Review Article

Neurological manifestations of COVID-19: A literature review

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Abstract

A novel coronavirus that started from the Wuhan province of China is affecting the whole world. As of this date, more than 222 million cases are reported with more than 4.60 million fatalities. Nepal has more than 771,000 cases reported with almost 11,000 death recorded to date. Though most of the patients present with flu-like symptoms, people with comorbidities like Diabetes mellitus, hypertension, lung, and heart disease most likely suffer from severe disease and even death. As reported, neurological manifestations are common in critically ill patients. The most common manifestation of CNS is headache, dizziness, and encephalopathy whereas loss of smell and taste is the common PNS manifestation. Other neurological complications seen are fatigue, myalgias, hemorrhage, altered consciousness, Guillain-Barre Syndrome, syncope, seizure, and stroke. Non-specific neurological symptoms may be present in the early stages which can mislead the treatment. In some cases, neurological manifestations precede the typical presentation of fever, cough, and shortness of breath and later develop into typical features. The virus enters the brain through 2 systems: hematogenous route or olfactory route. Angiotensin-converting enzyme-2 (ACE-2) is the port of entry to the brain for COVID-19(SARS-CoV-2) which was also the entry point for SARS-CoV. Covid-19 cases are increasing in the world and prevention and control of spread are a must. Understanding the neurological invasion pathogenesis, and manifestation will help the neurologists and physicians on frontlines to recognize early cases with nervous system involvement, neurological complications, and sequelae during and after the pandemic.

Introduction

The novel coronavirus emerged from the seafood wholesale market in the Wuhan, Hubei province of China as a cluster of unusual cases of pneumonia with unknown etiology, in December, 2019.1 Coronavirus has now spread to more than 221 different countries, and WHO has declared it as a global pandemic on 11 March 2020. Till September 9 of 2021, 222,770,512 cases of confirmed COVID-19 were reported and there were 4,600,060 fatalities. As of this date, the numbers of suspected and confirmed cases are increasing rapidly and have posed a serious threat to mankind although the number of recovered cases is also increasing as well.

Coronavirus is an enveloped positive-strand RNA virus with the capability to affect mainly the respiratory system as Severe Acute Respiratory Syndrome but it also has been shown to affect the enteric, hepatic, and nervous system. Apart from SARS-CoV-2, six coronaviruses can infect humans, four of them cause mild flu-like illness whereas two others are linked with severe illness.2 Severe Acute Respiratory Syndrome coronavirus(SARS-CoV) and the Middle East Respiratory Syndrome coronavirus(MERS-CoV) have high fatality and are zoonotic in origin.3 SARS-CoV-2 also shares homology with the other coronaviruses.

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Coronavirus transmits from close person to person contact, through respiratory droplets, transmission by touch, and even asymptomatic carriers can transmit the virus. The patient's presentation may vary but common symptoms at the onset of SARS-CoV-2 are fever, cough, and fatigue. They may also present with sputum production, headache, hemoptysis, dyspnea, diarrhea, and lymphopenia.4 Though primarily affecting the respiratory system it has a potential for neuroinvasion through the receptor expressed in the nervous system. More than one-third of patients experienced neurological symptoms such as headache, nausea, vomiting, dizziness, hypogeusia, hyposmia, impaired consciousness, acute cerebrovascular disease, ataxia, epilepsy, vision impairment, neuralgia, and skeletal muscular damage(myalgia).5 The neurological manifestation was seen commonly in severely ill patients than less severe illness(40 [45.5%] vs 38 [30.2%]). Headache and dizziness were the most common CNS symptoms and loss of taste and smell were the most common PNS symptoms. Patients with CNS symptoms had low lymphocyte count, low platelets, and high Blood Urea Nitrogen levels compared to those without CNS symptoms.6

Although since the start of the pandemic many researchers and scientists have their undivided attention

and manuscripts on COVID-19 are surging, it is a novel virus with many ongoing studies. We aim to provide the literature review of neurological involvement of COVID-19: mechanism, manifestation, potential complication, and its effects on neurological disorders.

For this literature review, multiple databases were used. Pubmed and Google Scholar were the primary databases with a subsequent proceeding. More than 200 articles were thoroughly reviewed. The following research terms were used: Coronavirus, Covid-19, SARS-CoV-2, COVID neurology, COVID pathogenesis, complication, etc. Searching of titles and abstracts was performed by authors. We included case-control studies, cohort studies, review articles, case reports published on the spectrum of neurological manifestations of coronavirus. The full text was reviewed in the second screening. Only pieces of literature published in English were included.

