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Review Article

Management of Post-Covid Encephalitis

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Abstract

Introduction: Despite covid 19 principally affecting the respiratory system, other biological systems such as the nervous system also get affected. Encephalitis is an inflammatory condition of the brain with significant morbidity and mortality rates. Encephalitis is almost always caused by a viral infection. The common symptoms of encephalitis include headache, fever, vomiting, convulsions, focal neurological deficits, and consciousness disorders. Diagnosis is mainly due to the PCR test of the cerebrospinal fluid. Management of encephalitis includes supportive care, antivirals, and steroids.

Aim of the Work: An overview is aimed at describing encephalitis post covid 19 infection and its management.

Methodology: The review is a thorough review of PUBMED articles from the year 1997 to 2021 relating to encephalitis post covid 19.

Conclusion: Since the advent of coronavirus infection by SAR CoV 2 in Wuhan, China, we have witnessed millions of cases across the world in a global pandemic. Many lives have been lost, and the disease has affected humans both socially and economically. Infection from SAR CoV 2 causes not only respiratory disease but also affects several other major organs such as the brain and nervous system. The minor anomaly to the nervous system results in loss of taste and smell function, but occasionally major anomaly like encephalitis also occurs. Encephalitis is essentially the inflammation of the brain tissue, which results in altered brain function, and even death. Management is unfortunately supportive, and the prognosis is generally poor.

Keywords: *Encephalitis; Brain Infection; Covid-19*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an illness also known as covid 19. It was first reported in Wuhan, China, in December 2019 and quickly became a global pandemic. As of December 29, 2021, there have been 281 million cases worldwide, with 5.4 million deaths. Most of the people with COVID-19 suffer a mild-to-moderate illness, while roughly 10% - 15% experience severe illness, and 5% develop a critical illness [1].

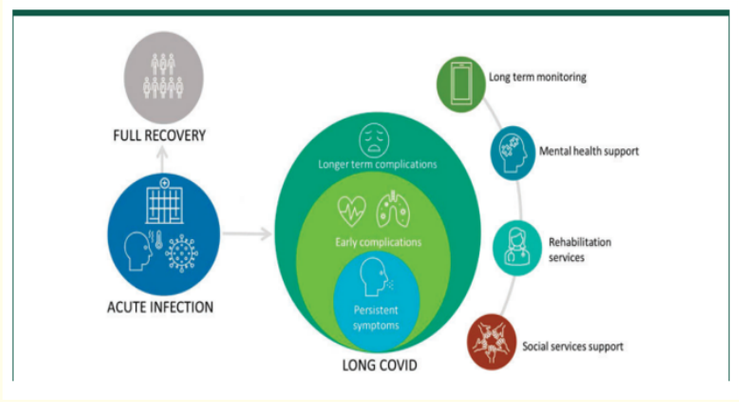

Figure 1: *Depiction of the clinical course of long Covid [2].*

Although Covid 19 primarily affects the respiratory system, it causes complications of other systems as well, such as neurological systems. Common complications of the neurological systems are anosmia and stroke, whereas a rare but dangerous complication is encephalitis [3].

Encephalitis is an inflammation of the brain parenchyma usually caused by a viral infection (Sar Cov 2 in this case) and patients present with fever, seizure, altered consciousness, and focal neurological deficits. The diagnostic test typically involves lumbar puncture and CSF analysis for Sar Cov 2, but imaging may also play a role. Management includes antiviral therapy, supportive treatment, and steroids. The first incidence of viral encephalitis associated with Sar Cov 2 was reported by Beijing Ditan. It was confirmed by genome sequencing of causative agent from the cerebrospinal fluid (CSF) [4].

Pathophysiology

It is well known that SARS-CoV-2 utilizes angiotensin-converting enzyme-2 (ACE 2) to infect cells. Cardiomyocytes, kidney epithelial cells, and vascular endothelial cells express angiotensin-converting enzyme-2 (ACE 2) on their cell surfaces which can be utilized by SARS CoV 2 to enter and infect the cells, thereby causing inflammation of myocardial/renal tissue and disseminated clotting across blood vessels [5].

