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Mini Review

Prolonged Encephalopathy in COVID 19

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Abstract

Coronavirus 2 (SARS CoV2 or CoV2) infection which is responsible for the COVID 19 pandemic has been noted to cause multi-organ involvement including lungs, heart, kidney, and the brain. Neurologic effects of this disease vary on a spectrum ranging from anosmia, delirium or confusion, strokes, seizures, encephalopathy and or encephalitis, and Guillain Barre-like syndrome. However, rarely prolonged encephalopathy has been observed. There is not a good amount of evidence behind all the factors contributing to the occurrence of this prolonged encephalopathy or delayed awakening. In this manuscript, we have reviewed the existing literature and highlighted various postulated etiological theories and the impact of factors including the patient, disease as well as physician-related, contributing to the delayed awakening. We have discussed the available management modalities for these group of patients as well based on the limited literature available thus far.

Keywords: COVID 19; Encephalopathy; Brain; SARS Cov2

Abbreviations: SARS CoV2 or CoV2: Coronavirus; COVID 19: Coronavirus disease 2019; ACE2: angiotensin converting enzyme 2; HIE: hypoxic ischemic injury; DPHL: delayed post hypoxic leukoencephalopathy; ARDS: acute respiratory distress syndrome; ADEM: acute disseminated encephalomyelitis; EEG: electroencephalography

Opinion

In addition to primary involvement of lungs, COVID 19 is also associated with cardiac, renal, and neurological manifestations. Neurologically it can present with a wide spectrum of neurological involvement with symptoms ranging from anosmia, ageusia, headaches, strokes (arterial and venous), encephalopathy/encephalitis, coma, and rarely prolonged encephalopathy, coma, and peripheral nervous system involvement including Guillain Barre Syndrome [1,2]. We conducted a literature review to explore the potential etiological factors and management of COVID 19 patients with prolonged encephalopathy. This is vital for clinicians taking care of these critically ill COVID 19 patients and having discussions with the families regarding predicting outcomes of prolonged encephalopathy with this new disease which is lacking a clear natural history.

Discussion

Prolonged Encephalopathy and delayed awakening in COVID 19 can be attributed to various factors which can be characterized as follows. COVID 19 can affect brain function in multiple ways including proposed direct neurotropism leading to direct invasion with possible devastating brain stem-medullary respiratory arrest which has been linked to expression of angiotensin-converting enzyme 2 (ACE2) within the central nervous system [3]. However, due to the low expression of ACE 2 in human brains and olfactory sensory neurons, the risk of direct brain invasion is small [1,4]. COVID 19 can also cause direct hypoxic insult to the brain secondary to viral pneumonitis and complicated by acute respiratory distress syndrome (ARDS) and sequelae of hypoxia including hypoxic-ischemic injury (HIE) seen in 1.4% of patients

with COVID 19 and delayed post hypoxic leukoencephalopathy (DPHL) which can be seen evident on MRI brain imaging [5]. The disease also affected caused myocarditis, myocardial infarction, and cardiac arrest which in turn contribute to HIE and encephalopathy [2]. Other factors commonly included host factors with activation of inflammatory cascades and aberrant immune response leading to the development of endotheliopathy and coagulopathy contributing to prothrombotic state leading to a higher occurrence of strokes both arterial and venous in origin which can contribute to encephalopathy due to mass effect, herniation due to large vessel occlusion strokes, seizures, basilar occlusion [6,7]. Multiple diffuse cerebral microbleeds involving corpus callosum as well were seen in a study looking at neuroimaging patterns in COVID 19 patients. These are proposed to be related to prolonged hypoxia and ARDS like physiology and/or microangiopathic process [8]. The host immune response can be characterized as parainfectious i.e., the bystander host damage occurring due to innate immune response to acute COVID 19 infection vs post-infectious i.e., abnormal adaptive autoimmune response occurring weeks following acute infection [9]. Parainfectious neurological manifestations contributing to prolonged encephalopathy include acute necrotizing encephalopathy reported in multiple studies, which otherwise is a rare disease process [10]. Post-infectious included more specifically acute disseminated encephalomyelitis (ADEM) leading to prolonged encephalopathy [9,11]. There is also a suggestion of cytokine storm contributing to the comatose state by upregulating systemic inflammation and increasing blood-brain barrier permeability, microglial and astrocytic activation, and further positive feedback inflammation and brain metabolism dysfunction [12]. Damage to Reticular Activation System in the Brainstem could also be one of the reasons for delayed wakefulness causing prolonged encephalopathy [3,13]. Subclinical seizures or non-convulsive seizures can also contribute to prolonged encephalopathy. The most common electroencephalographic abnormalities seen in a study by Antony et al included generalized slowing and epileptiform abnormalities especially in frontal lobes [14]. CSF Analysis does not show any characteristic pattern but generalized disturbances but rarely, some studies showed the presence of CoV2 directly in the CSF [15]. In addition, heavy and prolonged use of sedation and analgesia employed widely for the treatment of ventilator dyssynchrony and ARDS-like pathology due to COVID 19 contributes to delayed awakening in these critical patients. Patients should get periodic EEGs to avoid prolonged oversedation, when possible to prevent the above. Often, patients with cytokine storms and severe phenotype of the disease have multiorgan dysfunction including renal and hepatic derangement which can, in turn, contribute to the accumulation of toxic metabolites and further encephalopathy [16].

Management includes supportive care and nervous system pathology-based usual standard of care and treatment is offered. No specific treatment regimen has been proposed. Ranganathan et al reported improvement of prolonged COVID 19 encephalopathy after therapeutic plasma exchange including electrographic improvement as well. However, this lacks a randomized trial. This modality would also require the assistance of monitoring techniques such as cerebral perfusion monitoring and measurement of inflammatory marker levels [17]. Long-term outcomes in these critical patients are unknown due to a lack of natural history. Clinicians often face the tough reality of making decisions for these patients along with the families about whether or not to continue life-sustaining treatment in this cohort of patients. Various biomarkers can be of utility including EEG, MRI brain, and even functional MRI especially if it does not show visible radiographic damage and intact brain network connectivity. Latter can be helpful as this finding may be suggestive that the neurological prognosis in those cases may not be as grim as otherwise presumed. This should be brought up in discussion with families and individualized decision making encouraged in concordance with patients or family wishes [18].

Conclusion

COVID 19 has been implicated in causing prolonged encephalopathy in patients even after few weeks to months of acute illness. No definitive etiology or cause has been identified for it till now other than proposed mechanisms like the direct invasion of the virus into neurons, hypoxic-ischemic insult, inflammation, endotheliopathy, coagulopathy, cytokine storm, and multiorgan failure, damage to reticular Activation system in the brainstem, and iatrogenic including sedation and analgesia. Prognostication presents a particular challenge in these groups of patients as well due to unknown long-term outcomes.

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None.

Conflict of Interest

None.

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