Pathogenesis:

Many viruses have neurotropism and can invade the CNS infecting immune regulating cells in the CNS, damaging structures and functions of the nervous system like encephalitis due to viral infections, toxic encephalopathy due to severe systemic viral infections, Acute severe demyelinating lesions developing after viral infections.7 SARS-CoV-2 is similar to SARS-CoV(79.5%) and similar to bat coronavirus is as high as 95%. Phylogenetic studies have shown bats as the original host and reservoir of SARS-CoV-2 and transmitted to humans through the probable intermediate host pangolin.8

Though the pathophysiology of SARS-CoV-2 is poorly understood, the similarity of structure and genome with other coronaviruses can help us to predict pathogenesis. SARS-CoV-2 has a diameter of 60 nm to 140 nm and distinctive spikes, ranging from 9 nm to 12 nm, giving the virions the appearance of a solar corona. The infection starts with inhalation of the virus and is likely binding to the epithelial cells. SARS-CoV-2, just like SARS-CoV requires angiotensin-converting enzyme 2 (ACE-2)9 as a receptor to enter into cells but also does not use receptors used by other coronaviruses such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4). Its binding with host cell receptors is a causal factor for the pathogenesis of infection. Organs that have a significant number of ACE-2 receptors are vulnerable to the virus. Organs like the heart, kidneys, and testes are enriched with receptors and there is a broad distribution of receptors in the lungs, brain, liver, and intestine. Results in the Cryo-EM experiments demonstrated that SARS-CoV-2 had a ten times higher affinity to ACE2 comparing to SARS-CoV, which was consistent with the higher efficiency of infection of SARS-CoV-2.10 After the local propagation of the virus and transmission to the lower respiratory tract in the next few days robust immune response is generated. The immune system of the infected person will determine how severe the infection is going to be. In many people(~80%) disease will be mild and can be treated conservatively whereas 20% may develop severe disease and should be monitored carefully and treated symptomatically while awaiting antivirals and definitive treatment modality to be developed soon.

CNS Invasion

Though primarily a respiratory virus SARS-CoV-2 has shown its neurological involvement. Those reported cases could be complications related to viral infection, immune response, therapies, and recovery.11 According to one retrospective study of 214 patients from Wuhan, China, that 36.4% of patients had neurologic manifestations of the disease, including symptoms relating to the central nervous system (24.8%), peripheral nervous system (8.9%), and skeletal muscle injury (10.7%). Severely ill patients were more likely than less severely afflicted patients to exhibit neurologic symptoms (45.5% vs. 30.2%, respectively) including cerebrovascular disease (seen in 5.7% and 0.8%, respectively), impaired consciousness (14.8% vs. 2.4%), and skeletal muscle injury (19.3% vs. 4.8%).6 In one meta-analysis of 6 studies in patients with COVID-19, Cerebrovascular disease, hypertension, diabetes, chronic obstructive pulmonary disease, and cardiovascular disease were identified as the risk factors.12

As we can find the CNS symptoms in the COVID infected patients. It might be due to the direct injury or the indirect injury from the virus just like the SARS-CoV and MERS-CoV victims showed. There was edematous and hyperemic brain tissue in the autopsy of patients infected with COVID 19.

Similar to other respiratory viruses SARS-CoV-2 may enter into CNS through either a hematogenous route or retrograde neuronal pathway

As described by Mao et al. virus can spread from the cribriform plate(close to the olfactory bulb) to the brain tissue supported by the presence of anosmia and hyposmia.13,6 If the presence of these symptoms truly indicates the transnasal spread and shows the significance of neurological disease requires further study. As we know ACE-2 receptors are the functional receptors, these are present in brain vasculature, neurons, and glial tissues making them vulnerable. One case reported the presence of the virus in vascular endothelial cells and neurons on an autopsy of the confirmed COVID-19 patient.14 The virus in the circulation enters into cerebral circulation and through the interaction of viral spike protein with ACE-2 receptors of capillary endothelium damages the endothelial lining and enters in brain15. Inside the brain, it interacts with ACE-2 expressing neurons, which damages the neuron itself without significant inflammation- as seen in SARS-CoV.

