
Mohammed G. Abdellatif and Ahmed G. Arafa.

Department of Neurology and Psychological Medicine, Faculty of Medicine, Sohag University, Egypt.

ABSTRACT
The fast coronavirus pandemic invasion (COVID19) attributed to severe acute respiratory syndrome by coronavirus-2 (SARSCoV2) is becoming an international major health problem. It has been defined as a worldwide pandemic by the largest international health organization (the World Health Organization (WHO)) last March this year. Nearly all COVID-19 patients have dyspnea as the most prominent symptom. Neurologic manifestations may also present such as anosmia, headache, confusion, encephalitis Guillain Barre syndrome, and cerebrovascular stroke. Coronaviruses are well known to be neuroinvasive. Accumulating proof is present that coronaviruses disease is not a consistently restricted area of the respiratory system. The nervous system may be involved in vulnerable patients and may cause severe complications and death. Hyposmia is the most common peripheral neurological manifestation. Post-infectious, autoimmune complications in the recovery period may also happen. It is of high importance to understand and identify neurologic burden of helping treatment strategies as the current pandemic continues to grow. Many recent reports confirmed central nervous system involvement in COVID-19 infected patients. We will try to explore the neurologic symptoms and complications of the new mysterious outbreak.

Introduction
COVID-19 disease responsible virus is a member of Coronaviruses group [1]. It is a virus with a diameter equals 60–140 nm. It has only one RNA strand which has an envelope[2]. Its sheath made up of two lipid layers with four protein components recognized as N (nucleocapsid), E (envelope), S (spike), and M (membrane) [1]. The infected cell receptor and (S) protein connection is crucial for viral infection [3]. (SARSCoV2) has the feature of being a part of the group of the genus Beta-coronavirus (β-CoV) which is like the Middle-East viral respiratory syndrome by the coronavirus (MERS-CoV) as well as severe acute respiratory syndrome by the coronavirus (SARSCoV) – the source of SARS global epidemic at 2003 [4]. Spike protein mutation is in charge the re-evolution of the SARSCoV-2 worldwide outbreak [5]. Rapid transmission of coronaviruses was discussed before, and neurologic complications may happen due to indirect, direct, and post-infectious effects[6].

Pathophysiology
Macrophages and T cells are attacked by the SARS-CoV directly after attacking lung epithelial cells causing lymphopenia reducing CD8+ and CD4+ numbers and disturbed acquired immune response [3]. Cytokine storm is an exaggerated immune reaction in which huge amounts of inflammatory immunocytokines. Interleukin-6 (IL-6)
may be the main cause of severe inflammation and cell death [7]. The virus makes his way by mucous membranes, up to lungs crossing the respiratory system. It attacks specific receptors (angiotensin-converting enzyme 2 (ACE2) expressed in different body systems like respiratory, urinary, cardiac, and GIT systems [8]. Post-infection autoimmune response might happen in which adaptive immune response becomes directed against host epitopes causing tissue damage after the virus has been cleared [6]. In addition to inflammatory mechanism, thrombosis and pulmonary embolism have been observed in severe form of COVID 19. Elevated Troponin, d-dimer and fibrinogen levels were observed in severe cases. The hypercoagulable profiles seen in severe COVID 19 patients likely should indicate significant endothelial injury and losing the endothelium function of vasodilation, fibrinolysis, and anti-aggregation. Of note, the endothelial cells also express ACE2 [9]. CNS invasion has multiple possible mechanisms. Firstly, ACE-2 receptors are also found in glial cells in brain and spinal neurons. Hence it can attach, multiply and damage the neuronal tissue [10]. Secondly, disruption of blood brain barrier during the viremia causes the virus to enter the brain directly and/or through the synapse. Moreover, COVID 19 virus could invade the peripheral nerve terminals by which have access to the CNS [11]. At last, increased invasion of coronavirus to macrophages triggers macrophage and cytokines secretion [3]. This may result in macrophages trans passing to the nervous system and attacking myelin sheath and neurons [12].

