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Neurological manifestations of COVID-19: A brief review

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The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been predominantly a respiratory manifestation. Currently, with evolving literature, neurological signs are being increasingly recognized. Studies have reported that SARS-CoV-2 affects all aspects of the nervous system including the central nervous system (CNS), peripheral nervous system (PNS) and the muscular system as well. Not all patients have reverse transcription-polymerase chain reaction positive for the virus in the cerebrospinal fluid, and diagnosing the association of the virus with the myriad of neurological manifestations can be a challenge. It is important that clinicians have a high-index of suspicion for COVID-19 in patients presenting with new-onset neurological symptoms. This will lead to early diagnosis and specific management. Further studies are desired to unravel the varied neurological manifestations, treatment, outcome and long-term sequel in COVID-19 patients.

Key words COVID-19 - CSF - encephalopathy - intracranial pressure - ischaemic stroke - nervous system diseases - neuronal cells - SARS-CoV-2 - venous thromboembolism

Classical neurotropic viruses include herpes, Japanese encephalitis, polio, coxsackie, measles, mumps, rabies and influenza[1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a betacoronavirus which is a 29,903 bp single-stranded RNA virus that targets the angiotensin-converting enzyme (ACE)-2 receptors to gain entry into the host cells. The ACE-2 receptor is widely present in capillaries of respiratory and nervous systems[2]. SARS-CoV-2 has been documented to cause both central and peripheral nervous system (CNS and PNS) involvement. The current review is aimed to highlight the myriad of neurological manifestations due to SARS-CoV-2 infection.

Pathogenesis

Several theories have been put forward for the pathogenesis of neurological manifestations. These include direct entry of the virus through ACE-2 receptor, haematogenous spread and neuronal spread. The indirect mechanisms are inflammatory response, immune response and cytokine storm[2-4]. Among the proposed mechanisms, the emerging literature emphasizes the importance of cytokine storm in multi-organ manifestations. Cytokine storm syndrome and secondary haemophagocytic lymphohistiocytosis can occur in a subgroup of patients leading to hyperinflammatory syndrome.

Clinically, this is characterized by unremitting fever, cytopenia, hyperferritinemia and acute respiratory distress syndrome (ARDS). The cytokine profile shows increased interleukins (IL-2 and IL-7), granulocyte colony-stimulating factor, interferon-gamma inducible protein-10 and tumour necrosis factor-alpha. This can cause stroke, encephalopathy and skeletal muscle injury[4].

Solomon *et al*[5] reported neuropathological findings from autopsies of 18 consecutive patients with SARS-CoV-2 infection. Microscopic examination demonstrated acute hypoxic injury in the forebrain (cerebrum) and brainstem (cerebellum), with loss of neurons in the cerebral cortex, hippocampus and cerebellar Purkinje cell layer in all the patients. However, there were no thrombi or vasculitis documented. Foci of perivascular lymphocytes (in 2 patients) and focal leptomeningeal inflammation (in 1 patient) were rare findings. Noteworthy was the absence of microscopic abnormalities in the olfactory bulbs or tracts. Paniz-Mondolfi *et al*[6] established the presence of the SARS-CoV-2 in capillary endothelial and neural cells in the frontal lobe of the brain in an autopsy specimen. The viral particles were specifically present in small vesicles of these endothelial cells.

Clinical features

The prototype symptoms of COVID-19 are fever, non-productive cough, sore throat, difficulty in breathing along with abdominal pain, diarrhoea and conjunctivitis. The potential mechanisms of neurological manifestations of COVID-19 include direct viral infection (blood-brain barrier, infected leukocytes or neuronal transport), hypoxic brain injury (vasodilation, hypercarbia and aerobic metabolism leading to metabolite accumulation), immune mediated (cytokine storm or cell/antibody mediated) and vascular (direct involvement or coagulopathy, endothelial dysfunction, thrombotic microangiopathy and vasculitis)[7].

The neurological manifestations can broadly be categorized into CNS and PNS. The neurological manifestations are commonly observed in older age and critically ill patients. Varatharaj *et al*[8] reported clinical data of 125 patients with COVID-19 over a three-week period showcasing neurological or psychiatric disease. Notably, cerebrovascular event in 77 (62%) patients, ischaemic stroke in 57 (46%), intracerebral haemorrhages in nine (7%) and CNS vasculitis in one (<1%) patients were documented. This study also reported altered mental status in 31 per cent of patients, encephalopathy (13%) and neuropsychiatric diagnosis (18%)[8].

