Review Article

Potential Neurological Outcomes in COVID-19 Patients: A Review

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ABSTRACT:

Coronavirus emerged from Wuhan China, which has been a global challenge for healthcare authorities and individuals. Patients are presenting to the clinicians with neurological symptoms caused by COVID-19 or with preexisting neurological conditions with fear of contracting the virus. We have conducted a literature review on neurological outcomes in COVID-19 patients along with patients with underlying neurological conditions. We searched multiple databases including PubMed, Google Scholar, EBSCO, Semantic Scholar, and Wiley Online for information on neurological manifestations of patients suffering from coronavirus. Clinical data and co-morbidities of the patients were examined. Headache, dizziness, hyposmia, and stroke were among the symptoms reported. Emerging literature is suggesting that coronavirus patients along with respiratory symptoms are also experiencing neurological symptoms. Some medical emergencies such as stroke require immediate treatment to save the patients. Neurologists and clinicians need to recognize these symptoms in order to timely manage and treat the patients.

Keywords: Coronavirus, Manifestations, Neurology

How to cite this Article:
Lal A, Saleem MKM, Lakdawala YA. Potential Neurological Outcomes in COVID-19 Patients: A Review. J Bahria Uni Med Dental Coll. 2020; 10(4): 310-315

INTRODUCTION:

From a market in the city of Wuhan, Hubei, China in December 2019 marked the beginning of Novel Coronavirus which was identified from unknown cases of pneumonia.[1] Initially, the viral infection was disseminating in China, leading them to impose precautionary measures to contain and control the virus. However, the virus then started to transmit outside China, and as of now, has engulfed almost all of the countries. Keeping this in mind, on 11th March 2020, the World Health Organisation declared novel coronavirus as a pandemic and guided world health community information on necessary precautionary measures.[2] Additionally, with the rapid dissemination of this pathology, individuals as well as healthcare authorities came under immense pressure and stressed on control and protect oneself and the community. Many studies have suggested that the possible origin of coronavirus is from bats, the virus was transmitted from these bats and then infected mammals.[3] Coronavirus is suggested to infect many organ systems of the body including the central nervous system (CNS), hepatic, cardiovascular, and respiratory.[4] Primary physical effects of Novel coronavirus has been on the respiratory system, but nervous system outcomes have also been seen in patients.[5]

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Received: 29-Jul-2020
Accepted: 03-Sep-2020

Primarily, the mode of transmission for coronavirus has been through respiratory droplets by a close and direct human to human contact.[6] Furthermore, clinical features of the infected person include fever, dry cough, sore throat, and myalgia, although some patients may also experience neurological and stomach upset symptoms.[7] On one hand, individuals particularly elderly and with underlying co-morbidities are more prone to develop a severe infection as well as mortalities from it.[8] On the other hand, young individuals without any co-morbidities are facing morbidities and mortalities from this virus.[9] A major hurdle in containing this virus is identifying those people who are infected but remain symptomless and are disseminating the pathology around them.

Coronavirus genome has 4 genera consisting of alpha, beta, gamma, and delta, being of single-stranded positive-sense RNA.[10] One of the key topics regarding coronavirus has been its pathogenesis. Previously, many studies have suggested the mode of action of coronavirus in the human body. SARS-CoV after entering the human body initiates its action by binding to Angiotensin-Converting Enzyme 2 (ACE2), which has been suggested to be its primary mode of action.[10] Additionally, SARS-CoV also uses protease TMPRSS2 for S protein priming. In human ACE2 receptor is expressed in tissues like airway epithelium, kidneys, lungs parenchyma, vascular endothelium, and central nervous system.

Some reports have emerged stating the potential of SARS-CoV to invade the central nervous system and mediate its actions.[11] Although damage by this virus has been reported

in COVID-19 patients with different symptoms arising in them, the extent to which damage occurs is yet to be discovered. Studying the effects of novel coronavirus to CNS can open doorways to patients suffering from their effects, helping in formulating effective treatment modalities.

METHODOLOGY:

For this literature review, we used multiple databases such as PubMed, Google Scholar, EBSCO, Semantic Scholar, and Wiley Online along with the snowballing technique. A large number of articles was found in these databases using the following generic terms such as "Coronavirus", "COVID-19" and "Neurology".

A total of 1508 articles were found. After a discussion with all the authors who performed the literature review, 177 number of articles were screened for relevancy. Articles that were collected were screened based on information extracted from their titles, abstracts, and full text of the articles. The extracted articles were screened by looking at the following information: a) Title, b) Authors, c) Abstract, d) Journal, e) Main text, f) Article type and g) Publication Date. Articles were included on the basis of being related to Coronavirus along with neurological association with it. The exclusion of the articles was mainly due to not being related to the respective literature, not being in English language and articles that were not published in a journal.

