SARS-CoV-2 infection of the nervous system: A review of the literature on neurological involvement in novel coronavirus disease-(COVID-19)

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ABSTRACT

The novel coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is believed to have emerged from an animal source and has been spreading rapidly among humans. Recent evidence shows that SARS-CoV-2 exhibits neurotropic properties and causes neurological diseases. Here, we review the literature on neurological involvement in SARS-CoV-2 infections and the possible mechanisms of invasion of the nervous system by this virus, to provide a summary and critical analysis of the early reporting of neurological involvement in COVID-19. An exhaustive search of scientific articles on neurological involvement in COVID-19 was performed in the Web of Science, Scopus, Medline/PubMed, and several other databases. Nineteen relevant articles that had been published or were in preprint were carefully selected according to the inclusion and exclusion criteria. Based on our research, we found that patients with COVID-19 can present with neurological symptoms that can be broadly divided into central nervous system involvement, such as headache, dizziness, altered mental state, and disorientation, and peripheral nervous system involvement, such as anosmia and hypogeusia. Most of these patients are in the older age group and exhibit comorbidities, especially hypertension, and severe infection. In extreme presentations of COVID-19, some patients exhibit seizures, stroke, flaccid paraparesis, corticospinal weakness, and even coma. Moreover, the neurological manifestations can occur independently of the respiratory system. In conclusion, SARS-CoV-2 infection can cause multiple neurological syndromes in a more complex presentation. Therefore, this review elucidated the involvement of the nervous system in SARS-CoV-2 infection and will hopefully help improve the management of COVID-19.

KEYWORDS: Coronavirus disease 2019; COVID-19; coronavirus; severe acute respiratory syndrome coronavirus 2; SARS-CoV-2; pandemic; nervous system; central nervous system; CNS; peripheral nervous system; PNS

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the name that was attributed to the virus formerly known as the novel coronavirus, which is a newly emerged zoonotic virus that causes the coronavirus disease 2019 (COVID-19) [1]. SARS-CoV-2 infection was first reported in Wuhan, Hubei Province, China, on December 29, 2019, where four cases of an acute respiratory distress syndrome of unknown etiology were linked to a local Huanan South China Seafood Market; since then, this virus has caused a global pandemic [2]. In general, coronaviruses are common in animals, with some, namely, HCoV-229E, HCoV-OC43, HCoVNL63, and HCoV-HKU1, affecting humans and generally causing a mild respiratory illness [3,4]. However, several coronaviruses have caused outbreaks in the past two decades, including the severe acute respiratory syndrome coronavirus (SARS-CoV) outbreak of 2002/2003, which affected 8422 people across 26 countries and caused 916 deaths (i.e., a mortality rate of 11%) [5,6], as well as the Middle-East respiratory syndrome coronavirus (MERS-CoV) outbreak of 2012/2013, which affected 1386 people and caused 587 deaths [7]. Similar to that observed for SARS-CoV, patients infected by MERS-CoV suffered from pneumonia followed by severe acute respiratory distress syndrome and multiple organ failure.

SARS-CoV-2 infection results in a syndrome of various systemic and respiratory symptoms such as dry cough, breathing difficulty, fever, and fatigue, which sometimes can be critical by causing severe pneumonia and cardiorespiratory failure and requiring specialized management in intensive care units [8,9]. Recently, it has been documented that, in addition to systemic and respiratory symptoms, some patients with COVID-19 develop neurological symptoms. These symptoms include headache, altered consciousness, anosmia, and paresthesia, among many others

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[10]. In addition, an increasing number of cases of patients with COVID-19 that develop encephalopathy [11] and Guillain–Barré syndrome (GBS)-like manifestations is being reported [12,13]. Considering the ongoing global pandemic of COVID-19 and the descriptions of neurological manifestations in SARS-CoV-2 infection, it is necessary to alert clinicians regarding the high likelihood of nervous system involvement in this disease.

MATERIALS AND METHODS

An exhaustive search of scientific publications (original articles on relevant experimental and observational studies, case series, and reports) was conducted using the following online databases/online search engines: Google Scholar, Web of Science, Scopus, Medline/PubMed, bioRxiv, medRxiv, and ChemRxiv, as well as CNKI and WanFang Data (which are the two primary databases for biomedical research in mainland China). The search terms used were: "Neurological manifestations of COVID-19", "Neurological manifestations of novel coronavirus 2019", "Neurological manifestations of SARS-CoV-2" "Neurological complications of COVID-19", "Neurological complications of coronavirus 2019", and "Neurological complications of SARS-CoV-2." All relevant articles were analyzed for a possible neurological syndrome related to COVID-19. These articles had either been published or were in preprint from January 1, 2020, to April 25, 2020. Fifty articles were organized according to the search words. The reference lists of these articles were also searched and analyzed for additional findings or reports related to nervous system involvement in COVID-19. A flow chart of the search process is provided in Figure 1. These articles were then carefully filtered for their relevance based on the following selection criteria: Diagnosed cases of COVID-19, cases with the neurological manifestation of neurological syndrome, a clear description of the clinical cases, and studies carried out in animal models or diagnosed human patients with SARS-CoV-2 infection involving the central nervous system. The relationship between COVID-19 and the nervous system was explored and a brief review was then performed.

RESULTS

We reviewed more than 50 scientific articles on SARS-CoV-2 infection with relation to the nervous system that were either published or pre-published (accepted for publication and in preprint) in the past 4 months, including case reports, case series, experimental studies, observational studies, review articles, and letters to the editor. We look into the details of the neurological manifestations or complications of COVID-19 disease and reviewed the possible mechanism of viral transmission to the nervous system. After considering the selection criteria, 13 case reports, two case series, and four observational studies were included in the study.