The involvement of PNS manifests as altered smell and taste dysfunction (68 and 71%, respectively) as reported by Yan *et al*[9] and Bagheri *et al*[10] (48.23 and 83.38%, respectively). Guillain-Barre syndrome (GBS) has been documented in eight cases[11], and skeletal muscle damage has been reported by Mao *et al*[12] in 19.3 per cent of patients in the severely ill and 4.8 per cent of patients in the non-severe group. The various studies on neurological manifestations in COVID-19 patients are summarized in Table I[13-17].

Investigations

Cerebrospinal fluid (CSF) analysis

For intracranial invasion of COVID-19, the definitive test is to demonstrate COVID RNA in CSF by lumbar puncture, but practically, this remains difficult, especially in severely affected patients with multi-organ dysfunction who are on ventilatory support and in the presence of thrombocytopenia and raised prothrombin time. It has been seen that COVID-19 patients with neurological manifestations may not always have the reverse transcription-polymerase chain reaction (RT-PCR) positive in CSF[16,17].

Imaging findings

The neuroimaging and neurological findings in COVID-19 presented in a systematic review of 116 patients demonstrated normal imaging in 37 (41%) patients, whereas abnormal findings included acute cerebrovascular events (ischaemic and haemorrhagic types), demyelinating disorders (acute disseminated encephalomyelitis), myelitis, meningitis and encephalitis[18]. Magnetic resonance imaging (MRI) of brain may show features of raised intracranial pressure, multifocal infarcts or, in extreme cases, bilateral thalamic involvement in haemorrhagic necrotizing encephalopathy. In a study of 235 intensive care unit (ICU) patients of SARS-CoV-2, around 50 per cent had neurological symptoms and in 54 per cent patients neuroimaging was done[19]. Cortical signal abnormality in fluid-attenuated inversion recovery was found in 37 per cent, and cortical diffusion restriction, cortical blooming artefact and leptomeningeal enhancement were also seen in a few cases. Major differential diagnosis included infectious or autoimmune encephalitis, postictal state and hypoglycaemic and hypoxic encephalopathy[19]. MRI of a COVID-19 patient

Table I. Summary of various studies on neurological manifestations in coronavirus disease 2019 (COVID-19) patients

Author	Patients and study design	Neurological manifestations
Mao *et al*[13]	214 patients, retrospective study	36.4 per cent had neurological manifestation and were more common in severely affected patients. Incidence of stroke, impaired consciousness and skeletal muscle injury were compared in severe vs. non-severe COVID-19 patients and were found to be 5.7 vs. 0.8 per cent, 14.8 vs. 2.4 per cent and 19.3 vs. 4.8 per cent, respectively.
Li *et al*[14]	221 patients, single-centre retrospective study	11 patients had ischaemic CVA, 1 patient each had cortical venous sinus thrombosis and intracerebral haemorrhage each
Helms *et al*[15]	58 patients of COVID-19 with ARDS in ICU, observational case series	14 per cent had neurological symptoms at time of admission, while 69 per cent had when they were weaned off sedation. They reported confusion in 65 per cent, agitation in 69 per cent, UMN sign in 69 per cent and dysexecutive syndrome in 33 per cent.
Giacomelli *et al*[16]	Detailed questionnaire filled in 69 COVID-19 patients regarding impaired olfactory and gustatory function (cross-sectional study)	33.9 per cent reported either olfactory or taste impairment and 18.6 per cent reported both. These symptoms were significantly more common in young female patients.
Guan *et al*[17]	1099 COVID-19-positive patients with mean age of 47 yr, retrospective study	14.9 per cent reported myalgia. High levels of CK (>200 IU/l) were found in 12.5 per cent cases of non-severe and 19 per cent cases of severe COVID-19 patients. Rhabdomyolysis was found only in 0.2 per cent cases.

