CNS, and probably leave different niches of infection that can generate a variety of clinical symptoms from typical cough, fever, and pneumonia infection to a more complex presentation that includes neurological syndromes. Consequently, further studies are necessary to elucidate if this neurological syndrome is reversible or if it may refer to possible disabilities or if it may even promote other brain pathologies that may include encephalitis, multiple sclerosis, or others.

Appendix

A. Criteria

- (1) English language
- (2) Peer-reviewed journals and journals indexed in the Journal Citation Reports (JCR)
- (3) Published since January 2000
- (4) Empirical studies, systematic reviews, meta-analyses, clinical practice guidelines, or case report
- (5) Human participants
- (6) Words: “coronavirus” or “SARS-CoV” or “MERS” or “COVID-19” or “SARS-CoV-2” and “neurological syndrome” or “central nervous system” or “brain” or “brain infection” or “neurological disorder”
- (7) Clinical studies, case reports, journal articles, and systematic reviews
- (8) Issues: neurosciences neurology, psychiatry, behavioral sciences, or psychology

B. PubMed Search Words

“Coronavirus” OR “SARS-CoV” OR “MERS” OR “COVID-19” OR “SARS-CoV-2”) AND “neurological syndrome” OR “central nervous system” OR “brain” OR “brain infection” OR “neurological disorder.”

C. Scopus Search Words

TITLE-ABS-KEY (“coronavirus” OR “SARS-CoV” OR “MERS” OR “COVID-19” OR “SARS-CoV-2”) AND TITLE-

ABS-KEY (“neurological syndrome” OR “central nervous system” OR “brain” OR “brain infection” OR “neurological disorder”) AND (LIMIT-TO (LANGUAGE, “English”)) AND (LIMIT-TO (EXACTKEYWORD, “Human”) OR LIMIT-TO (EXACTKEYWORD, “Humans”).

D. Web of Science Search Words

Filters: English/2000/article, review, case report, and clinical trial.

Note: it does not allow putting *Human* as filter.

(TS = “coronavirus” OR TS = “SARS-CoV” OR TS = “MERS” OR TS = “COVID-19” OR TS = “SARS-CoV-2”) AND (TS = “neurological syndrome” OR TS = “central nervous system” OR TS = “brain” OR TS = “brain infection” OR TS = “neurological disorder”) AND (TS = “human” OR TS = “humans”)

E. Types of Documents

Articles or reviews or case reports.

F. Research Area

Neurosciences, Neurology, and Psychiatry or Behavioral Sciences or Psychology.

Period: From 2000: WOS, BCI, BIOSIS, CCC, DIIDW, KJD, MEDLINE, RSCI, and SCIELO.

Language = auto.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

Zegarra-Valdivia conceptualized the study; Zegarra-Valdivia and Chino-Vilca were involved in the methodology; Zegarra-Valdivia, Chino-Vilca, and Tairo-Cerron were responsible for the writing and preparation of the original draft; Zegarra-Valdivia, Chino-Vilca, Tairo-Cerron, Munive, Lastarria-Perez, and Ames-Guerrero contributed in writing, review, and editing. All authors have read and agreed to the final submitted version of the manuscript for publications.

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