

An Insight Into The Neurological Manifestations Of Covid-19 In The Emergency Department

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Abstract

As the COVID-19 pandemic continues to evolve, there is an increasing recognition that patients with COVID-19 infection may present with neurological symptoms as the primary manifestation. These symptoms can be related to Central Nervous System like headache, altered mental status, acute encephalitis, acute stroke, cerebral hemorrhage, seizures; or the peripheral nervous system like anosmia, hypogeusia, muscle pain and weakness, movement disorders, acute myelitis and Guillain-Barré syndrome, etc. In the absence of the classic presentation with fever or respiratory symptoms, an initial neurological presentation serves as a diagnostic dilemma. This review will aid acute care physicians to have a high index of clinical suspicion to consider COVID-19 infection as a differential diagnosis for any patient presenting with primary neurologic manifestations. This will help avoid delayed diagnosis, as well as reduce exposure to health care providers.

Keywords: COVID-19; SARS-CoV-2; neurological manifestations; emergency department

Introduction

Coronavirus disease 2019 (COVID-19) has been declared a global pandemic by the World Health Organization. Majority of COVID-19 cases present with an acute respiratory infection, the commonest symptoms being fever, sore throat, cough, shortness of breath, myalgia and pneumonia. Severe cases can progress to complications like acute respiratory distress syndrome and multiorgan failure. In addition to respiratory symptoms, some patients present with gastrointestinal symptoms like diarrhea, abdominal pain, nausea or neurological symptoms like headache, altered level of consciousness paresthesia, anosmia or hypogeusia. Patients with severe COVID-19 are more prone to suffer from neurological symptoms compared to those with mild or moderate disease.¹ As COVID-19 cases continue to rise, there is an increasing recognition of neurological signs as the only initial clinical manifestation of COVID-19 infection. This review on these neurological manifestations will aid acute care physicians to have a high index of clinical suspicion and also to adopt necessary precautions when managing these patients in the Emergency Department (ED).

Discussion

SARS-CoV-2 primarily affects the respiratory system, but it is also known to invade the nervous system, similar to other

coronaviruses like SARS-CoV-1 and MERS-CoV. The exact mechanism of neurological involvement is not yet known, but studies have proposed hematogenous spread or spread through the retrograde axonal route.^{2,3} Infection of endothelial cells of the blood vessels, which also have ACE-2 receptors, allows the hematogenous spread of the virus, which then crosses the blood-brain barrier, leading to various neurological disorders.⁴

Another possible route of entry for the virus from the nose to the brain, especially in patients presenting with anosmia, hypogeusia, is through infection of the olfactory neurons via the cribriform plate.⁵ Direct viral invasion of the brain cells leading to encephalitis is also proposed. Neurological manifestations may also occur in COVID-19 secondary to the inflammatory cytokine storm and suppressed immunologic response of infection; or due to hypoxia from severe respiratory involvement of the virus.⁶ SARS-CoV-2 virus enters the cells of the nervous system and skeletal muscles by binding to the angiotensin-converting enzyme-2 (ACE-2) receptor on their surface, thus presenting with symptoms suggestive of acute myelitis and Guillain-Barre Syndrome.⁷

Neurological complications of COVID-19 may co-relate with the disease severity, but the primary goal in the ED is to identify those patients who present only with neurological symptoms as the primary manifestation of COVID-19. In the absence of fever and respiratory symptoms, this can be very challenging and serves as a diagnostic dilemma. Since these patients may be contagious even in the absence of any

respiratory symptoms, such atypical presentations can lead to missed diagnosis. It can also increase the risk of exposure to other patients and healthcare workers caring for the patient. Hence measures should be taken to isolate these patients if there is any suspicion in the ED.

Certain vague neurological symptoms like headache, giddiness and altered level of consciousness may be due to underlying sepsis in COVID-19 patients. They may not represent a true neurological disorder. Some patients with COVID-19 show more specific neurological signs and symptoms. These can be divided into Central Nervous System (CNS) and peripheral nervous system (PNS) symptoms. The CNS symptoms include headache, altered mental status, acute encephalitis, acute stroke, cerebral hemorrhage and seizures. PNS manifestations include symptoms of peripheral nerve or skeletal muscle involvement, like anosmia, hyposmia, muscle pain and weakness, movement disorders, acute myelitis and Guillain–Barré syndrome.

Headache can be a non-specific symptom of any viral illness, but it can also be a manifestation of viral encephalitis or meningitis. Similarly, the differential diagnosis of altered mental status in a COVID-19 patient includes viral encephalitis or meningitis, encephalopathy, seizures and ischemic or hemorrhagic stroke.⁶

Thus, any patient who presents to the ED with headache, which is out of proportion to the fever and is associated with altered mental status and/or vomiting, should warrant further evaluation for encephalitis. RNA of SARS-CoV-2 has been detected in the cerebrospinal fluid of a patient diagnosed with encephalitis.⁸

COVID-19 infection is increasingly recognized to be associated with hypercoagulable state, as noted by elevated D-dimer levels. This may lead to a resultant increase in thrombo-embolic events, especially acute ischemic stroke, pulmonary embolism and rarely cerebral venous sinus thrombosis. Although rare compared to ischemic stroke, infection of endothelial cells of the blood vessels by the virus may increase the intra-luminal pressure of cerebral blood vessels, which combined with coagulopathy in COVID-19 patients, can lead to intracerebral hemorrhage.⁴ The occurrence of seizure in a COVID-19 patient can be due to invasion of the virus in CNS leading to a primary brain infection, or it may be secondary to reduced seizure threshold in a known epileptic patient. Electrolyte disturbances as well as neuronal injury due to hypoxia in severe pneumonia, sepsis or multiorgan failure may also precipitate seizures.⁶

A patient presenting with anosmia, dysgeusia or neuralgia should alert the physician regarding COVID-19 related involvement of the peripheral nerve involvement.⁹ Involvement of skeletal muscle in COVID-19 may be due to invasion of the skeletal muscles by the virus through ACE-2 receptors, causing damage to the skeletal muscle fibers, as noted by elevated creatinine kinase and lactate dehydroge-

nase (LDH) levels¹, and these patients may present with complaints of myalgia and weakness. A robust immune response and associated cytokine storm, often seen in patients with severe COVID-19, may even lead to renal failure and rhabdomyolysis.¹⁰

Guillain–Barré syndrome (GBS) is an immune-mediated disorder of the peripheral nerves and nerve roots. There are few case reports of GBS associated with COVID-19, but further studies are needed to determine if SARS-CoV-2 causes production of antibodies against the ganglioside.¹¹ Moreover, GBS due to Covid-19 should be distinguished from neuro-myopathy that occurs late in the course of severe disease states.¹²

Hence, during this evolving pandemic, emergency and acute care physicians should consider COVID-19 as a differential diagnosis in any patient presenting to the ED with central or peripheral neurological symptoms.¹ A detailed neurological examination followed by appropriate investigations, and early consult with a neurologist can help differentiate between primary or secondary involvement of the CNS/PNS in COVID-19 patients.

Conclusion

The COVID-19 pandemic presents emergency physicians with a unique challenge of patients presenting with neurological symptoms as the primary manifestation of COVID-19. These neurological symptoms may even precede classical presentation of typical respiratory symptoms. Thus, emergency physicians should consider COVID-19 infection as a differential diagnosis for any patient presenting to the ED with primary neurologic manifestations. This will help avoid delayed diagnosis, as well as reduce exposure to health care providers by adopting necessary precautions when managing these patients.

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