Neurological manifestation of SARS-CoV-2 infection

Anosmia and ageusia are among the neurological symptoms most commonly reported by patients with COVID-19. Eliezer et al. [14] reported a case of a young female who lost her sense of smell without any nasal obstruction. A computed tomography (CT) scan and magnetic resonance imaging (MRI) of the nasal cavity showed only bilateral inflamed olfactory clefts without any anomalies in the olfactory bulb and tract. Spinato et al. [15] conducted a study in Italy, in which they called 202 patients with COVID-19 through the phone to determine if they had any neurological symptoms. One hundred and three of these patients (64.4%) complained of anosmia and ageusia, among whom 24, 46, and 54 individuals developed thee symptoms prior, concomitantly, and after fever and cough, respectively, and six patients only had anosmia and ageusia without any fever. Anosmia and ageusia were also reported by Mao et al. [10], who performed an observational study of 214 patients with COVID-19. In that study, 78 (36.4%) patients developed neurological manifestations, which included CNS symptoms (such as dizziness, headache, and loss of consciousness) and peripheral nervous system (PNS) symptoms (such as anosmia and ageusia). In addition, 23 patients developed rhabdomyolysis of varying severity. Suwanwongse et al. [14] later reported an interesting case of rhabdomyolysis in an elderly patient with COVID-19 whose presentation was only bilateral lower-limb weakness without any fever or respiratory symptoms. Mao et al. [10] also reported six patients who developed ischemic stroke. This finding raises a concern regarding the inadequacy of the information available on cerebrovascular involvement in COVID-19 [16]. Therefore, Li et al. [17] carried out an observational study of 221 COVID-19 patients aimed at identifying the presence of cerebrovascular disease. The authors found that 11 (5%) of these patients developed acute ischemic stroke, one (0.5%) patient developed cerebral venous sinus thrombosis, whereas one other 1 (0.5%) patient developed cerebral hemorrhage. The majority of the patients with the cerebrovascular disease were elderly individuals, and 84.6% of them presented with severe SARS-CoV-2 infection. Furthermore, five of the 13 patients with the cerebrovascular disease died. Subsequently, Oxley et al. [18] published a case series of five young patients with COVID-19 who developed large vessel ischemic stroke, whereas intracranial bleeding was observed by Sharifi-Razavi et al. in one patient with this disease (2020) [19].

An observational study of 58 patients with COVID-19 who were admitted to a hospital in France for severe acute respiratory distress syndrome reported by Helms et al. [20] found that 39 (67%) of these patients developed diffuse corticospinal tract signs with enhanced tendon reflexes, ankle clonus, and bilateral extensor plantar reflexes. Three patients had a subclinical ischemic stroke, which was noted on MRI of the brain. That study also found that 15 (33%) of the 45 patients who were discharged had a dysexecutive syndrome such as inattention,

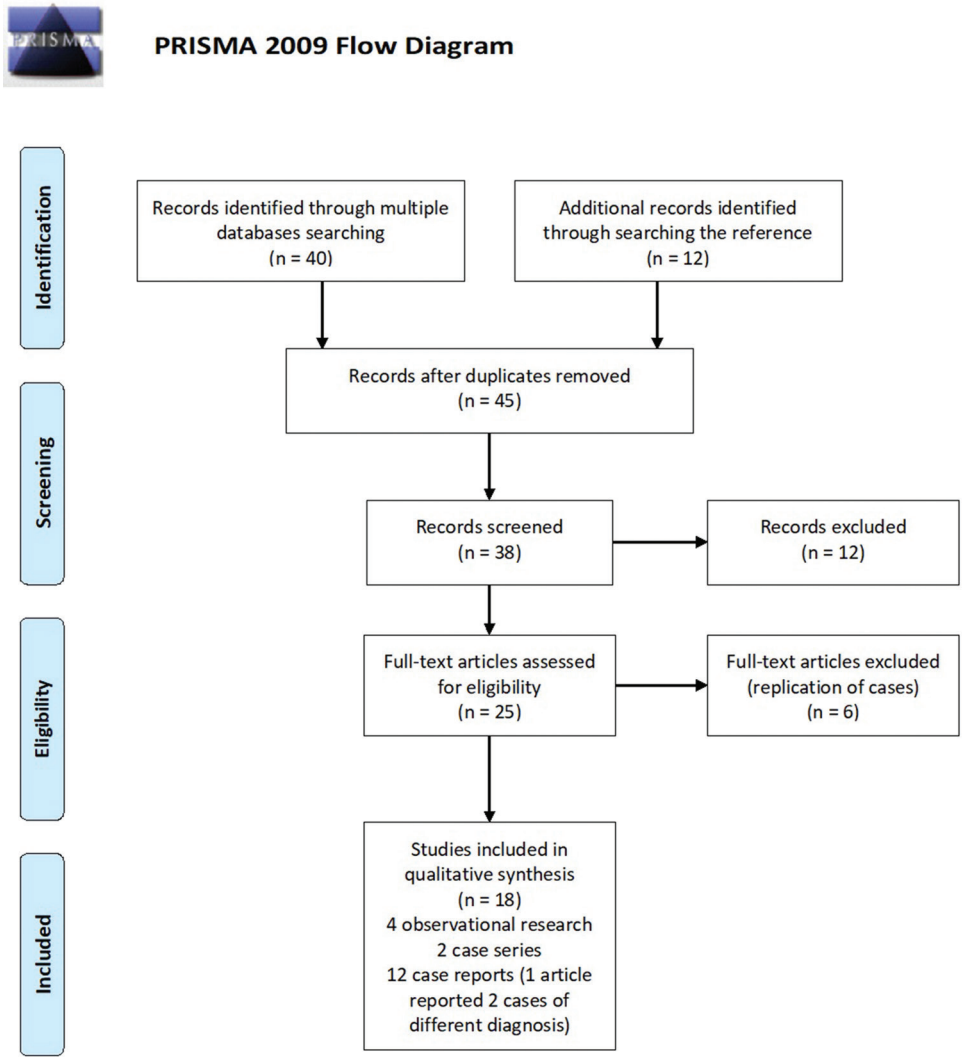

FIGURE 1. Flow chart of the literature search process according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

