Patterns of neurological deficits in COVID-19 infections: a literature review

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INTRODUCTION
COVID-19 is a highly contagious disease causing more than three million infections resulting in more than 240000 deaths.1 It is caused by severe acute respiratory syndrome of coronavirus-2 (SARS-CoV-2) and it is transmitted through droplets to the mouth, nose, or eye.2 The disease usually resolves without treatment. However, complications occur in the elderly and patients with chronic conditions resulting in a high mortality rate in these populations.3
The usual clinical presentation of COVID-19 is high fever, dry cough, fatigue, and anosmia with taste loss in many cases, especially females.2,4-7 The disease usually passes unnoticed; however, in some cases, was associated with many complications. One of the most fatal and morbid complications is neurological complications.6 Many studies had reported the development of neurologic signs and symptoms during the disease. In China, a study reported 36.4% of the patient had developed neurologic symptoms.3 The most common neurologic symptoms are dizziness, headache followed by impaired consciousness, and acute cerebrovascular disease.3,8,11 There were also reports of other diseases like vasculitis, movement disorders, encephalopathy, and encephalomyelitis.4,12-15 In a large population study, ischemic stroke was reported in 1% to 2.5% of COVID-19 patients.5 Another study reported cases of cerebral haemorrhage associated with coagulopathy and the patient had a brain aneurysm, which caused the hemorrhage.16-18 Moreover, COVID-19 was associated with acute encephalomyelitis, seizures, myoclonus, and CNS vasculitis.19-21 The exact underlying pathogenesis is still unknown, but it is due to either direct infection of neurons by the SARS-CoV-2 virus or through inflammatory conditions triggered by the virus.16,22-25 The entry of the SARS-CoV-2 virus into the cells is dependent upon the angiotensinogen converting enzyme 2 (ACE2) receptors which are abundant in the cerebral endothelial cells and neurons.23 The binding of the virus to the receptors impairs the renin-angiotensin system in the brain leading to loss of brain vascular autoregulation. The other mechanism of neurologic complication is mainly due to inflammatory conditions caused by cytokine storm leading to coagulopathy and immune disturbances.22 Another mechanism is the autoimmune response toward peripheral nerves as more cases of Guillain Barre syndrome are reported. It occurs mainly due to epitope mimicry between the neuronal protein and viral particles causing acute polyneuropathy.26,27 Identification of the possible neurologic complications of the SARS-CoV-2 infection will improve the management of the diseases. Moreover, it will help the prediction and the early prevention of the neurologic deficits, which is associated with high morbidity and mortality. Present review, reports the published literature for neurologic deficits in COVID-19 patients and the possible underlying pathogenesis.

SEARCH STRATEGY

A systematic search was conducted to identify relevant studies in the following databases; PubMed, Medline, Web of science, Embase, Google scholar and Scopus. The following search terms were used severe acute respiratory syndrome of coronavirus-2 or SARS-COV-2 or COVID-19 or coronavirus and brain or nerve or neuro. The reference lists were manually searched to identify additional relevant studies meeting inclusion criteria. Any study that reports the neurological deficits in COVID-19 patients was included and no restrictions were applied. Neurological complications of COVID-19 are widely prevalent in literature.23 The complications span a wide range of clinical diseases.6,25,28 The diseases were reported in 25 countries. The United States had the highest number of publications reporting the neurologic complications.6,25,28 The main reported pathogenesis is either viral infection of the neurons impairing ACE2 receptors or inflammatory conditions triggered by the virus (Figure 1).

Figure 1: Summary of neurological deficits and possible mechanisms in COVID-19 patients.