Pathogenesis of SARS-CoV in CNS

As it has been mentioned previously, SARS-CoV mainly mediates in action by binding to ACE2 receptors[12]. Central nervous system (CNS) has been found to have these receptors present, thereby, some infected individuals experiencing symptoms related to this organ system.[13] Although some studies do report that the mere presence of these receptors does not necessarily mean that virus is going to invade the particular organ system.[14] Previously, some studies have suggested that some patients with SARS only had the virus present exclusively in neurons.[15]

ACE2 receptors have also found to be present in glial cells and spinal neurons, where they can divide and multiply to damage the cells. Some studies have suggested that the primary mode by which coronavirus invades and damages the CNS is by the way of the olfactory bulb.[16] Through this route, the virus enters the olfactory bulb, and further damages other parts of the brain such as thalamus and brain stem. ACE2 receptors have also been strongly expressed in two areas of the brain responsible for the regulation of respiratory cycle, ventrolateral medulla, and nucleus of the tractus solitaries.[17] Prior studies have suggested that when SARS-CoV invades CNS, it induces direct neural death in the respiratory center of the medulla by upregulation of IL-1, IL-6, and TNF-alpha, thereby initiating inflammatory response.[18] Recently, an emerging hallmark of coronavirus has been coagulopathy, whereby "sepsis-induced coagulopathy" arises in patients being in hypercoagulation state, predisposing to conditions such as stroke.[19]

Neurological damage ensued by COVID-19

Talking about mechanisms by which SARS-CoV causes neurological damage, the virus gains entry into cerebral circulation and sluggishly moves forward. Once within the neuronal tissues, interaction with the ACE2 receptors commences its action.[13] Additionally, because the virus gains entry through the purposed olfactory route, disturbance in smell sensation has been noted in a handful of patients.[20] Moreover, immunological damage to CNS is initiated by cytokine storm whereby novel coronavirus induces innate immune system in the host to release cytokines such as IL-1, IL-6, and TNF-alpha, so producing an inflammatory response which damages the neuronal tissues.[21] Furthermore, all this leads to brain hypoxia, causing further damage.[22] Lastly, pneumonia is caused by the coronavirus, which further aggravates hypoxic brain injury.

Neurological Symptoms of COVID-19 Patients

Literature has stated many potential symptoms experienced by coronavirus patients. COVID-19 patients have neurological symptoms such as headache, myalgia, confusion, and dizziness.[23] Moreover, some patients also experienced hyposmia and dysgeusia as well.[24-26] Mao et al reported that some patients also suffered from cerebrovascular diseases including ischemic stroke and cerebral hemorrhage.[27] Some common neurological manifestations of COVID-19 have been listed in Table 1.

Central Nervous System Manifestations

Location	Manifestations
Central Nervous System	Headache
	Dizziness
	Cerebrovascular Disease
	Epilepsy
	Encephalopathy
	Ataxia
Peripheral Nervous System	Hypogeusia
	Hyposmia
	Neuralgia

1. Stroke:

Stroke has occurred in some coronavirus patients, presenting as a medical emergency.[28] Furthermore, stroke has occurred in coronavirus patients in both young and old age groups.[29] The purposed mechanism that might predispose a person to stroke is by hypercoagulation associated with COVID-19 which induces a sepsis-induced coagulopathy.[19] A study reports that stroke was more commonly associated with COVID-19 patients suffering from a severe infection, which has further contributed in the mortality rates.[30] Additionally, it has been suggested that some individuals who contract

the virus may already have cerebrovascular risk factors such as hypertension, diabetes, hyperlipidemia, and previous history of stroke, predisposing them to stroke when infected with the novel coronavirus.[30] Abnormal laboratory investigations include elevated levels of leukocyte count, C-reactive protein, D-dimer and ferritin levels.[31]

2. Seizures:

Many studies have reported incidents of seizures in patients suffering from coronavirus.[32,33] Initially, the COVID-19 patients presented only with usual symptoms, but later on developed complications such as seizures.[34]

3. Encephalitis:

Initially, the first case of coronavirus patients who suffered from encephalitis was reported from Japan[35]. Physically this patient experienced neck stiffness with Brain CT scan being normal. The mechanism by which SARS-CoV might lead to encephalitis is by direct viral invasion, attachment to ACE2 receptors through the blood-brain barrier.[33] It can be postulated that those patients who suffer from severe coronavirus infection are especially predisposed to suffer from neurological complications.

4. Encephalopathy:

Encephalopathy manifests in patients that suffer from severe COVID-19 infections.[36] Although, it has been suggested that disseminated intravascular coagulation and venous thromboembolism caused by this virus might cause encephalopathy.[37] An elderly patient suffering from COVID-19 has been reported to develop complications of encephalopathy.[38] From China, it has been reported that some patients also experienced hypoxic encephalopathy.[39] Furthermore, cases of acute necrotizing encephalopathy have also been reported in some patients, mechanism of which is mainly by cytokine storm causing a large amount of cytokine to be released and crossing the blood-brain barrier to cause injury.[40] Lastly, those individuals who have been suffering from encephalopathy may have been predisposed to stroke.[41]

5. Dizziness and Headache

Dizziness and headache have been regarded as one of the most common neurological symptoms experienced by COVID-19 patients.[27,42,43] Furthermore, the release of cytokines and chemokines by the macrophages during coronavirus infection might be associated with headache.[44] Although the commonality of these symptoms has been clearly stated, the precise pathophysiology and mechanism are still to be figured out.