disorientation, or poorly organized movements in response to commands. Another neurological syndrome that was frequently reported in patients with SARS-CoV-2 infection was GBS. Zhao et al. [12] reported the case of an elderly female in China who presented with sudden bilateral lower-limb weakness before developing low-grade fever and dry cough. She was treated successfully with an immunoglobulin infusion (IVIg) and lopinavir/ritonavir and was discharged well. A case series of five patients with COVID-19 and GBS from Italy was reported by Toscano et al. [13]. In that report, all five patients had respiratory symptoms before the onset of weakness, and only three of them had a fever. All of these patients were treated with IVIg. Two of the patients remained in the intensive care unit and required mechanical ventilation, two patients were discharge for physiotherapy with some recovery, and one patient was able to walk independently at discharge. There was also a case of Miller–Fischer syndrome that occurred in COVID-19 patients reported in the literature. Gutiérrez-Ortiz et al. [21] described a male patient who had a fever, anosmia, and ageusia for a few days before developing ataxia, vertical diplopia, and generalized areflexia. His cerebrospinal fluid (CSF) exhibited cytoalbuminological dissociation, and he was positive for the GD1b-IgG antibody. He was treated with IVIg and discharged well. In the same article, the authors also described another interesting case of COVID-19, who developed isolated multiple cranial neuropathies, which can be a mild spectrum of Miller–Fischer syndrome. The patient had a low-grade fever for 3 days before he developed diplopia. His CSF analysis was normal. His anti-ganglioside antibody level was not assessed, and he was not admitted because of logistics issues associated with an overcrowded hospital. He was noted to have recovered spontaneously during a telemedicine follow-up.

Three case reports described the development of acute encephalitis in patients with COVID-19 from China [22], Iran [23], and Japan [24], respectively. Two of the cases were young patients aged 24 and 30 years, while the other patient was 56 years old. All three patients presented with fever, cough, and impaired consciousness, while two of them developed generalized-onset tonic–clonic seizures. The outcome of two of these patients was good, while that of the third-one was not mentioned.

In a more extreme scenario, cases of acute necrotizing encephalopathy [25] and acute disseminated encephalomyelitis [26] were reported. Both of these patients presented with altered mental status and were treated with IVIg. Zhao et al. [27] reported a case of acute transverse myelitis in an elderly patient with COVID-19. He was treated with a 7-day course of IVIg and some recovery of his muscle strength was recorded. A brief summary of all the articles selected for this review is provided in Table 1.

Possible mechanism of SARS-CoV-2 invasion into the nervous system

SARS-CoV-2 is believed to invade the CNS from the peripheral nerve terminals through neural pathways, such as the olfactory nerves. The olfactory nerves have a unique anatomical organization that provides a channel between the olfactory bulb, located near the nasal cavity, and the brain [28]. Furthermore, there is evidence of the presence of SARS-CoV-2 genetic material and proteins in samples from nervous system tissues [29]. This suggests that the virus can directly invade and damage the nervous system. The virus also triggers an exaggerated immune response that attacks the nervous system, as observed in multiple cases of patients with severe COVID-19 who developed a cytokine storm syndrome, which is a hyperinflammatory state characterized by a fulminant hypercytokinemia leading to life-threatening multiorgan failure [30]. Among these cytokines, interleukin-6 (IL-6) is elevated in patients with COVID-19. The level of IL-6 is positively correlated with the severity of COVID-19 symptoms [31]. Moreover, IL-6 is an important pro-inflammatory mediator that is potentially responsible for the activation of immune cells in the brain and injury of the brain tissue [32]. Another plausible hypothesis is that the ectodomain of the spike protein of SARS-CoV-2 has a high binding affinity to the angiotensin-converting enzyme 2 (ACE2) receptor [33]. The ACE2 receptors are expressed abundantly in the capillary endothelium of multiple parts of the human body, including the brain, to which the virus may gain access through the blood-brain barrier and damage the nervous system [34]. It has been reported that glial cells and neurons in the brain also express ACE2 receptors [35], which renders them a potential target of SARS-CoV-2. In addition, as ACE2 is a vasoconstrictor and has a pro-inflammatory effect [36], it is also possible that ACE2 involvement in the brain during COVID-19 infection leads to autoregulatory disruption and blood pressure spikes, resulting in arterial wall rupture, which may be the pathophysiology underlying the intracranial bleeding observed in SARS-CoV-2 infection [19]. Conversely, ischemic stroke is not uncommon in patients infected with SARS-CoV-2. This may be explained by the fact that SARS-CoV-2 causes endothelial dysfunction [18] and increases coagulability, as evidenced by the increased levels of C-reactive

TABLE 1. Brief clinical summaries of the selected articles, which included 13 case reports, two case series, and four observational studies

