Neurological Manifestations of Covid-19

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Key points:

➢ 36.4% patients suffering from coronavirus might have neurological symptoms such as headache, dizziness, hypogeusia and hyposmia.
➢ Average incubation period of coronavirus is 5.2 days.
➢ Viral encephalitis, Infectious toxic encephalopathy, Acute cerebrovascular disease are the neurological diseases seen in the Covid-19 patients.
➢ Patients also have decreased platelet count making them more prone to cerebral hemorrhage.

Introduction

Coronavirus viruses are a group of RNA viruses that cause respiratory tract infections. The severity of illnesses, caused by these viruses, ranges from mild common cold (Rhinovirus) to very lethal Severe Acute Respiratory Syndrome (SARS), Middle Eastern Acute Respiratory Syndrome (MERS) and COVID-19.

In this article, efforts have been made to highlight some of the neurological manifestations of COVID-19 for which causative agent is Severe Acute Respiratory Syndrome Coronavirus – 2 (SARS-CoV-2) Fig 1.

In a recent study, conducted by Mao L et al., on 214 patients in China, it has been observed that the percentage of patients affected with COVID-19 exhibiting neurological symptoms, such as headaches, dizziness, hypogeusia and hyposmia was 36.4% (78/214). The study also concluded that patients with more severe onset of the illness were more likely to develop said symptoms. Another study also found the presence of SARS-CoV-2 in the cerebrospinal fluid (CSF) by genome sequencing.

Therefore, during this pandemic, it is imperative that health care profession do not disregard these symptoms, moreover they should be made aware of the neurological effect of this virus on the central nervous system (CNS) so that these could be effectively dealt with.

COVID-19

First case was reported in December 2019 in China with most common symptoms being cough, fever, dyspnea, and fatigue. Moreover, clinically chest X-ray were similar to those of pneumonia patients. It has an average incubation period of about 5.2 days. Furthermore, another clinical study also links intracranial infection like symptoms i.e. headache, epilepsy and hyposmia to this illness, but what’s more interesting is that some patients present with the aforementioned symptoms days before they even experiencing the common indications.

Risks

Patients suffering from Coronavirus illness are at risk of developing the following nervous system disorders;

1. Viral Encephalitis: Encephalitis means inflammation of brain tissue, a medical emergency needing immediate...
diagnosis and prompt management. If left untreated can lead to permanent neurological disability or death. Furthermore, the case study referred at 2, linked the presence of SARS-CoV-2 in CSF with Encephalitis, therefore it is particularly important that clinicians should also think of SARS-CoV-2 during differential diagnosis of Encephalitis and not only the usual culprits like Herpes Simplex Virus (HSV).

2. Infectious Toxic Encephalopathy: It is a reversible type of brain dysfunction syndrome where patients have altered brain status with symptoms ranging from headaches to delirium. It is caused by Systemic Toxemia (metabolic or bacterial toxin in blood), Hypoxia (lack of oxygen) and Metabolic disorders during acute infections. Pathological characteristics include cerebral edema with no indication of inflammation on CSF analysis. Viral infections especially those effecting the respiratory tract have long been linked with this condition. An autopsy of COVID-19 patient gives evidence of edema in brain 6 and as the patients of COVID-19 suffer from hypoxemia it is safe to assume that SARS-CoV-2 can cause toxic encephalopathy. Although more research is needed.

3. Acute Cerebrovascular Diseases: Viruses especially those that attack the respiratory system have the potential of damaging the brains blood supply. With regard to COVID-19 infection there is widespread release of cytokines, which are mediators of inflammations and there is high chance that they can cause ischemic damage to brain, furthermore COVID-19 patients also have decrease levels of platelets making them more prone to cerebral hemorrhage. Therefore, to prevent these complications of COVID-19 patients, already at high risk of cerebrovascular accidents e.g. hypertensive and diabetics, should be assessed swiftly, and preventative measure should be taken from the start of treatment.

**Mechanism**

The mechanisms of Coronaviruses effecting the Nervous system are shown in Fig 2. These are explained as follows:

1. Direct injury: From the case study mentioned earlier 2 which reports the presence of SARS-CoV-2 in CSF, which suggests a direct form of attack on the CNS.

2. Blood Circulation Pathway: As has been mentioned previously SARS-CoV-2 cause release of cytokines, which can make the blood brain barrier more permeable, and enables the virus to enter the brain's parenchyma leading to encephalitis. Although the evidence of this happening is not well documented, study of different viruses and their mechanism of action on the brain, might help in hypothesizing a better process by which SARS-CoV-2 enters the brain.

3. Neuronal Pathway: Is used by neurotropic viruses that utilize sensory and motor nerve ending to enter the CNS. SARS-CoV-2 uses the olfactory neuronal tract to enter the brain. It then causes inflammation and demyelination of neurons. This point is further strengthened by the fact when olfactory bulbs were removed from mice it restricted CoV from entering the CNS.

Fig. 2. The mechanisms of coronaviruses infections and neurological damage caused by coronaviruses. 3

4. Hypoxic Injury: SARS-CoV-2 mainly infects the respiratory tract. Its rapid proliferation, in the lungs, damages alveoli along with its microvasculature, leading to decreased oxygenation of blood. This starves the brain from oxygen and the brain starts to respire anaerobically, resulting in accumulation of metabolites like lactic acid, this cause wide spread vasodilation leading to brain edema. Prolonged brain edema increases intracranial pressure and can cause the brain to herniate through the foramen magnum cutting of its blood supply completely. Mental status quickly deteriorates starting from drowsiness to eventual coma.
5. **Angiotensin-converting Enzyme 2**: Angiotensin-converting enzyme 2 (ACE2) plays a key role in balancing blood pressure and prevention of Artheriosclerosis. Coronavirus bind to ACE2 receptors which may increase blood pressure and increase risk of cerebral hemorrhage. Given that SARS-CoV-2 viruses also target ACE2, COVID-19 patients are at high risk of cerebrovascular accidents.3

6. **Immune system**: Patients with severe viral infection may develop systemic inflammatory response syndrome (SIRS). In case of Coronavirus this might be due to the onset of pneumonia. SIRS, in patients of COVID-19, leads to multiple organ failure. Coronaviruses can hijack macrophages, microglia and astrocytes which results in large release of cytokines producing inflammation. If this inflammation happens in brain and is not treated can lead to dire consequences.3

7. **Other**: As Nerve cells lack major histocompatibility complex antigen, it proves to be rather difficult for Cytotoxic T cells to combat viruses in CNS.3

![Fig. 3. Pathogenesis of nervous system injury caused by coronaviruses.3](image)

**Conclusion:**
Patients with COVID-19 should be evaluated for neurological symptoms as soon as possible, and if symptoms are present, treatment planned for a patient should also incorporate protocol for management of these signs so that are not overlooked to avoid complications.

**References:**