Peripheral Nervous System Manifestations:

1. Anosmia and Hypogeusia:

Many studies report that anosmia and hypogeusia are one of the common and first neurological manifestations in coronavirus patients, and may even occur before the occurrence of respiratory symptoms.[34,45] In a study, nearly a quarter of the patient's sample reported experiencing anosmia, with improvement occurring after one week.[46] The virus primarily gains entry into the cerebral circulation by firstly passing through the olfactory bulb. This has been known to cause a disturbance in the smell sensation of the infected people. Studies further report that some patients might only experience disturbance in smell sensation and asked to self-isolate themselves.[45]

2. Skeletal Muscle Injury:

Although less common, skeletal muscle injury has also been on the neurological symptoms experienced by the patients.[47] An elderly person in China, known case of coronavirus, after being admitted to hospital was found to have limb weakness after the neurological examination was performed.[48] Similarly as stated before, skeletal muscle injury is also one of that neurological symptom experienced by patients with severe infection.[49]

Special Care For Patients With Underlying Neurological Conditions

Many patients, particularly those who are above 65 and with underlying medical conditions are more anxious and stressed to contract viruses and might suffer from severe infection. Mortality rates are keenly observed more in this age group. So, emphasis on special care and support for these patients is precisely required.

Multiple Sclerosis: Patients with multiple sclerosis are taking drugs that might predispose them to contract the virus more rapidly and suffer severe infection from it, as compared to a healthy individual. Currently, no consensus has been reached whether to modulate drug therapy for the patient and their susceptibility to contracting the virus.[50] Furthermore, no precise mechanism by which multiple sclerosis patients develop coronavirus infection is yet to be discerned.[51]Recently a study reported adamantanes being successfully used in patients and reported no change in their neurological functions.[52]

Parkinson's Disease: Due to the current situation, the clinical visits required by the Parkinson's Disease (PD) patients are suspended, which increases stress and confusion amongst them. It has been reported that some patients developed increased psychiatric symptoms such as hallucinations, anxiety, and psychosis.[53] Generally, patients have been inquiring about the COVID-19 pathology and their susceptibility to contracting the virus. Currently, no definitive association can be developed between the two pathologies.[54] Additionally, it has been suggested that Parkinson's patients with restricted lung capacity to axial akinesia are predisposed to develop coronavirus infection.[55] Lastly, the correlation between Parkinson's disease and coronavirus is currently unknown, but the subject matter has particularly generated stress among the sufferers of PD.[56]

Epilepsy: Epilepsy, being one of the common neurological disorders, is also highlighted here. Currently, the practice implemented is to keep epilepsy patients out of the hospitals due to the likelihood of contracting the virus and practicing home care.[57] Almost all of the drugs administered to the epileptic patients are not immunosuppressive so decreasing the chances of contracting the virus. Furthermore, it has been stated that patients with epilepsy are not more prone to contract the virus as well as suffering a severe infection from it.[58] Clinicians who are managing epileptic patients should guide their patients on which medications to take.[59]

Neuromuscular Disorders: Patients with neuromuscular disorders are currently on immunosuppressive drugs, increasing their likelihood of contracting the virus. Moreover, patients particularly suffering from Myasthenia Gravis and Lambert-Eaton Syndrome may have respiratory muscle weakness, which may predispose them to develop complications from the novel coronavirus if they contract it.[60] Those on immunosuppressive medicines should be extra-cautious and maintain social distancing more vigilantly.[60] Lastly, it has been stated that Hydroxychloroquine is known to exacerbate symptoms of myasthenia gravis and is, therefore, contraindicated in these patients.

CONCLUSION:

Currently, the entire global community is in grips of the novel coronavirus. However, understanding the neurological manifestations of coronavirus is being evolved rapidly, practitioners should look for these symptoms for timely management of the patients. Timely and early detection not only decreases morbidities but also promotes hassle-free recovery of the patients. Furthermore, additional knowledge on lab work, pathophysiology, and treatment options for these patients should be looked for so that better recovery of the patients can be expected. Knowledge of all these things will help neurologists, scientists, and clinicians to treat their patients optimally.

Author Contribution:
Abhishek Lal: Literature review, drafted the manuscript and formulated methodology
Mahnoor Khawaja M. Saleem: Literature review and dra fted the manuscript
Yousuf Ali Lakdawala: Conducted the final revision of the manuscript

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