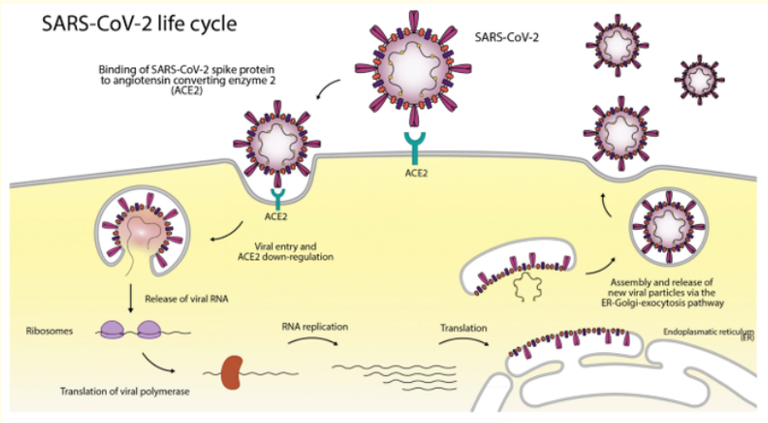

Figure 2: *SARS-CoV-2 life cycle: from binding to ACE2 receptor to shedding [6].*

Once the virus invades the body via the oro-nasal tract outside the CNS, it replicates. Viruses usually then take the hematogenous route to the spinal cord and brain parenchyma. Once the brain cells are invaded, the viruses and the inflammatory host response disrupt the neural cell function. It has also been hypothesized that the virus enters the CNS via the nasal epithelium. Recent studies have provided evidence of viruses entering the CNS vis olfactory sensory nerve endings [7]. Damage to the brain parenchyma occurs both by viral infections and resulting infiltration by immune cells, as shown by autopsied results. Considerable evidence also points out cerebrovascular injury and ischemia in the development of encephalitis. Such hypercoagulability related obstruction of arteries supplying to the nervous system may also be due to endothelial damage done by SAR CoV 2 [8].

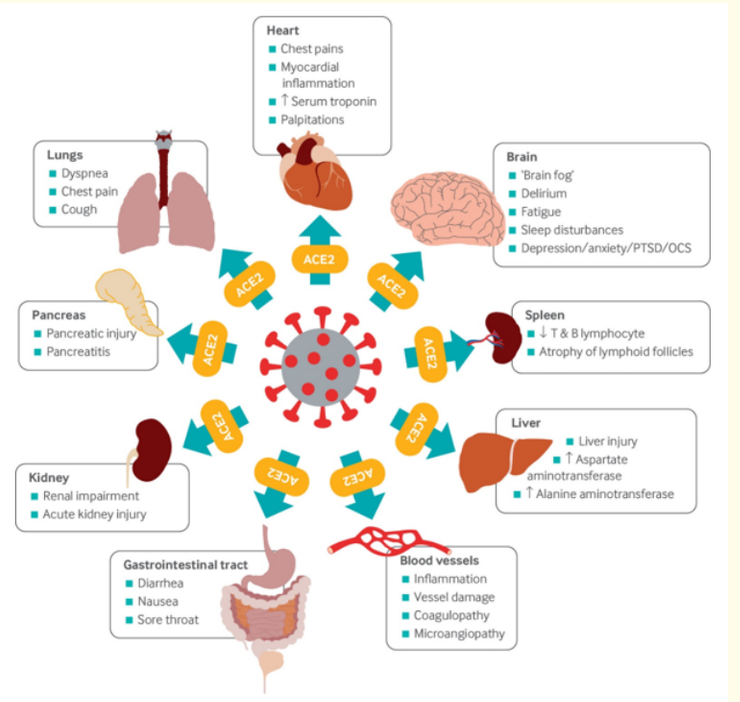

Figure 3: *Multi-organ complications of covid-19 and long covid. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor. Once these cells have been invaded, the virus can cause a multitude of damage, ultimately leading to numerous persistent symptoms, some of which are outlined here [9].*