No	Article name	Country	Types	Summary
1.	Mao et al. (2020) [12]	China	Observational study	1. 78 (36.4%) of 214 patients had severe neurological symptoms. 2. 53 patients had CNS symptoms (dizziness, headache, and loss of consciousness), six had stroke, one had ataxia, and one had seizure. 3. 19 patients had PNS symptoms (loss of taste, loss of smell, and neuralgia). 4. 23 patients developed rhabdomyolysis. 5. A patient with lymphopenia had more severe disease and, thus, more developed neurological manifestations. 6. Nervous system involvement was more common in patients with severe disease, and severe cases usually occurred in elderly patients with comorbidities (commonly hypertension, followed by diabetes mellitus, cardiocerebral disease, malignancy, and chronic kidney disease). 7. CNS involvement was associated with poor prognosis.
2.	Li et al. (2020) [19]	China	Observational study	1. 13 (5.88%) of 221 patients developed acute cerebrovascular disease. 2. 11 (5%) patients developed acute ischemic stroke; six of them were treated with oral antiplatelet and three of them died, whereas five patients were treated with a subcutaneous anticoagulant, and one died. 3. One (0.5%) patient developed cerebral venous sinus thrombosis and was treated with an anticoagulant, and another patient (0.5%) developed cerebral hemorrhage and died 22 days after the onset of stroke. 4. Five (38%) of 13 patients with cerebrovascular disease died. 5. Most patients with cerebrovascular disease were older (71.6±15.7 years), had cardiovascular risk factors (such as hypertension, diabetes mellitus, and dyslipidemia), and presented with severe COVID-19 (84.6% of patients with cerebrovascular disease presented with severe COVID-19). These patients were likely to develop a hypercoagulable state and increased inflammatory response, as evidence by the increased levels of C-reactive protein and D-dimer. 6. 12 of 13 patients with cerebrovascular disease had an extremely high level of D-dimer, in contrast to the lower D-dimer levels detected in patients without cerebrovascular disease. The level of C-reactive protein in patients with COVID-19 with cerebrovascular disease was higher than that of patients without cerebrovascular disease.

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TABLE 1. *(Continued)*

No	Article name	Country	Types	Summary
3.	Helms et al. (2020) [22]	France	Observational study	1. An observational study of 58 patients admitted to the hospital in France because of ARDS caused by COVID-19. The RT-PCR assays for SARS-CoV-2 in nasopharyngeal samples were positive. 2. Seven patients had underlying neurological disorders, such as transient ischemic attack, partial seizure, and some degree of cognitive impairment. 3. 40 patients (69%) developed agitations upon discontinuation of neuromuscular blockade, and 26 of the 40 patients develop confusion. 4. 39 patients (67%) had diffuse corticospinal tract signs such as increased deep tendon reflexes, clonus, and upgoing plantar reflexes. 5. 15 of the 45 discharged patients (33%) had impaired executive function such as poor attention, disorientation, or poor response to verbal commands. 6. 13 patients underwent MRI for unexplained encephalopathy; eight patients showed enhancement in leptomeningeal spaces, while bilateral frontotemporal hypoperfusion was observed in 11 patients. 7. Three asymptomatic patients were noted to have ischemic stroke, two of whom had a small focal hyperintensity on diffusion-weighted imaging and an overlapping reduced apparent diffusion coefficient, whereas one patient had a subacute ischemic stroke, as evidenced by superimposed increased diffusion-weighted imaging and apparent diffusion coefficient signals. 8. Eight patients underwent EEG: One patient had diffuse bifrontal slowing wave, consistent with encephalopathy. The others only showed nonspecific changes. 9. Seven patients underwent CSF analysis. No cells were found and all CSF samples were negative for RT-PCR for SARS-CoV-2. Two patients had matched oligoclonal bands with an identical electrophoretic pattern in the serum, and one patient had elevated protein and IgG levels.
4.	Spinato et al. (2020) [17]	Italy	Retrospective study	1. 221 patients were recruited into a telephone survey; 202 patients completed the survey. The median age was 56 years and 105 (72.4%) of the participants were women. 2. 130 (64.4%) of 202 patients had a reduced sense of smell or taste, while 45 (34.6%) of them also reported a blocked nose. 3. The onset of the reduced sense of smell or taste in relation to other symptoms occurred before other symptoms in 24 (11.9%), at the same time in 46 (22.8%), and after in 54 (26.7%) patients. Six of these patients (3%) reported an altered sense of smell or taste as the only symptom. 4. The author recommends testing and self-isolating patients with new onset of reduced sense of smell or taste during this pandemic.