Neurotrophic viruses like SARS-CoV-2 are also likely to travel to CNS by antegrade and retrograde transport with the help of kinesins and dyneins via sensory and motor nerve endings.16 Through afferent nerve endings of the vagus nerve from the lungs17 and enteric nerve and sympathetic afferent from the gastrointestinal can also be transported.18 Another presumed pathway of SARS-CoV-2 systemic dissemination and subsequent CNS entry is exosomal cellular transport.18 It is also proposed

inflammatory cytokines predominantly IL-6 can damage the brain resulting in cytokine storm syndrome. IL-6 is the main cytokine that leads to multiple organ failure in COVID-19 cases. The clinical improvement of critically ill patients using Tocilizumab(IL-6 receptor blocker) may support this fact.19

Although many pathogeneses are proposed and hypothesized, a detailed study is yet to be done and hopefully, we can fully understand the pathogenesis and mechanism of CNS invasion of SARS-CoV-2 in further detail soon.

CNS manifestations of COVID 19

Patients with COVID 19 usually have respiratory and digestive symptoms. However, due to some similarities with viral structure and infection pathways, the SARS CoV-2 virus sometimes invades the central nervous system and develops neurological signs. Some of the patients with neurological manifestations of COVID 19 presented initially with dizziness and headache followed days later by cough, throat pain, lymphopenia, and a ground-glass appearance on their respective chest computed tomography (CT) images. Nervous system manifestation was significantly more common in severe infection compared with non-severe infection.6

ACE-2 receptors are also expressed in CNS cells (neurons and glial cells)and endothelial cells.20The neurotrophic effect of COVID 19 is usually seen in the brainstem and medullary cardiopulmonary centers.21

Central Nervous System manifestations of Covid-19 can be divided into five groups. Infective, Vascular, Immunological, Extrapyramidal, and Miscellaneous. Infective includes Acute necrotizing hemorrhagic encephalitis, Viral encephalitis, Meningoencephalitis, Rhombencephalitis. Vascular include Ischemic stroke with large vessel occlusion, Intracerebral hemorrhage, subarachnoid hemorrhage, posterior reversible encephalopathy syndrome, and Microvascular occlusive disorder. Immunological features can be Post-infectious acute disseminated meningoencephalitis, Acute transverse myelitis, Anti-NMDA encephalitis, Generalized and diaphragmatic myoclonus, and Opsoclonus and ocular flutter. Extrapyramidal include Parkinsonism and Miscellaneous include Headache, Seizures, confusion, and dizziness.

Headache

Headache has now been recognized as one of the common initial symptoms of COVID-19. The incidence of headaches ranged from 15 to 20 percent. The exact reasons for the headache remained unexplained. Increased mental stress, excessive anxiety, and lifestyle changes are possible reasons for early headaches. Pre-existing migraine may get worse because of COVID-19-related stress.23COVID-19-associated acute headaches can be because of systemic viral infection, primary cough headache, and tension-type headache. Early headaches respond well to acetaminophen. Headaches appearing between the 7th and the 10th days of illness can be related to cytokine storms.24Hospital staff performing Covid-19 related duties described a new kind of PPE-associated headache. In a cross-sectional study, the authors noted that most healthcare workers had either PPE-associated headache or there was the aggravation of their pre-existing headaches. In a questionnaire-based study, 81% (128/158) respondents experienced de novo PPE-associated headaches. The majority (42/46) of participants with pre-existing headaches experienced that prolonged PPE usage triggered the disabling headache.25