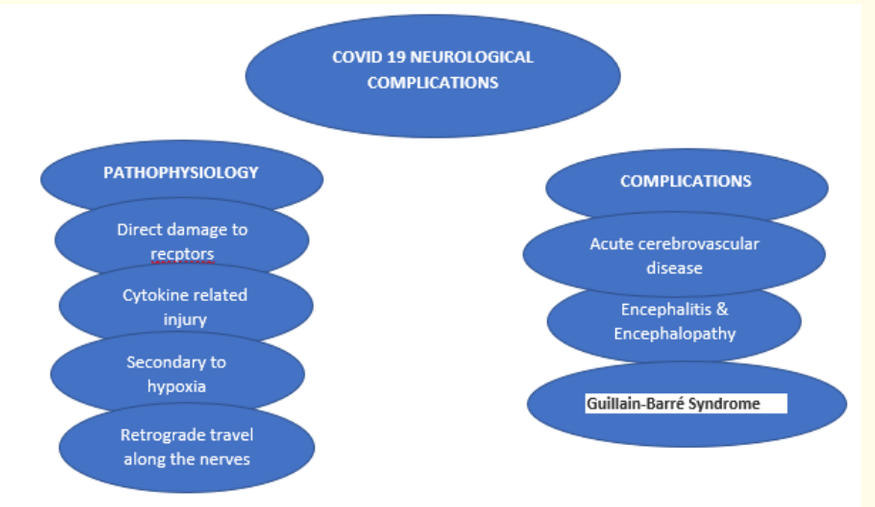

Figure 4: *COVID-19 and the neurologic system [10].*

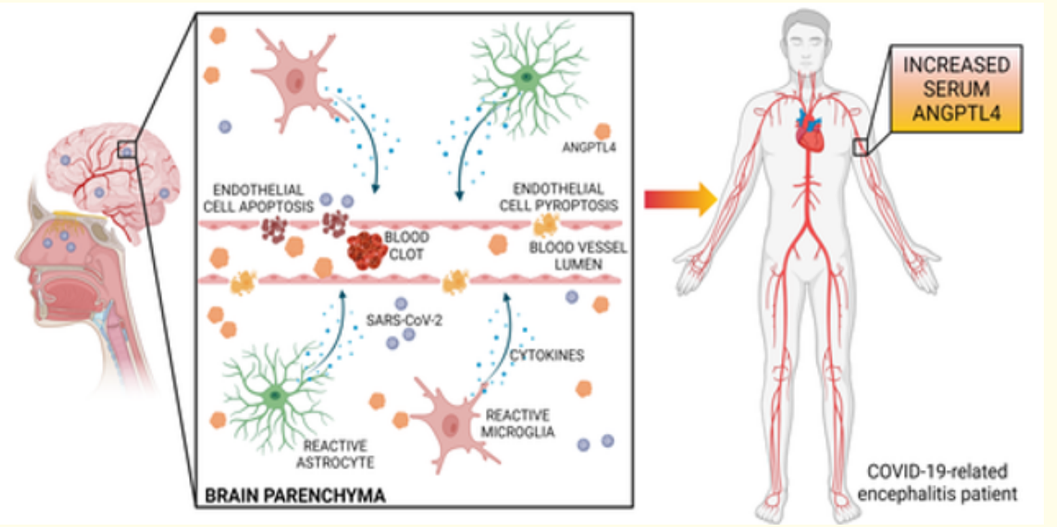

Figure 5

(SARS-CoV-2) entry into the central nervous system (CNS) utilizes the cribriform plate from olfactory mucosa activates the innate immune cells of the brain, such as astrocytes and microglia. Proinflammatory cytokines and chemokines are released by these immune cells, which increases the blood permeability and coagulability by activating the endothelial cells-occlusion of the blood vessels supplying the brain results in ischemia-related cerebral injury. The resulting hypoxia induces the upregulation of angiopoietin-like 4 (ANGPTL4) in the serum, which indicates the onset of encephalitis in Coivd 19 patients [11].

Clinical features

Common clinical features like fever, cough, dyspnea and diarrhea of Covid 19 almost always precedes SARS-CoV-2-associated encephalitis. Symptoms of viral encephalitis may consist of abnormal brain function (altered mental state, personality modification, and behavioral or verbal irregularities), movement disorders, and focal neurological signs, like hemiplegia, facioplegia, or abnormal sensation and seizures [12].