5.	Filatov et al. (2020) [13]	USA	Case report	1. A 74-year-old male with cardiocerebral vascular disease and a history of returning from Europe complained of fever, cough, headache, altered mental status, and encephalopathic symptoms (nonverbal, not obeying commands, but still able to move). There was no nuchal rigidity. 2. CT of the brain showed no acute changes, with left temporal encephalomalacia (he had a history of embolic stroke). EEG showed diffuse and focal slowing with sharply contoured waves in the left temporal region, which was consistent with encephalopathy, or focal left temporal lobe dysfunction, or even epileptogenicity. The CSF analysis was normal. 3. Anti-epileptic therapy was started based on the possibility of subclinical seizures, in view of the presence of encephalomalacia on brain CT and epileptiform discharges in the left temporal region. 4. He developed respiratory failure and was intubated and mechanically ventilated (poor prognosis). 5. Health care providers should be aware that patients with COVID-19 can develop encephalopathy in the acute setting.
6.	Zhao et al. (2020) [14]	China	Case report	1. A 61-year-old female with a history of travelling to Wuhan presented with sudden paraparesis and severe fatigue, which progressed within 1 day. There were no systemic or respiratory symptoms. Neurologically, she exhibited symmetrical lower-limb weakness (MRC 4/5). Her symptoms progressed with a muscle power of 4/5 and 3/5 in the upper and lower limbs, respectively. There was also decreased sensation to pinprick and light touch distally. 2. Blood investigations revealed lymphopenia and thrombocytopenia; CSF analysis revealed albuminocytological dissociation; NCS showed delayed distal latencies and absent F waves in the early course, in keeping with demyelinating neuropathy. 3. She was diagnosed as having GBS and was started on IVIg. She developed fever and dry cough in the ward. A CT scan of chest noted a bilateral ground glass appearance. An oropharyngeal swab for SARS-CoV-2 was positive on RT-PCR assay. She was started on antiviral drugs including arbidol, lopinavir, and ritonavir. Her muscle power and tendon reflexes returned to normal, and the cell count was normalized. 4. GBS in SARS-CoV-2 infection might follow the pattern of a para-infectious profile, rather than the classic post-infectious profile, in which the weakness overlaps with the period of SARS-CoV-2 infection.
7.	Karimi et al. (2020) [25]	Iran	Case report	1. A 30-year-old female who was a teetotaler with no known medical illness was admitted with generalized tonic–clonic seizure. She had a dry cough and fever for a few days before admission. In Ed, she was drowsy and disorientated to time. There was no stiff neck or nuchal rigidity. Her cranial nerves were intact, and her pupils were midsize and reactive to light and accommodation. There was no papilledema. She was able to move her extremities, and deep tendon reflexes were normal. 2. Blood and CSF analysis were all normal; her MRI brain was also normal; CT scan of the chest showed bilateral ground glass opacity; nasal and pharyngeal swabs were positive for COVID-19, while her CSF sample was negative for COVID-19. 3. She was treated with intravenous phenytoin and levetiracetam and was also administered chloroquine and Lopinavir-ritonavir. The fever and seizure were controlled. 4. The etiology of her seizure may be encephalitis and can be secondary to direct invasion of the virus to the brain, or a toxic effect of inflammatory cytokines.
8.	Poyiadji et al. (2020) [27]	USA	Case report	1. A female in her 50s who was an airline worker presented with a 3-day history of fever, cough, and altered mental state. Her nasopharyngeal swab was positive for SARS-CoV-2. 2. CSF analysis was normal, with no bacterial growth and negative results on the viral test. Plain brain CT showed symmetrical hypoattenuation within the medial thalami bilaterally. CT angiogram and CT venogram were normal. MRI of the brain showed characteristic hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions. This finding was suggestive of acute necrotizing encephalopathy. 3. She was started on IVIg but was not treated with steroids because of the risk of respiratory failure.