Neurologic Manifestations
Coronaviruses are mainly implicated in respiratory and gastrointestinal diseases [1]. The last Chinese outbreak reported 44,500 COVID-19 patients. 81% of cases had pneumonia, 14% had severe lung symptoms shortness of breath, and hypoxemia. Five percent had respiratory failure and other organs failure [13]. Systemic complications consisted of heart failure, and septic shock [14]. Neurologic manifestations were present in nearly 100 patients in Wuhan, China outbreak including disturbed level consciousness in 9% of patients and headache in 8% of patients[4]. Another study reported that 35.9% of patients were firstly presented by neurological complaints including headache, impaired consciousness, stroke, and seizures [15]. Kidney, liver, and cardiac injury may contribute to consequent neurological symptoms of COVID-19[16]. Also, Cytokine storm, hypercoagulability, arrhythmias, and cardiac failure which are major stroke etiologies[14].

Primary Neurologic manifestations.
Infected brain tissues by viral RNA was found post-mortem is clear evidence of viral CNS invasion [17]. Viral presence in CSF is also proved in severely ill patients [16]. CNS invasion mechanisms by SARS-CoV are still unclear. It may happen by nasal epithelial destruction then through the olfactory bulb [6]. Anosmia and taste sensation loss are among the early manifestations of COVID-19 infection [18]. Hyposmia is the most common peripheral neurological manifestation [19]. Anosmia post viral infection is a common cause of smell loss and is known to be associated with many human viral strains, including other coronaviruses [20]. Many reports evaluating mechanisms of COVID-19 – mediated smell sensation loss have suggested neurotrophic targeting of olfactory neurons vs infection of non-neural olfactory epithelial cells [21]. A recent report revealed two infected patients were firstly presented with
Guillain-Barré syndrome (GBS) variant and multiple cranial neuropathies. One patient presented with ophthalmoplegia, ataxia, and areflexia Miller Fisher Syndrome. The other one was presented with bilateral abducens paralysis and ageusia [22]. Also, hypoxic brain injury is a major mechanism of CNS damage secondary to respiratory failure [23]. COVID-19 patients are often complicated with high risk of cerebrovascular diseases, such as cardio-cerebrovascular disease, hypertension, and diabetes [24] or death, occurring mainly in elderly and chronically ill patients [25]. Estimated incidence of implicated health problems among COVID-19 patients in USA revealed that 0.7% of COVID-19 patients had underlying neurologic problems [26].

Secondary autoimmune neurologic manifestations
A recent report has revealed the first diagnosed COVID-19 with acute hemorrhagic encephalitis [27]. It shows the first case of COVID-19–associated acute necrotizing hemorrhagic encephalopathy which is a rare encephalopathy that has been associated with other viral infections. Another report showed the diagnosis of Guillain-Barré syndrome was established in the presentation of an infected patient with COVID-19. The timing association between the infection and appearance of acute polyneuropathy considered that infection was a direct cause of autoimmune polyneuropathy [28].

The existence of coronaviruses in the nervous system after the acute infection, may be responsible for immune induced inflammation and demyelination in vulnerable patients [6]. The appearance of Human CoV RNA particles in CSF of patients with acute demyelinating encephalomyelitis [29] and disseminated sclerosis [30] supports that theory.

Human-CoV infections also caused post-infection immune-mediated syndromes, such as GBS and encephalitis [31]. This may be attributed to the molecular similarity between Human-CoV and myelin basic protein (MBP) [32]. Interestingly, it was revealed that the infecting virus interacts with certain receptors [angio-tensin-converting enzyme-2 (ACE-2) receptors]. They are the main gate for host cellular invasion. This discovery lightens up the question whether ACE2 receptors expression inside the nervous system can influence the presumed role of SARS-CoV in damage to CNS and neurological complications and mortality [16].

CONCLUSION
During exploring the new Covid-19 pandemic across the world the awareness about COVID-19 neurologic burden as regard presentation and further complications must have high consideration due to the progressing accumulating evidence of CNS involvement during viral infection. The exact function of ACE-2 receptors in the COVID-19 infection raises the questions and concerns about the nature CNS involvement in COVID-19 infection.

References