Encephalopathy/Encephalitis/Acute Disseminated Encephalomyelitis

Based on larger cohort studies of hospitalized patients with COVID-19, it appears encephalopathy is one of the most common neurologic symptoms, although the incidence reported in studies is variable. SARS- Cov has been detected in brain tissue and CSF and there are now isolated reports indicating that SARS-CoV can invade the brain. One study found that approximately two-thirds of patients with COVID-19 related Acute Respiratory Distress Syndrome develop encephalopathy.26Encephalopathy and encephalitis are major complications of severe SARS-COV-2 infection. Hypoxic/metabolic changes produced by intense inflammatory response against the virus triggers cytokine storm and subsequently acute respiratory distress syndrome, encephalopathy, and multiple organ failure.27 Altered consciousness, ranging from mild confusion, delirium, to deep coma, is hallmark clinical features.27 Encephalopathy is common in older patients, the majority are more than 50 years of age. Many patients were already on mechanical ventilation. Lung abnormalities are noted in almost all of the patients, presenting with encephalopathy. Cortical and subcortical T2/FLAIR signal changes are common neuroimaging abnormalities.27The delirium/neurological symptoms in COVID-19 patients were responsible for longer mechanical ventilation compared to the patients without delirium/neurological symptoms.28 Poyiadji and colleagues reported the first case of COVID-19– associated acute hemorrhagic necrotizing encephalopathy (ANE) from the USA. In the case of hemorrhagic necrotizing encephalopathy, hemorrhagic lesions in the thalamus were noted.29 There are reported cases of Acute disseminated Encephalomyelitis(ADEM) presented with diarrhea progressed to ARDS. The neurological examination following extubation and cessation of sedative agents was notable for severe encephalopathy and quadriplegia. Axial FLAIR MRI images showed multiple periventricular white matter hyperintensity lesions, without corpus callosal involvement, finding consistent to ADEM. The pathophysiology of post-COVID-19 ADEM is likely similar to that proposed for other post- infectious ADEM.

Cerebrovascular events

In COVID-19, coagulopathies enhance the risk of cerebral arterial and venous thrombosis. One retrospective study of 219 patients from china showed 5% developed new-onset CVD in which 90.9% were ischaemic and 9.1% were hemorrhagic. New-onset CVD patients were significantly older, more likely to present with severe COVID-19, and were more likely to have cardiovascular risk factors, including hypertension, diabetes, and medical history of CVD.30 Severely affected patients with large cerebral infarcts had elevated D-dimer levels (≥1000 µg/L), indicating a coagulopathy and has also shown raise in CRP. In patients with stroke, the SARS-CoV-2 virus could not be demonstrated in CSF. COVID-19-related strokes happen in young patients with prior risk factors (diabetes and hypertension). Studies done in New York during the pandemic showed 25% of COVID 19 ELVO(Emergent Large Vessel Occlusion) stroke patients were 50 years or younger, which is higher than previously observed 10% among non-COVID ELVO patients.31 COVID-19-associated coagulopathy and vascular endothelial dysfunction were reasonable mechanisms. The median duration from the first symptoms of SARS- CoV-2 infection to CVD was 10 days (range 1–29). The overall mortality rate was 54.5%30 Studies have also shown COVID infection can accelerate the progression of stroke. The key factor of CVD in COVID is recognized as inflammation which triggers acute intravascular events by the interruption of blood supply. Also due to the

increased concentrations of proinflammatory cytokines and serum inflammatory factors(ex. Interleukin and CRP) in patients with infections are to be followed by a hypercoagulable state. ICH was reported in the MERS- CoV infection as a neurological complication. In critically ill patients, COVID-19 has been associated with coagulopathies such as DIC, thrombocytopenia, Elevated D-dimer, and prolonged prothrombin time which can result in hemorrhage. SARS-CoV-2 uses the ACE-2 receptor, an important constituent of the counterregulatory pathway of the RAS which regulates blood pressure. SARS-CoV-2 induced ACE-2 downregulation may lead to vasoconstriction and cerebral autoregulation dysfunction with a subsequent rise in blood pressure and possible arterial wall rupture and hemorrhage.

Seizures

Out of 20 studies 48 patients were reported to have seizures. In certain individuals, there is a lowering of seizure threshold after CNS viral infection and subsequent activation of neuro-inflammatory pathways, which facilitate epileptogenesis.32 Local irritation with the inflammatory markers of SARS-CoV infection may also precipitate a seizure. Viral encephalitis and metabolic derangements may be the other possible mechanisms. It has also shown the previous history of seizure is a risk factor for SARS-CoV-2 associated seizure.

PNS manifestation of COVID-19

It has been shown through various studies that COVID-19 can affect the Peripheral Nervous System. Out of that Anosmia, loss of taste sensation, Guillain Barre syndrome, and Bell's palsy are the major manifestations.