(Contd...)

TABLE 1. *(Continued)*

No	Article name	Country	Types	Summary
9.	Xinhua [24]	China	Case report	1. A 56-year-old SARS-CoV-2 positive patient with severe symptoms developed reduced consciousness. 2. CT brain was normal; CSF analysis noted positivity for SARS-CoV-2. 3. The patient was diagnosed with SARS-CoV-2 encephalitis, was admitted for 1 month, and was managed and discharged well. 4. The director of the ICU stated that a patient with COVID-19 and reduced consciousness should be investigated for the possibility of CNS infections and should have a timely CSF analysis to avoid diagnosis delay and reduce the mortality rate of COVID-19.
10.	Moriguchi et al. (2020) [26]	Japan	Case report	A 24-year-old male without a history of recent travelling complained of fever, headache, generalized fatigue, and sore throat for 5 days. The symptoms were progressive in nature, and he was brought to the hospital by ambulance after he was found unconscious. He developed GTC seizure in the ambulance, which lasted for 1 min. Upon arrival to the ED, his GCS was 6/15 and he was hemodynamically stable. He had neck stiffness. While in the ED, he developed multiple episodes of GTC. 1. Blood investigations revealed leukocytosis with neutrophilic predominance, relative lymphopenia, and raised C-reactive protein levels. Brain CT showed no cerebral edema; CT scan of the chest revealed a ground glass appearance over the bilateral lower lobes and the right upper lobe. Lumbar puncture revealed a high opening pressure of 32 mmH20, and CSF analysis showed a clear fluid, raised white cell count (monocyte predominance), and no blood cells. RT-PCR for SARS-CoV-2 was negative in the nasopharyngeal swab, but positive in the CSF. 2. MRI–DWI revealed a hyperintensity along the wall of the inferior horn of the right lateral ventricle. FLAIR showed right mesial temporal lobe and hippocampus with slight hippocampal atrophy. These findings were suggestive of right lateral ventriculitis and encephalitis over the right mesial lobe and hippocampus. 3. He was started on IV levetiracetam, IV favipiravir, IV ceftriaxone, IV vancomycin, acyclovir, and steroids. 4. The author recommended that encephalitis and cerebropathy can be an indication to investigate for SARS-CoV-2 infection, as unconscious patients are potentially infected by SARS-CoV-2, which can result in horizontal infection.
11.	Eliezer et al. (2020) [16]	France	Case report	1. A 40-year-old female presented with a history of dry cough, headache, and myalgia for a few days, with otherwise no fever or rhinorrhea. She presented with acute loss of smell without any nasal obstruction. 2. CT of the nasal cavity revealed inflammatory obstruction of the olfactory clefts bilaterally. MRI of the nasal cavity confirmed the CT finding, and revealed no anomalies in the olfactory bulbs and tracts. She was investigated for COVID-19 because her husband was a PUI; she tested positive. 3. Coronaviruses may invade the CNS through the cribriform plate, which is located near the olfactory bulb.
12.	Suwanwongse et al. (2020) [18]	USA	Case report	1. An 88-year-old male with underlying hypertension, chronic kidney disease, heart failure with reduced ejection fraction, benign prostatic hypertrophy, bilateral knee osteoarthritis, and mild cognitive impairment presented with acute onset bilateral painful thigh weakness causing him to be unable to stand up from the toilet bowl. He had a dry cough, but denied fever and other respiratory or gastrointestinal tract symptoms. His regular medications included simvastatin, donepezil, furosemide, losartan, metoprolol succinate, and tamsulosin, which had not been changed in the past year. On examination, he had fever and was tachypneic. 2. His blood investigations show raised CPK, at 13,581 U/L (normal range, 20-200 U/L), and LDH, at 364 U/L (normal range, 120-250 U/L). In view of the fever and cough, a PCR test for COVID-19 from a nasopharyngeal swab was performed, he tested positive. 3. He was treated with oral hydroxychloroquine for 5 days. His symptoms clinically improved and his CPK decreased gradually. 4. Rhabdomyolysis can occur as an initial presentation of COVID-19 or later on at any time during the course of the illness. Therefore, clinicians should consider a high suspicion of rhabdomyolysis in patients with COVID-19 who have localized muscle pain or weakness.
13.	Zhao et al. (2020) [29]	China	Case report	1. A 66-year-old male with COVID-19 presented with high-grade fever and fatigue for 2 days, and eventually developed acute flaccid paraplegia and urinary and bowel incontinence. His neurological examination showed a muscle power of 3/5 with normal reflexes in the bilateral upper limbs and 0/5 with hyporeflexia in the lower limbs bilaterally. Sensory levels were intact in the arms, but were globally impaired in both legs. There was a sensory level at T10, with paresthesia and numbness below that level, and reduced deep tendon reflexes in the lower limbs. 2. His nasopharyngeal swab was positive for SARS-CoV-2; CT of the chest revealed bilateral patchy changes; blood investigations showed very markedly raised serum ferritin, C-reactive protein, IL-6, and PCT. CSF analysis and MRI were not performed. 3. He was treated with ganciclovir for 14 days, lopinavir/ritonavir for 5 days, moxifloxacin for 6 days, meropenem for 8 days, glutathione for 12 days, dexamethasone for 10 days, IVIg for 7 days, mecobalamin for 14 days, and pantoprazole for 10 days. His muscle power in both upper limbs recovered to grade 4/5, and that in the lower limbs was grade 1/5. CT scan of the chest was repeated and showed improvement of the previous lesions. He was discharged to a designated hospital for isolation and rehabilitation therapy.
14.	Sharifi-Razavi et al. (2020) [21]	Iran	Case report	1. A 79-year-old male presented with a 3-day history of fever and cough. There was no history of hypertension or oral anticoagulation therapy. On admission, he was febrile, tachycardic, and tachypneic. His GCS dropped to 7/15, and the plantar reflexes were upgoing bilaterally. Chest examination revealed coarse crackles in the left lower lobe. 2. Blood investigations revealed lymphopenia and high ESR and C-reactive protein. CT of the thorax revealed ground glass opacity in the left lower lobe and CT of the brain showed a massive intracranial hemorrhage in the right hemisphere, with intraventricular and subarachnoid hemorrhage. RT-PCR of an oropharyngeal swab confirmed SARS-CoV-2 infection.