CVA, cerebrovascular accident; ARDS, acute respiratory distress syndrome; ICU, intensive care unit; UMN, upper motor neuron; CK, creatine kinase

reported by Poyiadji *et al*[20] revealed haemorrhagic rim-enhancing lesion in bilateral thalami, subinsular region and medial temporal region. A study done by Palmer[21] in a young COVID-19-infected male with anosmia found normal olfactory bulb volume and signal, but he suggested that hybrid imaging (single-photon emission computed tomography-MRI with nasal thallium-21 and magnetization prepared gradient echo sequence) may demonstrate the abnormality.

Electroencephalogram

In a retrospective review of 36 COVID-19 patients, pathological EEGs recorded did not reveal any specific patterns in these patients. The abnormal patterns were similar to other critically ill patients or brain pathologies[22].

Treatment

Neurological manifestations have to be dealt with in accordance with the usual therapy; for example, GBS with intravenous immunoglobulin[23,24], raised intracranial pressure by mannitol along with other measures and seizures with various anti-epileptic drugs (AEDs) keeping in mind specific renal and hepatic side effects of each drug. Patients should continue their AEDs as before as these drugs do not pose an increased risk for developing COVID-19 infection except for adrenocorticotrophic hormone (given specifically in tuberous sclerosis).

In patients with ischaemic stroke, anticoagulation is recommended. A study from China[25] reported a patient who had limb ischaemia along with bilateral infarcts in the brain and on evaluation was found to have raised antiphospholipid antibodies. These antibodies can get transiently elevated in certain infections and critical illness just like acute-phase reactants and can cause multifocal thrombosis[25]. In patients of intracranial haemorrhage, optimal blood pressure control should be targeted[12].

Attention must be paid regarding prophylaxis of venous thromboembolism in critically ill patients. There are various risk factors including infection, immobilization, mechanical ventilation, respiratory failure and indwelling central venous catheter. Compression stockings, intermittent pneumatic compression and cautious use of anticoagulants are recommended[26]. The Association of British Neurologists[27] has formulated guidelines to deal with the patients with various neurological illnesses who

are at an increased risk of developing COVID-19. The risk is divided into three categories - low, moderate and high. Mild-to-moderate forms of common neurological diseases such as Parkinson's disease (PD), multiple sclerosis and epilepsy do not confer any increased risk as long as swallowing and breathing mechanisms are normal. Patients with these neurological conditions falling into low or normal risk are considered at high-risk if concomitant lung or kidney disease is also present. Diseases causing weakness of bulbar and respiratory muscles are considered high-risk and need special attention[27]. These include motor neuron disease, myasthenia gravis, myopathies and GBS. Those patients who are on immunosuppressive drugs such as azathioprine, mycophenolate mofetil or methotrexate are at a high-risk for COVID-19. The use of any of these with prednisolone 20 mg daily or higher is considered high-risk. The risk-benefit ratio should be assessed, and decision should be individualized in each patient[27].

Patients with advanced PD are at a high-risk for COVID-19 as there is respiratory muscle rigidity along with impairment of cough reflex. PD patients have reduced number of ACE-2 receptors on dopaminergic neurons, and COVID-19 infection worsens the symptoms leading to increased requirement of the dopaminergic drug. Patients with advanced disease who underwent deep brain stimulation or were on levodopa, were more vulnerable and had mortality close to 50 per cent[28].

Thus, there is a multitude of neurological manifestations of COVID-19 with various plausible pathophysiologies as summarized in Table II[29-32]. The ongoing studies relevant to prevalence, pathology and treatment are summarized in Table III.

Regional differences in neurological manifestations

In a study from Wuhan in China in 214 patients[13], 36.4 per cent had nervous system manifestations. CNS manifestations were more common than PNS and skeletal muscle injury. Dizziness (16.8%) and headache (13.1%) were the most common CNS manifestations. Taste and smell impairment was noted in 5.6 and 5.1 per cent, respectively[13]. In the UK, a large cross-specialty surveillance study of acute neurological and psychiatric complications was conducted in 125 patients which found stoke as the most common CNS manifestation (62%), followed by encephalopathic symptoms in 31 per cent[8]. In a multicentre European study by Lechien *et al*[33] on COVID-19 patients, 85.6 per cent had abnormality of smell and 88.8 per cent showed gustatory abnormality, and smell and taste abnormality was more prevalent in Europeans than in Chinese.