Loss of taste/smell sensation

Anosmia and taste-related changes are associated with COVID-19, these support the idea of the olfactory invasion route of the COVID-19 virus. The prevalence of anosmia and taste alteration in hospitalized patients was found to be 34 percent in one study33, however, they did not report the timing of symptoms onset compared to other symptoms. In line with this study, another cross-sectional study was performed and prevalence, intensity, and timing of altered taste/smell sensation in COVID-19 patients were analyzed. The results showed 64.4 percent showed an altered sensation of taste and smell. Regarding the timing of alteration in sense of smell or taste onset compared to other symptoms, they reported that (11.9%) before other symptoms, (22.8%) at the same time, and (26.7%) after other symptoms showed taste and smell alterations.34 Lechien et al. reported the time course of the aforementioned disorders. The olfactory dysfunction appeared before, in unison, and after the appearance of general symptoms in 11.8, 22.8, and 65.4% of the cases, respectively. This olfactory abnormality persisted after the resolution of other symptoms in 63.0% of cases.35 They also found out 85.6 percent of patients with mild to moderate COVID-19, had olfactory or gustatory dysfunction. Out of those patients, 79.6 percent showed anosmia, and 20.4 percent showed hyposmia during the disease course. Furthermore, phantosmia and parosmia were also reported in 12.6 and 32.4 percent respectively.

Guillain Barre Syndrome

Although mechanisms of induction of GBS by SARS-COV-2 are not clear, it is suggested that it may contribute to the production of antibodies against specific gangliosides which may, in turn, produce certain forms of GBS. Toscano et al. reported 5 cases of Guillain-Barré syndrome in COVID-19 patients. The interval between the onset of viral illness and the first symptom onset was between 5 and 10 days. Lower limb weakness, paresthesia and facial diplegia followed by ataxia and paresthesia were the first symptoms reported among different patients. Generalized, flaccid quadriparesis or tetraplegia evolved for 36 hours to 4 days and three received mechanical ventilation. CSF study showed raised lymphocytes in all cases in the study but showed raised protein levels in just two patients out of five. However, CSF RT-PCR for COVID-19 was negative in all patients. All the patients were treated with IVIG, two received a second dose of IVIG, and one required plasma exchange. Out of these two patients remained in the ICU and were receiving mechanical ventilation, two were undergoing physical therapy, and one was discharged without any residual symptoms after four weeks of treatment.36

Four other case reports of GBS were reported in America, Iran, Italy, and China. All were aged between the mid-50s to 70s. All presented with flu-like symptoms preceding GBS-like symptoms except the Chinese patient, who presented with neurological symptoms first and respiratory symptoms only later on the 8th day of admission. In all four cases, nerve conduction and the neurological study showed demyelinating neuropathy. Albuminocytogic dissociation was seen in all cases. They were treated with IVIG with variable responses.

Two GBS variants Miller Fisher syndrome and Polyneuritis canalis associated with COVID-19 were described in case series in Spain. The case of GBS was a 50-year-old man who presented with ageusia, anosmia, right internuclear ophthalmoparesis, right fascicular oculomotor palsy, ataxia, areflexia, albuminocytologic dissociation, and positive testing for GD1b-IgG antibodies five days after having cough, fever, malaise, headache, and low back pain. Case of Polyneuritis Canalis was a 39-year-old male who presented with ageusia, areflexia, bilateral abducens nerve palsy, and albuminocytologic dissociation after having diarrhea, low-grade fever, and poor general condition three days prior. Oropharyngeal swab for COVID-19 is positive in both cases but negative in CSF. The GBS case was treated with IVIG and Polyneuritis canalis treated with acetaminophen with complete neurological recovery with residual anosmia and ageusia in GBS37.

Bell's Palsy

One case of Bell's Palsy was reported in China was a 65-year-old lady admitted to the hospital for a left facial droop preceded by 2 days history of pain in the mastoid region. There was no preceding cough, fever, or any respiratory symptoms. There was left lower motor neuron facial paralysis on physical examination. However throat swab RT PCR was positive and the CT chest showed ground-glass opacity in the lung. She was treated with umifenovir and ribavirin and facial paralysis was improved.38

Conclusion:

Our study extensively reviewed the available articles for the neurological manifestation of COVID-19 but since the pandemic is still undergoing there is a possibility of the emergence of new signs and symptoms. Respiratory symptoms are the most common symptoms. In CNS headache and dizziness are common symptoms while the loss of smell and taste are common in PNS. It transmits ten times faster than the other coronaviruses and transmits through personal contact, respiratory droplets, and touch. It has also been shown it can even transmit via asymptomatic carriers. So, awareness among people is important regarding safety measures. Neurological symptoms are highly likely in severely ill patients. The high degree of suspicion, accurate diagnostic tests, careful collection of data, and its analysis can decrease the neurological burden. The cooperation of all health workers is required to tackle this dire public health issue.

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