(Contd...)

TABLE 1. *(Continued)*

No	Article name	Country	Types	Summary
15.	Zhang et al. (2020) [28]	USA	Case report	1. A right-handed female in her early forties presented to the ED with a 2-day history of dysphagia, dysarthria, and encephalopathy. She had hypertension and dyslipidemia, which were controlled well. She had a headache and myalgia for 11 days before admission. In the ED, she had fever and was mildly tachypneic with some hypoxemia. The chest examination revealed diffused rhonchi. She was alert and able to follow commands sluggishly. She had dysarthria and expressive aphasia. There was bulbar impairment, as evidenced by dysphagia with difficulty to handle secretions. There was no meningism sign. Her pupils were equal and reactive, but she had a right gaze preference and a mild left facial asymmetry. She had mildly decreased muscle strength bilaterally, and her deep tendon reflexes were normal. 2. There was mild leukocytosis with lymphopenia. Her chest X-ray revealed patchy consolidation in the right lower lung. A plain CT scan of the brain showed multifocal patchy areas of white matter hypoattenuation, with no evidence of intracranial bleeding. CSF and EEG were normal. MRI of the brain showed extensive patchy areas of abnormal signal over the frontoparietal white matter, basal ganglia, anterior temporal lobes, external capsules, and thalami bilaterally. Some of the foci exhibited DWI changes and corresponding apparent diffusion coefficient changes, with minimal enhancement. MRA of the brain and neck was normal. These findings were suggestive of ADEM. 3. She was treated with hydroxychloroquine, ceftriaxone, and a 5-day course of IVIg. There were signs of improvement, as she was able to handle secretions better, become less dysarthric, and was afebrile with no respiratory symptoms. 4. ADEM has been described in cases of MESRS-CoV and coronavirus OC43 infection.
16.	Consuelo Gutiérrez-Ortiz et al. (2020) [23]	Spain	Case report (two patients)	1. 1st patient: A 50-year-old male with bronchial asthma presented with a 2-day history of vertical diplopia, perioral paresthesia, and unstable gait. He had preceding fever, cough, malaise, headache, and low-back pain 5 days before admission, which were associated with anosmia and ageusia. On examination, there was no facial weakness, no ptosis, normal muscle strength and tone, and no sensory abnormality was detected. Generalized areflexia was noted, and he had a broad-based ataxic gait. Finger-to-nose and heel-to-shin tests were normal. He showed severe limitations in the adduction and downgaze movements of his right eye, and left eye nystagmus on left gaze, which were consistent with right internuclear ophthalmoparesis and right fascicular oculomotor palsy. No fatigability was noted. 2. Blood investigations showed lymphopenia and a raised C-reactive protein level. The serum anti-ganglioside antibodies (GM1, GM2, GM3, GD1a, GD1b, GD3, GT1a, GT1b, GQ1b, and anti-sulfatide antibodies) were tested and the anti-GD1b-IgG antibody alone was present. His oropharyngeal swab test for COVID-19 was positive on a qualitative RT-PCR assay. CSF analysis shows cytoalbuminological dissociation, sterile cultures, and negative serologies, including the RT-PCR for COVID-19. Chest X-ray and plain brain CT were normal. He was treated with IVIg 0.4 g/kg for 5 days. The cranial neuropathies and the ataxia improved significantly and he was discharged 2 weeks after admission, with residual anosmia and ageusia. 3. 2nd patient: A 39-year-old male with no known medical illness presented with acute onset of diplopia. He had diarrhea, fever, and a generally poor condition 3 days before presentation, without any respiratory symptoms. On examination, he was conscious, alert, and well oriented. His respiratory, cardiovascular, and abdominal examinations were normal. There were severe abduction deficits in both eyes, and fixation nystagmus, with the upper gaze being more impaired. This was consistent with bilateral abducens palsy. All deep tendon reflexes were absent. Otherwise, the remaining neurological examination was normal. 4. His oropharyngeal swab test for COVID-19 by qRT-PCR assay was positive. CSF analysis was normal. Chest X-ray and plain CT of the brain were normal. He was discharge home, and upon follow-up through telephone 2 weeks later revealed that he had a complete neurological recovery with no ageusia, normal eye movements, and deep tendon reflexes. 5. This article reported an acute ataxic neuropathy, which can be present in the absence of ophthalmoplegia, as in the 1st patient, and an acute ophthalmoplegia, which may present in the absence of ataxia, as in the 2nd patient.
17.	Gianpaolo Toscano et al. (2020) [15]	Italy	Case series	1. A series of five patients who had GBS after SARS-CoV-2 infection. 2. Four patients presented with lower-limb weakness and paresthesia which progression to generalized, flaccid tetraplegia over a period of 36 h-4 days. Three of them required mechanical ventilation. 3. One patient presented with facial diplegia followed by ataxia and paresthesia. 4. CSF analysis revealed that all five patients had a normal CSF white cell count and three of them had a raised CSF protein level. Anti-ganglioside antibodies were tested in the three patients but were negative. RT-PCR assay of the CSF was negative for SARS-CoV-2 in all patients. 5. An electrophysiological study revealed low compound muscle action potential amplitudes in all patients; two of them had prolonged motor distal latencies. Electromyogram revealed fibrillation potentials in three patients. In another patient, they were absent initially but were present at day 12. MRI with gadolinium showed enhancement of the caudal nerve roots in two patients, enhancement of the facial nerve in one patient, and no changes in two patients. 6. All patients were treated with IVIg; two of them received two courses of IVIg, and one was started on plasma exchange. 7. Two patients were receiving mechanical ventilation in the ICU, two patients were undergoing physical therapy for flaccid paraplegia, and 1 was discharged and could walk independently at the time of reporting. 8. The author recommended that GBS in COVID-19 had to be distinguished from critical illness neuropathy and/or myopathy, which usually occur much later in the course of the disease. The interval of 5-10 days between the onset of the viral illness and the muscle weakness was similar to GBS precipitated by other infections.

(Contd...)

TABLE 1. *(Continued)*

No	Article name	Country	Types	Summary
18.	Oxley et al. (2020) [20]	USA	Case series	1. A series of five patients with large vessel stroke. 2. 1st patient: A 33-year-old male with no known medical illness and a history chills, cough, and headache presented with left-sided hemiplegia with facial drooping, gaze preference, homonymous hemianopia, dysarthria, and sensory deficit at 28 hours after onset. CT scan and CT angiography revealed right internal carotid artery stenosis. He was started on antiplatelet initially followed by direct oral anticoagulant therapy. He was discharged to a rehabilitation facility. 3. 2nd patient: A 37-year-old male with no known medical illness who had no respiratory symptoms presented with reduced consciousness, dysphasia, right-sided hemiplegia, dysarthria, and sensory deficit at 16 hours after onset. CT scan and CT angiography revealed left middle cerebral artery stenosis. He underwent mechanical thrombectomy and was started on anticoagulation. He was discharged home. 4. 3rd patient: A 39-year-old male with hypertension and dyslipidemia presented with reduced consciousness, gaze preference to the right, left homonymous hemianopia, left-sided hemiplegia, and ataxia at 8 hours after onset. CT scan and CT angiography revealed right posterior cerebral artery stenosis. He underwent mechanical thrombectomy and was started on antiplatelet therapy. He was still intubated and sedated in the ICU, with multiorgan failure, at the time of reporting. 5. 4th patient: A 44-year-old male with undiagnosed diabetes mellitus presented with reduced consciousness, global dysphasia, right-sided hemiplegia, and gaze preference at 2 hours after onset. CT scan and CT angiography revealed left middle cerebral artery stenosis. He was administered intravenous thrombolysis and underwent mechanical clot retrieval and hemicraniectomy; he was also started on aspirin. He was still in the stroke unit at the time of reporting. 6. 5th patient: A 49-year-old male with mild stroke and diabetes mellitus presented with reduced consciousness, left-sided hemiplegia and facial weakness, and dysarthria at 8 h after onset. CT scan and CT angiography revealed right middle cerebral artery stenosis. He underwent mechanical clot retrieval with stent insertion and was started on double antiplatelet therapy. He was discharged to a rehabilitation facility. 7. The author suggested that coagulopathy and abnormal endothelial function of the blood vessels are complications of COVID-19.