CEREBROVASCULAR DISEASES

Based on the literature, approximately 1-3% of COVID-19 patients were diagnosed with acute ischemic stroke (AIS).5,15 It was reported in many studies that patients who have underlying comorbidities had a transient ischemic attack or acute ischemic stroke.5,15 Surprisingly, there were reports that acute ischemic attack occurred in young adults without any cardiovascular nor thromboembolic risk factors.12,29 It is explained that SARS-CoV-2 is the underlying cause in these cases due to its systemic effect. In these patients, there was a rise of the fibrinogen in 94% of cases, platelet in 62% of patients, interleukin-6, and D-dimer in 100% of cases.30 Besides, the inflammatory conditions associated with SARS-CoV-2 as evidenced by the elevated level of C-reactive protein, interleukin-7, IL-6, and other inflammatory markers, were another cause of the high incidence of ischemic stroke.15 Another possible reason was the effect of SARS-CoV-2 on the cardiovascular system leading to arrhythmias.14 Another proposed mechanism was through the interaction of the SARS-CoV-2 virus with ACE2 receptors that are present in the endothelial cells leading to impairment of the renin-angiotensin system resulting in endothelial dysfunction.5

It is estimated that about 0.5% of the COVID-19 patients suffer from intracranial hemorrhage.3 It was reported in critically ill patients because they suffered from coagulopathy including thrombocytopenia, elevated D-dimer, and disseminated intravascular coagulation. The intracranial hemorrhage incidence increased with any surgical procedures.17 As mentioned before, the effect of SARS-CoV-2 on ACE 2 receptors leads to vasoconstri-
ction and impairment of cerebral autoregulation. The failure of the autoregulation leads to blood pressure spikes leading to hemorrhage.\textsuperscript{5} 5-15\% of COVID-19 patients had venous and arterial thromboembolic complications. Most patients had disseminated intravascular coagulopathy and pulmonary thrombotic microangiopathy.\textsuperscript{16,31} Also, the cytokine storm was found to suppress the anticoagulant pathways releasing the Von Willebrand factor causing thromboembolic manifestation in these patients.\textsuperscript{16,31}

**Encephalopathy**

Encephalopathy was reported in 7.5\% to 31\% of COVID-19 patients.\textsuperscript{3} The patients are usually presented with a decreased level of consciousness. Many types of encephalopathy were reported including leukoencephalopathy, posterior reversible encephalopathy syndrome, encephalitis, and acute necrotizing encephalopathy.\textsuperscript{3} For leukoencephalopathy, it was reported in 18 patients and was diagnosed within 10-14 days after the infection.\textsuperscript{32} The diagnostic criteria reported in 11 critically ill COVID-19 patients’ studies were diffuse white matter T2 hyperintensity and restricted diffusion. However, these findings are non-specific but it was reported in cases of carbon monoxide poisoning and cardiopulmonary arrests.\textsuperscript{32} Another reported form is acute necrotizing encephalopathy (ANE) which was reported in 8 patients who have developed cytokine storm that causes damage to the blood-brain barrier which induces edema, cerebral hypoxia, and necrosis.\textsuperscript{25} For encephalitis, it was reported in 22 patients and SARS-CoV-2 was detected in post-mortem brain tissues.\textsuperscript{18,32} The patients usually present with a disturbed level of consciousness. The possible mechanism of encephalitis in COVID-19 is attributed to a high level of inflammatory cytokines that damages the blood-brain barrier.\textsuperscript{18,32} Another mechanism is through trigeminal and olfactory nerve infiltration by the virus causing neuronal death.\textsuperscript{18,33} Ten COVID-19 patients were diagnosed with posterior reversible encephalopathy syndrome (PRES) and were presented with visual disturbance, seizures, headache, and disturbed level of consciousness.\textsuperscript{10,34} It was usually affecting the parietal and occipital regions bilaterally and there was vasogenic edema in these areas. The exact underlying pathogenesis of PRES in COVID-19 patients is still unknown. It is hypothesized that it is caused by endothelial dysfunction and instability caused by cytokine storm which will increase the extravasation from the brain capillaries disrupting the blood-brain barrier.\textsuperscript{10,34} A study suggested that it is caused mainly by uncontrolled hypertension causing capillary dysfunction.\textsuperscript{10}

**Seizures**

Seizures were reported in many studies and approximately 48 COVID-19 patients developed at least one epileptic attack.\textsuperscript{4,20,22,35} It is suggested that SARS-CoV-2 infections of neurons are known to lower the threshold for seizures, and it is an important epileptogenic factor.\textsuperscript{35} Also, inflammatory conditions irritate the cortical structures causing seizures. In critically ill patients, other factors predispose to seizures including metabolic and electrolyte imbalance causing seizures.\textsuperscript{20} EEG findings support the presence of an epileptic focus in the brain represented by epileptiform activity in the form of frontal sharp waves, and generalized background slowing.\textsuperscript{36,37}