Investigations

Neuroimaging: CT and MRI are usually undertaken in suspected cases of encephalitis, with MRI being superior to CT [11]. Diffusion-weighted imaging is better when compared to conventional MRI for revealing the early signal abnormalities in viral encephalitis. MRI in cases of SAR Cov 2 infection may show small acute/subacute lacunar infarcts and a patchy area of T2 bright signals in the cortical and periventricular regions concerning cerebritis [13].

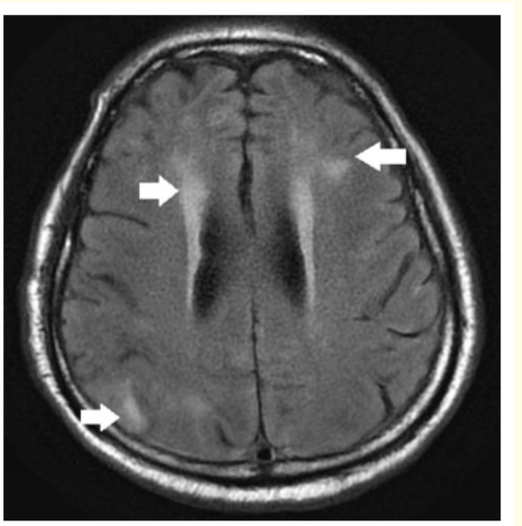

Figure 6: *Magnetic resonance imaging (MRI) brain without contrast showing lateral periventricular and right parieto-occipital bright signals concerning cerebritis [14].*

EEG: EEG is a sensitive marker of cerebral dysfunction that may show changes in the brain during the early stages of encephalitis. EEG manifests as diffuse slow waves, and some patients present with a focal epileptic wave or generalized delta activity. Severely abnormal EEG findings do not usually associate with the magnitude of disease in the acute phase of illness, but quickly improving EEG findings often suggests a good prognosis [15].

CSF analysis

The conclusive diagnosis of SAR CoV 2 associated encephalitis largely depends on virus isolation from CSF. SAR COV 2 RNA is analyzed using polymerase chain reaction [16].

Treatment

The treatment of viral encephalitis is largely supportive as there is no particular medical therapy for Covid 19 viral infection. Covid 19 patients with encephalitis may require ICU admission and occasionally mechanical ventilation as well. Antivirals are usually prescribed in most viral encephalitis cases, and hydroxychloroquine may be prescribed against the SAR Cov 2 virus. If seizures occur, they may need to be managed with valproic acid or phenytoin [17].

To counter the severe inflammation, an immunosuppressive drug such as Tocilizumab can be utilized. It is a humanized anti-interleukin (IL)-6 receptor monoclonal antibody, which blocks IL-6-mediated signal transduction. It has shown to be effective against Autoimmune Encephalitis in a cohort study [18]. It is recommended usage dose is 8 mg/kg as a single intravenous dose for patients who require high-flow oxygen or more aggressive respiratory support. In the United Kingdom, the National Health Service suggests Tocilizumab as an adjunct to dexamethasone in patients with severe Covid 19 illness. The efficacy of Tocilizumab is proven by a meta-analysis of 27 randomized trials of over 10,000 patients admitted with COVID-19. the study revealed that mortality in patients who received Tocilizumab was lower than in the placebo group [19].

Other studies have also demonstrated the benefit of intravenous immunoglobulin (IVIG) in infectious encephalitis and earlier use in immune-mediated encephalitis (IVIG) [20]. Rituximab is an anti-CD20 chimeric monoclonal antibody that exhibits potential in Autoimmune Encephalitis management in observational studies [21]. However, the recent results from trials do not seem to demonstrate any benefit of monoclonal antibodies in general against Covid 19 [22].

Conclusion

Since the advent of coronavirus infection by SAR CoV 2 in Wuhan, China, we have witnessed millions of cases across the world in a global pandemic. Many lives have been lost, and the disease has affected humans both socially and economically. Infection from SAR CoV 2 causes not only respiratory disease but also affects several other major organs such as the brain and nervous system. The minor anomaly to the nervous system results in loss of taste and smell function, but occasionally major anomaly like encephalitis also occurs. Encephalitis is essentially the inflammation of the brain tissue, which results in altered brain function, and even death. Management is unfortunately supportive, and the prognosis is generally poor.

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