CNS: Central nervous system; PNS: Peripheral nervous system; COVID-19: Coronavirus disease-19; ARDS: Acute respiratory distress syndrome; RT-PCR: Reverse transcriptase-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; MRI: Magnetic resonance imaging; CSF: Cerebrospinal fluid, CT: Computed tomography; EEG: Electroencephalogram; NCS: Nerve conduction study; GBS: Guillain–Barré syndrome; IVIg: Intravenous immunoglobulins; GCS: Glasgow coma scale; GTC: Generalized tonic–clonic; DWI: Diffuse weighted imaging; FLAIR: Fluid-attenuated inversion recovery; IV: Intravenous; CPK: Creatine phosphokinase; LDH: Lactate dehydrogenase; MRA: Magnetic resonance angiography; ADEM: Acute demyelinating encephalomyelitis

protein and D-dimer observed in these patients [17,18,37]. Another hypothesis proposes that SARS-CoV-2 also affects the nervous system in a simpler way, that is, the severe hypoxia resulting from pneumonia and acute respiratory distress syndrome causes cerebral edema and ischemic stroke [38].

DISCUSSION

SARS-CoV-2 belongs to the genus of beta-coronaviruses, which are zoonotic viruses that can infect both animals and humans. It is the seventh type of coronavirus to affect humans and the third-one to cause a global pandemic. Infection with SARS-CoV-2 can cause a typical systemic and respiratory clinical syndrome that includes symptoms such as fever, cough, shortness of breath, myalgia, and fatigue. Other clinical presentations that are consider non-typical of this virus are diarrhea, anorexia, conjunctival congestion, nausea, and vomiting, among many others [39]. About 20-30% of patients may exhibit progression to more critical conditions, such as acute respiratory distress syndrome, septic shock, disseminated intravascular coagulation, acute heart failure, and acute kidney injury [40]. The incubation period for SARS-CoV-2 infection is about 2-14 days [41]. The transmission has been confirmed to occur rapidly from human to human, and it is thought to occur through direct contact with respiratory droplets from an infected individual [42]. As a result of a lack of awareness regarding infection control, especially in hospitals and international airports, the infection with this virus has spread rapidly across borders and has caused a massive global pandemic [43]. To date, there are more than 6 million confirmed cases of COVID-19, and more than 350,000 deaths have occurred in more than 150 countries around the world.

As shown in previous studies of SARS-CoV and MERS-CoV, beta-coronaviruses are neurotropic and exhibit neurovirulent properties [44]. Since SARS-CoV-2 has 79% and 52% genetic similarity with SARS-CoV and MERS-CoV, respectively [45], it is possible that it possesses similar properties and is capable of infecting the nervous system. Multiple hypotheses have been put forward regarding the possible mechanisms through which SARS-CoV-2 affects the nervous system. These include direct invasion of SARS-CoV-2 into the nervous system, as evidence by the discovery of the viral protein in the CSF of a patient with COVID-19 who was suspected of developing encephalitis [24,30]. The route of invasion can be either through retrograde movement through the olfactory nerve [29] or the hematogenous route, as the presence of ACE2 receptors in the brain may facilitate the movement of the virus through the brain's circulation [35,36]. Another possible route of invasion is through the hyperactivation of the host immune response and to the triggering of a hyperinflammatory state with multiorgan failure, in a condition

called cytokine storm syndrome [31]. This is only to name a few of the many suggested possible mechanisms through which SARS-CoV-2 can affect the nervous system. However, the exact mechanism is still not fully understood, and further studies are needed to explore this subject.

There is evidence showing the association between SARS-CoV-2 infection and nervous system involvement. This association can occur regardless of the involvement of the respiratory system. Moreover, it is observed more commonly among patients who are admitted to the hospital with severe illness and in elderly patients with multiple comorbidities [10]. The neurological manifestations of COVID-19 disease can be broadly divided into CNS and PNS symptoms. The most commonly reported CNS presentations to include impaired consciousness, headache, dizziness, confusion, and agitation 10,20]. Regarding PNS involvement, loss of taste, loss of smell, and neuralgia are the commonly reported symptoms [14-16]. Furthermore, some patients develop more sinister neurological syndromes such as GBS [12,13], acute ischemic stroke [10,17,18], intracranial haemorrhage [19], acute myelitis [27], acute encephalitis [22-24], acute necrotizing encephalopathy [25], and acute disseminated encephalomyelitis [26].

Another major concern regarding the involvement of the nervous system in SARS-CoV-2 infection is the possibility of long-term or permanent neurological disabilities. This is because the neurological syndrome can last longer than the lung infection itself [46]. Moreover, other types of coronaviruses are linked to the development of CNS dysfunction, such as multiple sclerosis [47]. Therefore, further studies are deemed necessary to elucidate the prognosis and potential reversibility of the neurological syndromes of COVID-19, as well as the impact of SARS-CoV-2 infection in promoting other neurological diseases, such as multiple sclerosis.

This study had limitations, as most of the articles analyzed here were case reports, and only a few research articles pertained to observational studies from a single center with a very limited number of cases. Finally, this article used mainly descriptive analyses to review and summarize the clinical cases of COVID-19 with nervous system involvement.

CONCLUSION

Based on the evidence gathered from the scientific literature, this review raises the possibility of nervous system involvement in COVID-19. Therefore, it would be prudent to evaluate all patients with COVID-19 for neurological symptoms, and to rule out SARS-COV-2 infection in any patient presenting with unusual neurological symptoms, to improve the prognosis of COVID-19 by delivering appropriate management in a timely fashion.

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