**Cranial nerve diseases**

Anosmia and ageusia are highly prevalent in COVID-19 patients affecting about 88\% of cases.\textsuperscript{7} These symptoms usually appear before the respiratory symptoms and it is not accompanied by nasal swelling nor rhinitis. It is most common in young females and it is usually resolved spontaneously.\textsuperscript{7} It is mainly caused due to abnormality of the olfactory bulb which was found to be thinner and hyperintense in MRI images of COVID-19 patients.\textsuperscript{38} In addition to olfactory nerve affections, visual impairment was reported in 12 patients who had posterior ischemic optic neuropathy.\textsuperscript{39} It is caused by direct invasion of the SARS-CoV-2 virus of the optic nerve or due to systemic inflammatory conditions in COVID-19 patients.\textsuperscript{39} Moreover, patients developed impaired eye movement due to the right abducens nerve palsy and affection of the sixth cranial nerve. Nine patients were reported to have trigeminal neuropathy which was accompanied by Herpes Zoster infection.\textsuperscript{40}

**Guillain-Barre syndrome**

Acute polyneuropathy was reported in many cases of SARS-CoV-2 infection within 5 to 10 days after infections.\textsuperscript{27} It starts with the weakness of the limbs in an ascending manner. The patients lost the ability to walk but most patients recovered after receiving the necessary treatment; other patients required mechanical ventilation.\textsuperscript{27} It is mainly caused by epito mimicry to the neural proteins.\textsuperscript{26} It has a high incidence in COVID-19 patients and was estimated to affect up to 21\% of cases.\textsuperscript{5,26-28}

**Demyelinating diseases**

Five patients were diagnosed with acute demyelinating diseases; all of these patients were adults. Two of these patients were treated with methylprednisolone and intravenous immunoglobulins and the remaining patients died.\textsuperscript{13,21,41-43} Another study reported exacerbation of multiple sclerosis, however, it was not proved in many patients, thus, it might not be caused by the virus itself.\textsuperscript{1,44}

**Encephalomyelitis**

Encephalomyelitis was reported in four adult patients who had a history of respiratory symptoms and were diagnosed as COVID-19 patients.\textsuperscript{42,45} For myelitis, acute myelitis was diagnosed in five patients and it was idiopathic transverse myelitis.\textsuperscript{46} Another study reported a 69 year old woman with acute necrotizing myelitis.\textsuperscript{33}
Another rare complication is optic neuropathy which was reported in only patients.23

**Movement disorders**

Movements disorders were reported in four patients.19,47 Three of these patients were diagnosed with generalized myoclonus with both positive and negative jerks affecting the facial, trapezius, and upper extremities muscles. The patients were sensitive to sensory stimuli and voluntary movement. The patients improved after receiving immunotherapy.19 The remaining patient had developed generalized myoclonus, disturbed level of consciousness, and symptoms of Parkinson’s like disease which improved spontaneously.47 It might be caused by antiviral antibodies causing Parkinson’s symptoms as reported before in coronavirus.47,48

**Cerebral vasculitis**

Only one case was reported to have developed cerebral vasculitis.5 A 65 year old man had developed lower extremities rash followed by extensive diffuse cortical ischemia as well as ischemic lesions in other organs including liver, kidney, and spleen.5 It is suggested that there is a high level of SARS-CoV-2 complications in the brain mainly due to the high abundance of ACE-2 receptors in blood vessels of the brain and neurons.17,49

**CONCLUSION**

Based on current review, neurologic deficits in COVID-19 patients spans a wide range of diseases affecting different parts of the nervous system through different mechanisms. There are high morbidity and mortality of neurologic deficits in COVID-19 patients. That is why proper identification of the pathogenesis will help prevent these deficits.

**Funding:** No funding sources

**Conflict of interest:** None declared

**Ethical approval:** Not required

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Cite this article as: Alghanmi MMA, Wahboob ST, Rashdi HHA, Aloitaibi AA, Alqahtani YS, Alrabghi SS, et al. Patterns of neurological deficits in COVID-19 infections: A literature review. Int J Community Med Public Health 2021;8:xxx-xx.