Predictors of neurological dysfunction

There is an overlap among the predictors of COVID-19 and stroke, namely age, cardiovascular disease, cardiac arrhythmia diabetes mellitus, smoking and coronary artery disease. Patients with pre-existing neurological disorders, *viz*. multiple

Table II. Neurological manifestations of COVID-19 and their possible aetiology

Symptom	Aetiology
Headache	Hypertension, stroke, meningoencephalitis[29], insomnia[30]
Altered sensorium	Accelerated hypertension, stroke, meningoencephalitis[29]
Focal weakness, imbalance of gait	Stroke, GBS[29]
Loss of smell and taste	Neuronal[3] or conductive[31]
Seizures	Stroke, meningoencephalitis, hypertensive encephalopathy[29]
Severe myalgia	Myositis[29]
Manifestation	Pathophysiology
Accelerated hypertension causing encephalopathy	Unchecked renin-angiotensin pathway[32]
Ischaemic stroke	Hypercoagulability[29], vasculitis[5,7], comorbidities
Haemorrhagic stroke	Accelerated hypertension[32], hypoxic injury[3], thrombocytopenia
Meningoencephalitis	Blood-borne dissemination[3], immune response[3]
GBS	Axonal neuropathy or demyelination
ADEM	Immune response[3], cytokine storm[4]
Myositis	Direct muscle damage, massive inflammatory reaction, immune response[29]

GBS, Guillain-Barre syndrome; ADEM, acute disseminated encephalomyelitis

Table III. Ongoing trials for COVID-19 and neurological manifestations

Trial number	Title	Patient profile	Type of study	Recruitment
NCT04367350	Prospective registry of COVID-19 patients with neuromuscular involvement	SARS-CoV-2 infection who are admitted to the intensive care unit	Observational cohort study planned for 500 adult COVID-19 patients with follow up for two years	Started March 2020
NCT04453670	Neuropathology in adults intensive care unit patients with COVID-19	Suspected or confirmed SARS related to coronavirus 2 infection patients in ICU who died	Single-centre observational autopsy study in France to evaluate brain damages in patients including macroscopic and histology examinations and virology analyses	Started March 2020
NCT04374045	Testing for dysautonomia in patients hospitalized for SARS-CoV-2 infection (COVID-19): COVIDANS study (COVIDANS)	All admitted COVID-19 patients will have a continuous recording of the heart rhythm during their hospitalization	Observational prospective cohort study planned for 25 patients	Started April 2020
NCT04422275	Coronavirus smell therapy for anosmia recovery (Co-STAR)	Convalescent COVID-19 patients with persistent (*i.e.* >3 months) decreased sense of smell with decreased olfactory function will be assigned to one of two nasal saline lavage interventions through a randomization schedule and will be requested to rinse each nasal cavity once daily for 12 wk and to keep track of their daily use through a paper dairy or specially created app to track compliance	This will be a 2 × 2 factorial double-blinded, placebo-controlled, randomized clinical trial	Estimated start study date June 2021
NCT04366934	Study of the pathogenesis of olfactory disorders in COVID-19 (COVIDSMELL)	The molecular and cellular anomalies of the olfactory epithelium of COVID-19 patients with isolated anosmia will be evaluated by comparison with the olfactory epithelium of non-infected individuals	This study is a case-control study	Started May 2020

sclerosis and autoimmune syndromes such as neuromyelitis optica, angiitis, myasthenia gravis and inflammatory polyneuropathies, are on a large variety of immunosuppressive agents. These therapies can hamper the host immune response to COVID-19. Furthermore, pre-existing neurodegenerative disease in patients makes them vulnerable to infection. The therapy during COVID-19 management such as hydroxychloroquine sulphate, anticoagulants and remdesivir can also be associated with new-onset neurological manifestations[34].

Conclusion

The neurological manifestations in patients with COVID-19 are varied and can emerge standalone or during the clinical course. Upholding a high-index of suspicion for COVID-19 in patients presenting with new-onset neurological symptoms will expedite an early diagnosis. Further studies are desired to unravel these varied neurological manifestations, treatment, outcome and long-term sequelae in COVID-19 patients.

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